Disclaimer: The following information is fictional and is only intended for the purpose of illustrating key concepts for results data entry in the Protocol Registration and Results System (PRS).

Fractional Factorial Study Design Example

(The Charleston Adolescent Wellness Study [CAWS])

Methods

Study Design

This was a study using a fractional factorial design to identify intervention strategies to reduce depression and anxiety among adolescents attending public high schools. The study also measured levels of salivary cortisol, which have sometimes been associated with depression and anxiety, as an exploratory outcome. The intervention period was November 1, 2017, to May 30, 2018, with access to interventions maintained during school holidays (e.g., Thanksgiving, winter break, spring break).

Study Participants

Participants were recruited from public high schools in Charleston, SC. Students who provided consent or who provided assent and had parental permission for screening were assessed for depression using the Center for Epidemiological Studies Depression Scale (CES-D) in a classroom by the school counselor. The CES-D is a 20-item brief measure that assesses how frequently respondents experience symptoms of depression. Responses are scored from 0 (none of the time) to 3 (most or all of the time) for each item and then summed for a final score ranging from 0 to 60. Individuals eligible to participate in the study had mild to moderate depression (CES-D score between 9 and 39); had parental permission if the individual was younger than age 18; and were adolescents (age range 13–19 years) enrolled in freshman, sophomore, or junior classes (to allow them time to complete the study before graduation). They also had access to a cell phone to receive text messages and access to the internet at home or school. The exclusion criteria were having severe depression (CES-D score > 39); currently receiving psychotherapy, medication therapy, or both for depression; and being enrolled in the senior class.

The study protocol was reviewed and approved by the Charleston University College of Arts and Sciences Institutional Review Board. Written informed consent was received from each participant age 18 or older or from a parent or guardian if the participant was younger than age 18. Written assent was obtained from all participants under age 18.

Randomization and Intervention Arms (Conditions)

Individuals who met the eligibility criteria were randomized to one of eight intervention arms or conditions (Table 1). The intervention strategies tested included two levels of each of the following:

1. Counseling—Participants received counseling either in person in a school-based setting or online in a web-based setting. Both modalities used cognitive behavioral therapy (CBT) provided by counselors who were licensed clinical social workers trained to work with adolescents. Counseling sessions of both types occurred weekly during the seven-month intervention period, except during school holidays. During breaks, participants were granted access to counseling on an as-needed basis, up to once a

week. We considered in-person CBT to be the "high" level of counseling and web-based CBT to be the "low" level.

2. Text messages—Participants either received text messages (the "yes" text message factor level) or did not (the "no" text message factor level). Participants randomized to the "yes" text message factor level received short text messages to support their therapy. Texts were sent daily during the seven-month intervention period, including during school holidays. We assumed that participants who received the text messages read them, although our technology and participants' mobile devices did not all allow tracking to determine whether participants actually opened each message.
3. Web-based interactive exercises—Participants either were given access to online videos and interactive exercises such as quizzes (the "yes" interactive factor level) or had no access to these web-based materials (the "no" interactive factor level). New interactive sessions were available each week during the seven-month intervention period, regardless of school holidays, for those in the "yes" interactive factor level. We tracked participants' accessing of and interaction with these web-based materials through an online reporting system.
4. Web-based matched success stories—Participants were given online access every two weeks to either a highly matched story about another adolescent who had overcome depression (the "high" matched factor level) or a minimally matched story (the "low" matched factor level). For the "high" matched factor level, the stories were tailored to the participant's sex, age, grade, and ethnicity. For the "low" matched factor level, the stories were matched only to the participant's sex. New stories were available biweekly for the seven-month intervention period, regardless of school holidays. We tracked participants' accessing of and interaction with these web-based materials through an online reporting system.

Outcome Measures

The two primary outcomes measured in this study were differences in depression and anxiety scores from the first counseling session (pre-intervention) to the last counseling session seven months later, at the end of the intervention. We administered the pretests and posttests either in person during the first and last in-person counseling sessions or online during the first and last web-based counseling sessions. Depression was measured using the CES-D, which was also used at screening to determine study eligibility. The measure was repeated during the first counseling session because some participants did not start the intervention immediately after the eligibility assessment. Anxiety was measured using the seven-item anxiety subscale of the Hospital Anxiety and Depression Scale (HADS). Each item on the HADS Anxiety subscale (HADS-A) is scored from 0 to 3; all item scores are summed for a total score ranging from 0 to 21, with higher scores indicating higher levels of anxiety.

