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TRIAL PRINCIPAL INVESTIGATORS	Janet Page-Reeves, PhD
SAP AUTHOR(s)	Cristina Murray-Krezan, PhD

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1 Introduction

We will conduct a randomized controlled trial of "Tertulias," an innovative social isolation peer support group model, with 240 women of Mexican origin to contribute to the science of a holistic, multi-level (individual, family, and group) intervention to reduce health disparities related to social isolation and depression among this population. Our transdisciplinary team will use a rigorous, mixed-methods, community-engaged approach that includes a cutting-edge biological assessment of hair cortisol as a biomarker for chronic stress.

2 Study Aims and Endpoints

2.1 Study Aims

2.1.1 To measure whether a culturally situated peer group intervention will reduce depression and stress associated with the experience of immigration.

2.1.2 To test whether an intervention using a "women's funds of knowledge" approach results in improved resilience, knowledge and empowerment.

2.1.3 To investigate whether a culturally situated peer group intervention using a women's funds of knowledge approach can give participants' a sense and experience of social and physical connection ("emplacement") that is lost in the process of immigration.

2.2 Outcomes

The objectives described above will be measured with the following endpoints. Intervention arms are described in Section 3.2.

2.2.1 Primary Outcomes

The primary endpoints are changes from baseline to 12 months in:

2.2.1.1 Depression as measured by the Center for Epidemiologic Studies Depression Scale (CES-D)[1,2]

2.2.1.2 Resilience as measured by the Connor-Davidson Resilience Scale-25 (CD-RISC 25)[3]

2.2.1.3 Social support as measured by The Social Support Scale (MOS-SSS)[4]

2.2.2 Secondary Outcomes

2.2.2.1 Changes in stress from baseline to 12 months as measured by the Perceived Stress Scale-14 (PSS-14)[5]

2.2.2.2 Knowledge and empowerment in the intervention arm only at 12 months, measured by the Trauma-Informed Practice Scale (TIPS)[6,7]

2.2.2.3 Changes from baseline to 12 months in social connectedness as measured by Social Network Analysis[8]

2.2.3 Exploratory Outcomes

2.2.3.1 Changes in hair cortisol levels from baseline to 12 months

3 Study Methods

3.1 General Study Design and Plan

This is a multisite randomized controlled trial (RCT) assessing the effectiveness of the Tertulias intervention for women of Mexican origin as compared to usual care. Participants will be recruited from the community in Albuquerque, New Mexico. They must be women who are 18 years or older, speak Spanish fluently, and have income <250% of the Federal Poverty Limit. We will advertise at

community locations, focusing on two sites in Albuquerque, NM, and invite potential participants to join a live informational Zoom session to learn more about the project. If eligible and interested, the participant will be consented and randomized to one of the two arms. Within four weeks of randomization the participant will be contacted to complete the baseline interview. One year following enrollment, participants will complete a 12-month interview. See Figure 1 for the study CONSORT diagram. Primary and secondary outcomes measures are obtained from follow-up interviews.

3.2 Intervention Arms

3.2.1 Arm 1: Control

Using a modified Attention Control Placebo (ACP) design to reduce attrition over the 12 months, control arm participants will receive a bimonthly phone call from our project coordinator to check in with them, make sure their contact information is correct, and let them know that the study is continuing.

3.2.2 Arm 2: Intervention

We will conduct Tertulias structured dialogue groups using the model we developed and tested through our preliminary research (see Page-Reeves et al. 2021).[9] Each group will have approximately10 women and will meet weekly for 2 hours over a 12-month period. Group meetings will be conducted in Spanish, led by a team of two FMI facilitators using our structured dialogue approach. Because of required safety restrictions related to the COVID-19 pandemic, our original intention to hold these groups in-person was amended to hold the groups remotely by Zoom. We will work further with each Arm 2 participant to ensure that they know how to use Zoom and have electronic access.

