

**Promoting Physical Activity Among Cancer Survivors:  
Meta-Analysis and Meta-CART Analysis of Randomized Controlled Trials**

Paschal Sheeran, University of North Carolina at Chapel Hill

Charles Abraham, University of Melbourne

Katelyn Jones, University of North Carolina at Chapel Hill

Megan E. Villegas, University of North Carolina at Chapel Hill

Aya Avishai, University of North Carolina at Chapel Hill

Yael R. Symes, University of North Carolina at Chapel Hill

Halie Ellinger, University of North Carolina at Chapel Hill

Eleanor Miles, University of Sussex

Kathleen M. Gates, University of North Carolina at Chapel Hill

Charles E. Wright, University of North Carolina at Chapel Hill

Kurt M. Ribisl, University of North Carolina at Chapel Hill

Deborah K. Mayer, University of North Carolina at Chapel Hill

Paschal Sheeran, Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, Chapel Hill. USA.

Charles Abraham, School of Psychological Sciences, University of Melbourne, Victoria 3010, Australia.

Katelyn Jones, Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, Chapel Hill. USA.

Megan E. Villegas, Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, Chapel Hill. USA.

Aya Avishai, Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, Chapel Hill. USA.

Yael R. Symes, Department of Health Behavior, University of North Carolina at Chapel Hill, Chapel Hill. USA.

Halie Ellinger, Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, Chapel Hill. USA.

Eleanor Miles, Department of Psychology, University of Sussex, Falmer, UK.

Kathleen M. Gates, Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, Chapel Hill. USA.

Charles E. Wright, Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, Chapel Hill. USA.

Kurt M. Ribisl, Department of Health Behavior, University of North Carolina at Chapel Hill, Chapel Hill and UNC Lineberger Comprehensive Cancer Center, Chapel Hill. USA.

Deborah K. Mayer, School of Nursing, University of North Carolina at Chapel Hill, UNC Lineberger Comprehensive Cancer Center, Chapel Hill. USA.

We thank Jennifer Walker and Rachael Posey (Medical Librarians) for invaluable assistance with the computerized literature searches.

Direct correspondence to: Paschal Sheeran, Department of Psychology and Neuroscience, 323B Davie Hall, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599. Email: [psheeran@unc.edu](mailto:psheeran@unc.edu)

### Abstract

*Objective:* We conducted a meta-analysis of physical activity interventions among cancer survivors in order to (a) quantify the magnitude of intervention effects on physical activity, and (b) determine what combination of intervention strategies maximizes behavior change.

*Methods:* Out of 32,626 records that were located using computerized searches, 138 independent tests ( $N = 13,050$ ) met the inclusion criteria for the review. We developed a bespoke taxonomy of 34 categories of techniques designed to promote psychological change, and categorized sample, intervention, and methodological characteristics. Random effects meta-analysis and meta-regressions were conducted; effect size data were also submitted to Meta-CART analysis.

*Results:* The sample-weighted average effect size for physical activity interventions was  $d_+ = .35$ , equivalent to an increase of 1,149 steps per day. Effect sizes exhibited both publication bias and small sample bias but remained significantly different from zero, albeit of smaller magnitude ( $d_+ \geq .20$ ), after correction for bias. Meta-CART analysis indicated that the major difference in effectiveness was attributable to supervised versus unsupervised programs ( $d_+ = .49$  vs.  $.26$ ). Greater contact time was associated with larger effects in supervised programs. For unsupervised programs, establishing outcome expectations, greater contact time, and targeting overweight or sedentary participants each predicted greater program effectiveness, whereas prompting barrier identification and providing workbooks were associated with smaller effect sizes.

*Conclusion:* The present review indicates that interventions have a small but significant effect on physical activity among cancer survivors, and offers insights into how the effectiveness of future interventions might be improved.