We also measured an exploratory outcome: the differences in salivary cortisol levels among participants from baseline to the end of the intervention period. Cortisol, a stress hormone, is measured in nanomoles per liter (nmol/l), with a range of 9 to 33 reported in studies of nondepressed people. Higher cortisol levels are associated with higher levels of anxiety. During the first counseling session, counselors taught participants how to collect salivary cortisol samples at home for the baseline measure. Participants received a Salivette sampling

kit so that they could collect the sample 30 minutes after waking. They were asked to not eat, drink, smoke, chew gum, brush their teeth, or use mouthwash for at least 30 minutes prior to providing the sample, which they collected by chewing on a synthetic cotton roll. That day, participants brought their sample kits to school, where they were picked up by the study team for quality control and analysis. The day after the interventions ended, participants repeated the procedure.

Data Analysis

We used a balanced fractional factorial, 2^{4-1}, resolution IV design with eight conditions to estimate the main effects of all four factors. This design decreases by half the number of conditions that would be required for a full factorial analysis of four factors (i.e., $2^4 = 16$ conditions). Each main effect is aliased (or confounded) with a three-way interaction of the remaining three factors; however, the effect of each three-way interaction is assumed to be negligible. For this study, the main effects of the factors on posttest outcomes, or the time x factor interactions, are the most important. We had no empirical support for an effect of two-way interactions between the factors in this study; therefore, their effects were not estimated. Table 1 shows the specific combinations of each of the two-level intervention factors in the experimental design. Each factor was implemented an equal number of times at high or low levels, or present (yes) or absent (no) levels.

We designed the study to have 80% power at $\alpha = 0.05$ to detect a significant effect for the main effect of a factor on the three outcomes: depression, anxiety, and cortisol levels. We used effect coding to indicate condition membership by factor level, and analysis of variance (ANOVA) to model the primary and exploratory outcomes. The underlying assumptions of the ANOVA model were tested and were supported for all outcomes. Analyses were performed with SAS 9.4 software (SAS Institute).

Table 1. Experimental conditions analyzed for the fractional factorial design.

Condition	CBT Counseling Type	Text Messages	Interactive Exercises	Matched Stories	Participants Assigned *(N = 400)*	Participants Analyzed *(n = 320)*
1	In person	Yes	Yes	High	50	40
2	In person	Yes	No	Low	50	40
3	In person	No	Yes	Low	50	40
4	In person	No	No	High	50	40
5	Web based	Yes	Yes	Low	50	40
6	Web based	Yes	No	High	50	40
7	Web based	No	Yes	High	50	40
8	Web based	No	No	Low	50	40

Results

Study Participants

A total of 400 participants were randomized into the intervention strategies (Table 2). The criteria for study completion and analysis were as follows:

- Attending more than 12 in-person counseling sessions or more than 12 web-based counseling sessions
- Accessing the success stories more than six times
- Maintaining cellular service for the duration of the study, for those randomized to the "yes" text message factor level
- Participating in more than 12 web-based interactive exercises, for those randomized to the "yes" interactive factor level
- Completing the pre-intervention and post-intervention CES-D and HADS-A measures
- Providing pre-intervention and post-intervention salivary cortisol samples

The 80 participants whose data were not included in the final analyses failed to meet one or more of these criteria. Five participants per condition withdrew from the study, and four participants per condition were lost to follow-up before they had attended the minimum number of counseling sessions or accessed the minimum number of web-based activities (i.e., interactive exercises, success stories). One participant per condition in Conditions 1, 2, 5, and 6 lost his or her cell phone. One participant per condition in Conditions 3, 4, 7, and 8 failed to provide saliva samples. There were no systematic or significant differences between the assigned and analyzed populations or among the eight study conditions. Demographic information for participants, by assigned study condition, is available in the appendix (Table A-1).

Table 2. Participant characteristics for the assigned population, N=400.

Characteristic	**Total** *(N = 400)*
Age in years *(mean, SD)*	16.0 (1.7)
Female *(number, percentage)*	229 (57%)
Race *(number, percentage)*	
American Indian/Alaska Native	2 (0.5%)
Asian	25 (6%)
Black or African American	111 (28%)
Native Hawaiian or Other Pacific Islander	2 (0.5%)
White	260 (65%)
Ethnicity *(number, percentage)*	
Hispanic or Latino	54 (14%)
School-related risks *(number, percentage)*	
Previous in-school suspension	45 (11%)
Repeated a grade	18 (5%)

Outcomes

Means for the two primary outcomes and the exploratory outcome are presented in Table 3. A total of 160 participants were analyzed for each factor level.