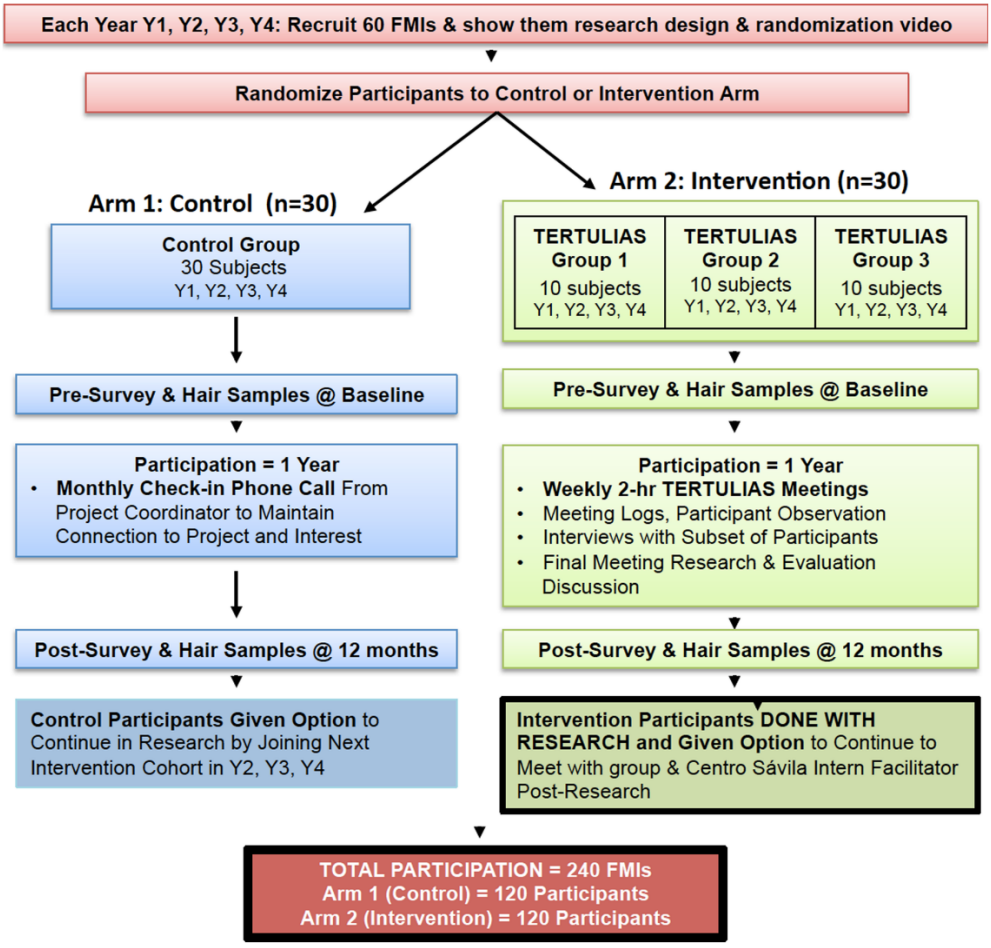

Figure 1. CONSORT diagram for the Tertulias study.

3.3 Study Population

3.3.1 Inclusion Criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

- Adult women 18+
- Born in Mexico
- Speak Spanish fluently
- Self-report income under 250% FPL

3.3.2 Exclusion Criteria

Anyone who is incarcerated or who does not meet the inclusion criteria will be excluded.

3.4 Randomization and Blinding

3.4.1 Randomization

Participants will be randomized to either the Tertulias intervention or usual care. A stratified, block randomization design will be used to stratify by site and cohort (year) with randomly permuted block sizes of 4, 8, and 12. The intervention arm allocation will be programmed in R 4.0 or higher using the package `blockrand`[10] and outputted as a .CSV file. A digital allocation plan will be provided to a research team member where they recorded the participant's name into each assignment. This file will be stored on a secured computer accessible only by that particular research team member. The treatment arm will be recorded in REDCap. Enrollment will be continuous with the goal of reaching the target sample size. Some sites may enroll more or less than the target for each arm.