*Keywords:* cancer survivors, physical activity, exercise, meta-analysis, randomized trial

## **Promoting Physical Activity Among Cancer Survivors:**

### **Meta-Analysis and Meta-CART Analysis of Randomized Controlled Trials**

As of January 2016, 15.5 million Americans (~5% of the U.S. population) were cancer survivors, and this number is projected to increase to 20.3 million by 2026 and to 26.1 million by 2040 (National Cancer Institute, 2017). Although cancer treatments (e.g., chemotherapy, radiation therapy) can improve survival rates, they have multiple negative side effects including suppressed immune function, fatigue, and reduced quality of life (e.g., Jacobs & Shulman, 2017; Mustian, Sprod, Janelins, & Peppone, 2012; Schmitz et al., 2005). Physical activity is safe for cancer survivors (Schmitz et al., 2010) and is a key non-pharmacological intervention for the effective management of acute, chronic, and late side effects (e.g., Mustian et al., 2012).

Numerous systematic reviews and meta-analyses have confirmed that physical activity interventions have a positive impact on physiological and psychological outcomes among cancer survivors (e.g., Ballard-Barbach et al., 2012; Ferrer, Huedo-Medina, Johnson, Ryan, & Pescatello, 2011; Fong et al., 2012; Meneses-Echávez, González-Jiménez, & Ramírez-Vélez, 2015; Mishra et al., 1996; Speck, Courneya, Mâsse, Duval, & Schmitz, 2010; Winzer, Whiteman, Reeves, & Paratz, 2011; Wolin, Ruiz, Tuchman, & Lucia, 2010). However, there is little research investigating which of these interventions are most effective in promoting physical activity, the behavior change that leads to these outcomes. The present meta-analysis addresses two questions: (1) How effective are interventions in promoting physical activity among cancer survivors? and (2) Which strategies lead to greater effectiveness?

### ***Previous Reviews of Physical Activity Among Cancer Survivors***

A systematic review of 27 observational studies found consistent evidence that physical activity is associated with reduced all-cause, breast cancer-specific, and colon cancer-specific

mortality among cancer survivors (Ballard-Barbach et al., 2012). Meta-analyses of randomized controlled trials (RCTs) that included biomarker endpoints suggest that physical activity promotes beneficial changes in insulin-like growth factor axis proteins, insulin, inflammation, and immune function (Ballard-Barbach et al., 2012; Fong et al., 2012; Winzer et al., 2011). Meta-analyses of RCTs also indicate improvements in weight, body composition, cardiorespiratory fitness, and muscle strength (Fong et al., 2012; Schmitz et al., 2005; Speck et al., 2010; Wolin et al., 2010). Quantitative syntheses of RCTs also indicate that physical activity interventions lead to fewer symptoms, improved quality of life, and increased wellbeing among cancer survivors (Cramp & Bryon-Daniel, 2012; Ferrer et al., 2011; Fong et al., 2012; Meneses-Echávez et al., 2015; Mishra et al., 1996).

Although physical activity has the potential to reduce cancer risk and to improve quality of life among cancer survivors, less research has focused on how effective are interventions to increase the amount of physical activity that cancer survivors undertake. We located 5 systematic reviews that investigated this issue (Bluethmann et al., 2015; Rossi, Friel, Carter, & Garber, 2017; Speck et al., 2010; Spencer & Wheeler, 2016; Stacey et al., 2014). The number of RCTs included in these reviews was modest, ranging from 3 (Spencer & Wheeler, 2016) to 14 (Bluethmann et al., 2015). Moreover, these reviews were circumscribed by a focus on particular theoretical perspectives such as social cognitive theory (Stacey et al., 2014) or motivational interviewing (Spencer & Wheeler, 2016), particular samples (e.g., breast cancer survivors; Bluethmann et al., 2015; Rossi et al., 2017), or particular settings (e.g., unsupervised programs; Speck et al., 2010). These considerations underline the need for a comprehensive review that quantifies the impact of physical activity interventions for cancer survivors across different intervention approaches, samples, and settings.

### ***Identifying Modifiable Determinants of Intervention Effectiveness: Meta-CART and Iterative Meta-Regression Analysis***

Merely assessing the overall effectiveness of interventions does not clarify which intervention strategies are effective in promoting physical activity, or offer guidance about which strategies should be deployed for in future interventions (Abraham & Michie, 2008; Sheeran, Klein, & Rothman, 2017). To address this issue, we coded categories of psychological change techniques and intervention features for each RCT included in the current review, and used meta-regression and Meta-CART analyses to identify strategies that predicted larger effect sizes.