Table 3. Means and standard deviations for the three outcome measures pre- and post-intervention for the four factors (CBT counseling type, texts, interactive, and matched stories) by factor level, N=320.

Factor Level	Depression: CES-D* score (mean, SD)		Anxiety: HADS-A† score (mean, SD)		Cortisol Levels in nmol/L (mean, SD)	
	Pre	Post	Pre	Post	Pre	Post
CBT‡ Counseling Type						
In person (n = 160)	25.62 (6.81)	18.99 (7.32)	9.81 (2.57)	7.46 (3.01)	19.54 (11.99)	10.35 (13.63)
Web based (n = 160)	24.33 (7.11)	20.38 (7.98)	9.56 (2.58)	8.30 (2.97)	28.22 (9.58)	26.31 (8.78)
Text Messages						
Yes (n = 160)	25.01 (6.97)	19.65 (7.65)	9.68 (2.56)	7.46 (2.95)	27.1 (15.62)	17.3 (10.60)
No (n = 160)	25.59 (5.99)	22.45 (6.01)	9.82 (2.53)	9.01 (2.10)	22.3 (12.33)	20.28 (10.27)
Interactive Exercises						
Yes (n = 160)	23.31 (7.09)	17.57 (8.09)	9.69 (2.57)	7.85 (3.01)	26.3 (7.91)	18.6 (8.98)
No (n = 160)	25.61 (6.59)	23.55 (5.89)	9.68 (2.54)	7.76 (2.83)	30.1 (13.24)	29.4 (9.25)
Matched Stories						
High (n = 160)	25.61 (6.79)	18.53 (7.31)	9.81 (2.57)	7.61 (2.95)	26.7 (12.65)	16.9 (11.63)
Low (n = 160)	24.99 (6.91)	18.06 (8.11)	9.86 (3.02)	9.12 (2.29)	17.9 (18.71)	14.21 (13.12)

* Center for Epidemiological Studies Depression Scale
† Hospital Anxiety and Depression Scale (HADS) Anxiety subscale
‡ Cognitive Behavioral Therapy

Table 4 reports the main effects of each factor and time, and the interaction effect of time x factor, with F statistics and p-values. In general, there were significant time effects and time x factor interactions, and the high, or present, level of each factor had a larger effect on pretest-to-posttest reductions in outcome measures than the low, or absent, level. In-person CBT counseling, compared with web-based counseling, produced significantly larger reductions over time in participants'

depression (F = 3.871, p < 0.001), anxiety (F = 1.573, p < 0.001), and cortisol levels (F = 10.508, p < 0.001). Participants who received text messages had significantly larger reductions in all three outcomes from pretest to posttest than those in the "no" text message factor level (depression: F = 3.204, p < 0.001; anxiety: F = 2.035, p = 0.047; cortisol levels: F = 11.230, p < 0.001). Participants who accessed the web-based interactive exercises, in contrast to those in the "no" interactive factor level, had significant reductions over time in all three outcomes (depression: F = 5.312, p < 0.001; anxiety: F = 0.116, p = 0.05; cortisol levels: F = 10.104, p < 0.001). Participants who had access to the highly matched stories experienced significantly larger reductions from pretest to posttest in depression (F = 0.217, p = 0.05), anxiety (F = 2.107, p = 0.03), and cortisol levels (F = 8.819, p < 0.001), compared with participants who had access to stories with low levels of matching.

Table 4. Analysis of Variance (ANOVA) comparing main effects of each factor by factor level, the main effect of time, and the time x factor interaction for the three outcomes measures, N=320

	Depression (CES-D* score)		Anxiety (HADS-A† score)		Cortisol Levels (nmol/l)	
	F	p-value	F	p-value	F	p-value
CBT‡ Counseling Type						
In person vs. Web based	0.061	0.780	0.358	< 0.001	14.940	< 0.001
Time	15.27	< 0.001	5.211	< 0.001	16.021	< 0.001
Time x Factor	3.871	< 0.001	1.573	< 0.001	10.508	< 0.001
Text Messages						
Yes vs. No	2.049	0.049	1.025	0.822	1.104	0.877
Time	12.268	< 0.001	4.373	< 0.001	17.060	< 0.001
Time x Factor	3.204	< 0.001	2.035	0.047	11.230	< 0.001
Interactive Exercises						
Yes vs. No	5.021	< 0.001	0.061	0.120	8.853	< 0.001
Time	11.258	< 0.001	5.427	< 0.001	12.124	< 0.001
Time x Factor	5.312	< 0.001	0.116	0.050	10.104	< 0.001
Matched Stories						
High vs. Low	0.661	0.073	0.946	0.060	6.967	< 0.001
Time	20.221	< 0.001	4.244	0.009	19.471	< 0.001
Time x Factor	0.217	0.050	2.107	0.030	8.819	< 0.001