3.4.2 Blinding

This is an unblinded study. Research staff will only have access to blinded reports with treatment groups indicated by "Arm A" and "Arm B" until the final analysis is performed.

3.5 Study Assessments

3.5.1 Data Collection

We will gather data through in-person data collection appointments at baseline and 12 months. Data collection appointments will be in-person in order to gather hair samples unless there are safety concerns (e.g., COVID-19 illness in the participant's home, a COVID-19-positive test within the past 2 weeks, fever, cough, travel outside the state within the past 14 days, etc.). In the case of participants with these concerns, we will conduct the survey by phone and gather the hair sample at another time if resolution of the concern is able to be made within the timeframe of a week after starting the meetings. All in-person data collection appointments will be conducted using COVID-19 safety procedures involving screening questions, temperature check, hand sanitizer, and face masks for both the data collector and the participant. Additionally, data collectors will also wear face shields, gloves, and shoe covers.

3.5.2 Study Assessments

3.5.2.1 Baseline

We will collect basic participant characteristics such as age, marital status, education level, employment status, number of children, number of family living in their location, whether they speak English, and overall health status. Additionally, we administer the CES-D (depression), the CD-RISC (resilience), the MOS-SS (social support), and PSS (perceived stress) instruments, as well as questions about their social networks. We will also collect hair samples (see Page-Reeves et al. 2021).[9]

3.5.2.2 12-month follow-up

We will administer the CES-D (depression), the CD-RISC (resilience), the MOS-SS (social support), PSS (perceived stress), and the TIPS (empowerment) instruments (Tertulias group only). Additionally, we will ask questions about their social networks and collect hair samples.

3.5.3 Visit Windows

Participants are randomized, and hence considered enrolled, following completion of consent and the baseline interview. The 12-month follow-up assessment occurs within a 4-week window starting at 12 months post-baseline. After the 4-week window, participants will be considered lost to follow-up.

3.6 Description of Variables

3.6.1 Description of Outcome Variables

Table 1 describes the outcome variables and data sources.

Table 1. Outcome variables and sources

Outcome	Endpoint	Data Source
Primary Outcomes		
Depression	Difference in changes of the summed score on the Center for Epidemiologic Studies Depression Scale (CES-D) between baseline and 12 months.	Baseline and 12-month interviews
Resilience	Difference in changes of the summer score on the Connor-Davidson Resilience Scale-25 (CD-RISC 25)	Baseline and 12-month interviews
Social Support	Difference in changes of the summer score on the Social Support Scale (MOS-SSS)	Baseline and 12-month interviews
Secondary Outcomes		
Stress	(a) Difference in changes of the summer score on the Social Support Scale (MOS-SSS) (b) Change (either direction) of hair cortisol levels	(a) Baseline and 12-month interviews (b) Baseline and 12-month hair sample
Knowledge and Empowerment	Subscale summed scores on the Trauma Informed Practice Scale (TIPS)	12-month interview (Tertulias group only)
Social Network Analysis		1-month interview

3.6.2 Description of Other Measures

Table 2 lists other outcomes, covariates, potential mediators and moderators.

Table 2. Description of other potential covariates

Variable	Data Source	Data Type
Sociodemographics		
• Age	Baseline	Continuous
• Race	Eligibility Screener	Categorical
• Marital status	Baseline Interview	Categorical
• Income	Baseline Interview	Continuous
• Education	Baseline Interview	Categorical
• Speaks English	Baseline Interview	Categorical
• Access to internet	Baseline Interview	Categorical
• Access to a computer	Baseline Interview	Categorical
• Family in Albuquerque	Baseline Interview	Categorical
• Know neighbor's name	Baseline Interview	Categorical

Table 2. Description of other potential covariates

Variable	Data Source	Data Type
• Interaction with family in Mexico	Baseline Interview	Categorical

4 Sample Size

We will recruit a total of 240 participants through our two partner agencies that both have a large clientele with our target population. Sample size estimates accommodate 33% attrition**.** With the expectation that 100 participants will complete the study in each arm, the following minimum hypothesized changes in outcome measures will be detected with >80% power, assuming type I error α = 0.017 for three primary outcome measures (one in each Aim):

1. An 8-point decrease in depression as measured by the CES-D for the Intervention arm, from baseline to 12 months, with at least a 6.5-point greater decrease than control participants (between arms effect size Cohen's *d* = 0.43 with SD = 15), as shown to be feasible in prior work.[11,12]
2. Cohen's *d* effect size ≥0.33 comparing arms on the changes over time of the CD-RISC scores, indicating increased resiliency in the intervention arm as compared to the control arm.[13–15]
3. Decreased social isolation as measured by the MOS-SSS in the intervention arm as compared to the control arm over time with Cohen's *d* ≥ 0.5 (SD =16).[16–18]

5 General Analysis Considerations

5.1 Timing of Analyses

The study databases will be locked to data entry 90 days following the last enrolled participant's final study interview. This allows for time to complete quality control queries while analyses are started. Any additional queries identified following the data lock will be addressed and any final query resolutions to the data will be hard-coded into the data management programs and documented in the code. Analyses described in this SAP will commence once the locked data set is created and will be completed during the final year of the study.

5.2 Analysis Populations

5.2.1 Intention to Treat (ITT) Population

All subjects who consented, were randomized into either arm, and completed the baseline interview are considered enrolled and comprise the ITT population. Participants who complete the informed consent, are randomized but do not complete the baseline interview will be excluded from analysis.

5.2.2 Per Protocol (PP) Population

All subjects who consented, enrolled, and were randomized into either arm and who completed the 12-month follow-up interview.

5.3 Covariates and Subgroups

5.3.1 Covariates

Potential covariates are listed in Table 2.

5.3.1 Subgroups

This is a multisite study consisting of two sites. The data will be pooled across sites to assess the primary and secondary outcomes. Randomization is stratified by site and cohort and they will be included in all analyses as influential covariates and interaction effects between each of site and cohort with treatment arm will be assessed. Additional post-hoc subgroup analyses may be performed as exploratory analyses.

5.4 Missing Data

The extent of missing data will be examined, and the patterns of missing data will be assessed for randomness. This will be accomplished in part by comparing participant characteristics of those who complete the 12-month survey and related instruments to those who do not, using the non-missing data from all participants. In addition to these checks for patterns of missingness, we will evaluate whether multiple imputation methods might be appropriate. We will analyze the data using both case deletion and multiple imputation approaches and compare the results from the two methods. Should the two approaches differ markedly, we will conclude that the data missingness did not occur completely at random and will perform additional sensitivity analyses prior to reporting the results that are the least sensitive to the observed pattern of missing data.

5.5 Summary of Study Data

Descriptive statistics (e.g., means, standard deviations, medians, frequencies, and percentages) will be calculated to summarize characteristics of the study arms and to identify any variables that may differ between them thus implying need for inclusion in modeling. In general, should any outcome measures have substantial departure from normality, remedial measures such as appropriate transformations or robust methods will be used for analyses.

5.6 Subject Disposition

Study status of subjects will be summarized with descriptive statistics, as described above, throughout the study. For the 12-month follow-up visit, we will summarize the number and proportion of subjects whose interview occurred, how many dropped out, were withdrawn from the study and for what reasons, and how many were lost-to-follow-up.

5.7 Protocol Deviations

Reported protocol deviations are missed visits and visits that occurred beyond the defined window period (+ 60 days from target date). We will report the total number of deviations and the frequency and percentage of each reason. Individual listings will also be produced.

5.8 Outcome Analyses

Analyses comparing demographic and clinical characteristics of the treatment arms will be assessed as follows:

Continuous variables:

- ANOVA or Mann Whitney tests will be used to compare across 3 or more groups
- *t* tests or Wilcoxon rank sum tests for comparing 2 groups

Categorical variables:

- Tests of proportions for comparing 2 groups
- $\chi 2$ tests, or Fisher exact tests, as appropriate for the data type for 2 or more categories
- Logistic regression for interaction effects between group and given variable.