* Center for Epidemiological Studies Depression Scale
† Hospital Anxiety and Depression Scale (HADS) Anxiety subscale
‡ Cognitive Behavioral Therapy

Adverse Events

The Charleston Adolescent Wellness Study (CAWS) research staff recorded all adverse events (AEs) reported for any participant. Counselors reported psychiatric disorders identified during their sessions (either in person or web based) to CAWS staff after the session in which they identified the disorder had ended. School personnel reported truancy and in-school suspensions. Researchers obtained police reports for participants who were arrested during the study.

As shown in Table 5, there were 24 AEs in 6% of the 400 participants. (Each participant for whom an event was reported experienced only one event.) Only three psychiatric disorders were reported, and none were related to the intervention for depression and anxiety. None of the AEs were life threatening or required hospitalization or residential mental health treatment (i.e., none were serious).

Table 5. Number of non-serious adverse events, number of events by intervention condition (cond.) as defined in Table 1, during the seven-month intervention period, N=400.

Adverse Event	**Cond. 1** *(n = 50)*	**Cond. 2** *(n = 50)*	**Cond. 3** *(n = 50)*	**Cond. 4** *(n = 50)*	**Cond. 5** *(n = 50)*	**Cond. 6** *(n = 50)*	**Cond. 7** *(n = 50)*	**Cond. 8** *(n = 50)*
Total non-serious AEs	1	2	1	2	3	4	4	7
Psychiatric disorder*	0	0	0	0	0	0	1	2
In-school suspension	0	1	0	1	1	0	0	0
Running away	0	0	0	0	1	1	0	0
Misdemeanor arrest†	1	0	0	1	1	1	0	3
Felony arrest‡	0	0	0	0	0	1	2	2
Truancy	0	1	1	0	0	1	1	0

* In addition to the mild-to-moderate depression diagnosed at baseline. None were serious enough to require residential mental health treatment.
† For example, stealing, drug possession
‡ For example, fighting, drug possession

Appendix

Table A-1. Participant characteristics at baseline by assigned condition (cond.) as defined in Table 1, N=400.

Variable	Cond. 1 *(n = 50)*	Cond. 2 *(n = 50)*	Cond. 3 *(n = 50)*	Cond. 4 *(n = 50)*	Cond. 5 *(n = 50)*	Cond. 6 *(n = 50)*	Cond. 7 *(n = 50)*	Cond. 8 *(n = 50)*	Total *(n = 400)*
Age in years (*mean, SD)*	16.1 (2.2)	15.9 (1.9)	15.8 (1.1)	16.3 (1.5)	15.5 (2.0)	15.3 (1.4)	16.4 (1.8)	16.5 (1.2)	16.0 (1.7)
Female *(number, percentage)*	30 (60%)	32 (64%)	26 (52%)	27 (54%)	29 (58%)	31 (62%)	26 (52%)	28 (56%)	229 (57%)
Race *(number, percentage)*									
American Indian/Alaska Native	0	1 (2%)	0	0	0	0	1 (2%)	0	2 (0.5%)
Asian	3 (6%)	4 (8%)	2 (4%)	1 (2%)	5 (10%)	6 (12%)	4 (8%)	0	25 (6%)
Black or African American	10 (20%)	15 (30%)	12 (24%)	16 (32%)	13 (26%)	14 (28%)	20 (40%)	11 (22%)	111 (28%)
Native Hawaiian or Other Pacific Islander	0	0	1 (2%)	0	0	1 (2%)	0	0	2 (0.5%)
White	37 (74%)	30 (60%)	35 (70%)	33 (66%)	32 (64%)	29 (58%)	25 (50%)	39 (78%)	260 (65%)
Ethnicity *(number, percentage)*									
Hispanic or Latino	6 (12%)	10 (20%)	7 (14%)	5 (10%)	3 (6%)	11 (22%)	8 (16%)	4 (8%)	54 (14%)
School-related risks *(number, percentage)*									
Previous in-school suspension	9 (18%)	2 (4%)	7 (14%)	6 (12%)	8 (16%)	4 (8%)	2 (4%)	7 (14%)	45 (11%)
Repeated a grade	1 (2%)	3 (6%)	1 (2%)	2 (4%)	1 (2%)	3 (6%)	4 (8%)	3 (6%)	18 (5%)