Such analyses will be used to assess baseline homogeneity of the treatment groups as well as to help us identify potential covariates to be included in linear models for assessment of outcome measures; however, clinically relevant covariates will also be included regardless of the outcomes of these analyses. All analyses will be performed in SAS 9.4.[19]

5.9 Baseline Descriptive Analyses

Intervention arms will be compared on baseline characteristics using descriptive statistics. Planned comparisons are for the variables described in Table 2.

5.10 Primary Outcome Analysis

5.10.1 Primary Hypotheses

5.10.1.1 Primary Hypothesis 1

We hypothesize that the Tertulias arm will have at least an 8-point decrease in depression as measured by the CES-D, from baseline to 12 months, with at least a 6.5-point greater decrease

than control participants (between arms effect size Cohen's $d = 0.43$ with SD = 15)

5.10.1.2 Primary Hypothesis 2

We hypothesize that the Tertulias arm will increase their resilience more than the control arm, from baseline to 12 months, by a Cohen's d effect size ≥0.33.

5.10.1.3 Primary Hypothesis 3

We hypothesize that the Tertulias arm will decrease their social isolation more than the control arm, from baseline to 12 months, as measured by the MOS-SS with Cohen's $d \geq 0.5$.

5.10.2 Primary Analysis

Unadjusted mean changes for depression, resilience, and social support scores over time will be calculated and compared between the study arms. Linear mixed models will be fitted to the measures with the primary independent variable of interest Study Arm. **Covariates will include** age, marital status, number of children, other family or close friend living in same location as participant, speaks English, employed, and health status. The interest will be in the interaction between time point and intervention arm. Least squares mean estimates for the changes over time and their 98.3% confidence intervals will be reported for each arm. Additionally, we will report the coefficient, its standard error, and p-value for the interaction between time point and intervention arm from the linear mixed model.

Should our data assumptions of normality not be met, appropriate transformations will be identified or alternative generalized linear mixed models with alternate distributions will be fit. Our reporting will still follow as described above. We may need to use the delta method to calculate confidence intervals for point estimates on the original instrument scale.

5.11 Secondary Outcome Analyses

5.11.1 Secondary Hypotheses

5.11.1.1 Secondary Hypothesis 1

We hypothesize that perceived stress (PSS-14) will decrease by a Cohen's $d = 0.50$ more in the Tertulias arm over this time period than in the control arm.

5.11.1.2 Secondary Hypothesis 2

We hypothesize that, compared to participants in the control arm, those in the Tertulias arm will increase their social connectedness as assessed by Social Network Analysis.

5.11.2 Secondary Analysis

Analyses for the PSS outcome will mirror those described in the Primary Analysis section (5.10.2); however, 95% confidence intervals will be reported instead.

The TIPS subscales will be summarized with descriptive statistics, with means and 95% confidence intervals reported. This data is only collected in the Tertulias arm at 12 months.

Social Network Analysis (SNA) will include analyses of the networks of support surrounding respondents in their daily lives as well as analyses of the networks that grow within the Tertulias groups. Information about support in their daily lives will be classic egocentric network data, and will include who they can turn to for help with personal problems, for transportation to doctor visits if needed, for information about resources and assistance, and who they have fun with. Further information collected about these people (the respondents alters) include their age, education, ethnicity, their relationship to the respondent, how they met, and how often they interact, how close the respondent feels to them, and how close the respondents' connections are to each other. Ego network analyses will examine changes in the size, closeness, network overlap (transitivity) and composition of respondents' daily life networks over the course of the study, and how these relate to other well-being measures. The information on relationships within the Tertulias groups will be complete network data

(sociocentric), using the survey responses of all participants in each group. Respondents are asked about types of support received from each co-member of their group. Tertulias network analyses will examine changes in the density, segregation, and inequality in the ties of support between the members across the study. We will also examine the correlates of connections (who becomes connected to whom) and how relationships in the group are related to engagement with the project and well-being outcomes. Network analytic strategies will include visualization, descriptive measures, and inferential models.

5.12 Exploratory Outcome Analyses

Cortisol levels will be compared to the established averages and determined to be within normal limits or not. Pregnancy (determined by a question on the survey) will be considered in our analysis. Summary measures (means or medians and corresponding 95% CIs, as appropriate) will be computed for hair cortisol measures at each time point and the mean changes and 95% CIs over time in each arm will be compared between arms. Correlational analysis will be performed to understand how hair cortisol levels, as a marker for stress, is related to our primary and secondary outcome measures.

5.13 Sub-Group Analyses

We will conduct exploratory analyses to see if patient sex or gender, or race/ethnicity has an effect on primary outcomes or retention. Adjusted odds ratios and their 95% confidence intervals will be calculated from interaction effects between treatment group and sex or gender from the specified linear models for the primary and secondary outcome measures.

5.14 Post-Hoc Analyses

The Tertulias leadership team will encourage collaboration across all sites and investigators and provide guidance to promote and support scientific research dissemination. Research “ideas” for abstracts, manuscripts and presentation will be generated on “Concept Sheets” and submitted for review to the Tertulias Leadership group. Concept sheets will each have detailed analysis plans for the proposed study question/s. All papers will include a biostatistician in the collaborative/authorship group. In general, we expect both descriptive and comparative analyses will be conducted on cross-sectional and longitudinal data collected in the Tertulias study.

5.15 Safety Analyses

All adverse events (AEs) will be categorized and graded for severity as described above. (S)AEs will be summarized via the methods described in section 5.9, by site and overall. SAEs will be individually listed for DSMB review and will also be categorized and summarized similarly to AEs. We report AEs and SAEs by number of events (# AEs may be > N), as well as by the subject’s most severe AE and its severity (#AEs ≤ N). These analyses will be performed on the ITT population defined in Section 5.2.1.

5.15.1 Adverse Events

The Tertulias protocol defines an adverse event (AE) as any unfavorable and unintended symptom or disease that an investigator or study staff learns about which occurs during a participant’s enrollment in the study, if it is considered by the site study team to be possibly related to a study treatment or procedure (“possibly related” means there is a reasonable possibility that AE may have been caused by research procedures).

5.15.2 Serious Adverse Events

5.15.2.1 Definition of SAE

The Tertulias protocol defines a serious adverse event (SAE) as an AE that an investigator or study staff learns about that is fatal, life-threatening, requires inpatient rehospitalization, or is medically significant and which the investigators and/or clinicians regard as serious based on appropriate medical judgment. With the exception of fatalities, other SAEs documented in this study are considered those possibly related to the study.

5.15.3 Relationship to Study Intervention and Severity of (S)AEs

All (S)AEs will be rated as Mild, Moderate, or Severe and will be used as a factor in determining expectedness of an event. All (serious) adverse events will have their relationships to the study intervention assessed and rated as either Definitely Related, Probably Related, Unlikely to be Related, or Not related.

5.15.4 Pregnancies

Pregnant people are not excluded from participating in this study. No special consideration is needed for pregnant individuals in this study.

6 References

1. The CES-D Scale - Lenore Sawyer Radloff, 1977. Accessed June 23, 2024. https://journals.sagepub.com/doi/abs/10.1177/014662167700100306
2. Orme JG, Reis J, Herz EJ. Factorial and discriminant validity of the center for epidemiological studies depression (CES-D) scale. *J Clin Psychol*. 1986;42(1):28-33. doi:10.1002/1097-4679(198601)42:1
3. Connor KM, Davidson JRT. Development of a new resilience scale: The Connor-Davidson Resilience Scale (CD-RISC). *Depress Anxiety*. 2003;18(2):76-82. doi:10.1002/da.10113
4. Sherbourne CD, Stewart AL. The MOS social support survey. *Soc Sci Med 1982*. 1991;32(6):705-714. doi:10.1016/0277-9536(91)90150-b
5. Cohen S, Kamarck T, Mermelstein R. A Global Measure of Perceived Stress. *J Health Soc Behav*. 1983;24(4):385-396. doi:10.2307/2136404
6. DEVELOPMENT AND VALIDATION OF THE TRAUMA-INFORMED PRACTICE SCALES - Goodman - 2016 - Journal of Community Psychology - Wiley Online Library. Accessed June 23, 2024. https://onlinelibrary.wiley.com/doi/full/10.1002/jcop.21799
7. Sullivan CM, Goodman L. A Guide for Using The Trauma-Informed Practice (TIP) Scales. Accessed June 23, 2024. https://rpp.wtgrantfoundation.org/wp-content/uploads/2019/09/Trauma-Informed-Practice-English-version1-1.pdf
8. Freeman LC. Centrality in social networks conceptual clarification. *Soc Netw*. 1978;1(3):215-239. doi:10.1016/0378-8733(78)90021-7
9. Page-Reeves J, Murray-Krezan C, Regino L, et al. A randomized control trial to test a peer support group approach for reducing social isolation and depression among female Mexican immigrants. *BMC Public Health*. 2021;21(1):119. doi:10.1186/s12889-020-09867-z
10. Champely S. pwr: Basic Functions for Power Analysis. Published online February 1, 2006:1.3-0. doi:10.32614/CRAN.package.pwr
11. Beeber LS, Holditch-Davis D, Perreira K, et al. Short-term in-home intervention reduces depressive symptoms in Early Head Start Latina mothers of infants and toddlers. *Res Nurs Health*. 2010;33(1):60-76. doi:10.1002/nur.20363
12. Results From a Pilot Promotora Program to Reduce Depression and Stress Among Immigrant Latinas - Anh N. Tran, India J. Ornelas, Mimi Kim, Georgina Perez, Melissa Green, Michelle J. Lyn, Giselle Corbie-Smith, 2014. Accessed June 23, 2024 https://journals.sagepub.com/doi/full/10.1177/1524839913511635
13. Steinhardt M, Dolbier C. Evaluation of a Resilience Intervention to Enhance Coping Strategies and Protective Factors and Decrease Symptomatology. *J Am Coll Health*. 2008;56(4):445-453. doi:10.3200/JACH.56.44.445-454
14. Davidson J, Baldwin D, Stein DJ, et al. Treatment of Posttraumatic Stress Disorder With Venlafaxine Extended Release: A 6-Month Randomized Controlled Trial. *Arch Gen Psychiatry*. 2006;63(10):1158-1165. doi:10.1001/archpsyc.63.10.1158
15. Burton LE, Qeadan F, Burge MR. Efficacy of equine-assisted psychotherapy in veterans with posttraumatic stress disorder. *J Integr Med*. 2019;17(1):14-19. doi:10.1016/j.joim.2018.11.001
16. Mitschke DB, Aguirre RTP, Sharma B. Common Threads: Improving the Mental Health of Bhutanese Refugee Women Through Shared Learning. *Soc Work Ment Health*. 2013;11(3):249-266. doi:10.1080/15332985.2013.769926
17. Carlson LE, Tamagawa R, Stephen J, Drysdale E, Zhong L, Speca M. Randomized-controlled trial of mindfulness-based cancer recovery versus supportive expressive group therapy among distressed breast cancer survivors (MINDSET): long-term follow-up results. *Psychooncology*. 2016;25(7):750-759. doi:10.1002/pon.4150
18. Carlson LE, Doll R, Stephen J, et al. Randomized Controlled Trial of Mindfulness-Based Cancer Recovery Versus Supportive Expressive Group Therapy for Distressed Survivors of Breast Cancer (MINDSET). *J Clin Oncol*. 2013;31(25):3119-3126. doi:10.1200/JCO.2012.47.5210
19. SAS Institute Inc. SAS 9.4. Published online 2012.
20. R: The R Project for Statistical Computing. Accessed June 23, 2024. https://www.r-project.org/