Psychological change techniques are mechanism-based intervention contents that are designed to generate a specified psychological change (e.g., increase information, promote motivation, or enhance self-efficacy). Abraham and Michie (2008) demonstrated that it is possible to reliably identify and categorize change techniques from intervention descriptions, and Michie et al. (2009) showed that meta-regression can identify techniques that are associated with greater effectiveness of interventions to promote physical activity (see also, Greaves et al., 2011).

Intervention features refer to characteristics of the intervention that could potentially be changed in order to improve intervention effectiveness. Key intervention features examined here were the setting (e.g., home vs. clinic/hospital), mode of delivery (e.g., one-to-one vs. group session vs. online), intensity (i.e., duration, contact time, number of sessions), source (e.g., researcher vs. nurse vs. physical therapist), and program type (i.e., supervised vs. unsupervised physical activity). We also coded characteristics of the sample (e.g., age, gender), cancer (type of cancer, stage), and methodological features (e.g., self-report vs. objective measure of physical activity).

We used classification and regression trees analysis (CART; Breiman, Friedman, Olshen, & Stone, 1984) to test what combination of change techniques and intervention features predict

effect sizes. CART generates a tree structure that specifies what combination of intervention features maximally predict effect sizes. CART iteratively selects features that provide the best split of individuals into homologous groups according to their effect sizes. We complemented the CART analysis with a novel approach inspired by CART that we termed *iterative meta-regression analysis* (IMRA). For each split in the tree identified by CART, we undertook meta-regressions of effect sizes on intervention strategies whenever that strategy was used in at least four tests. These meta-regressions were iterative in that the analyses were repeated for each significant split until there were either too few tests to permit further meta-regression analysis, or no significant associations were observed between effect sizes and techniques/features (i.e., further splits could not be identified). Combining IMRA with CART analysis in this way maximizes information about how factors combine to predict effect sizes.

Thus, the aims of the present meta-analysis were twofold: (1) To quantify the effectiveness of interventions in promoting physical activity among cancer survivors, and (2) To determine what combination of change techniques and intervention features is associated with greater effectiveness.

## **Method**

The meta-analysis was registered at Prospero (CRD42016051281) and followed PRISMA guidelines (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009).

### ***Search Strategy***

Studies were obtained via (a) a computerized search of relevant databases (CINAHL, PubMed, EMBASE, MEDLINE, PsycINFO, Web of Science, Cochrane Library, and ProQuest). Search terms were optimized for each database by a medical librarian; the search was initiated on September 18, 2015 and was last updated on October 5, 2016; (b) a manual search of the

reference lists of previous reviews and papers that met the inclusion criteria for the review, and (c) requests for unpublished studies via emails to key researchers and the listservs of professional societies (American Society of Preventive Oncology, European Health Psychology Society, Office of Cancer Survivorship at the National Cancer Institute, Social Personality and Health Network, Society of Behavioral Medicine, Society for Research on Nicotine and Tobacco, and the UK Centre for Tobacco and Alcohol Studies).

The computerized search strategy included terms for (a) cancer survivors (e.g., *cancer survivor*, *cancer patient*), (b) randomized controlled trial (e.g., *trial*, *intervention*), and (c) physical activity (e.g., *exercise*, *physical activity*) (see Table S1 in the Supplementary Materials for the precise search terms used in each database). There were five inclusion criteria for the review. First, the study used a randomized controlled design, meaning that participants were allocated at random to a treatment versus a control condition. Second, an intervention to promote physical activity was tested. Third, participants were cancer survivors. We used the National Cancer Institute's definition of a survivor, which states that in the context of cancer, "...a person is considered to be a survivor from the time of diagnosis until the end of life" (NCI Dictionary of Cancer Terms, 2017). Fourth, a measure of physical activity (moderate/vigorous physical activity, walking, energy expenditure, resistance training, sedentary behavior, or meeting physical activity guidelines) was obtained for treatment and control conditions following the intervention. Fifth, the report was written in English.

Figure 1 shows the flow of information through the phases of the present review. The computerized database search identified 32,626 articles and theses. De-duplication removed 1,853 articles, leaving 30,773. Titles and abstracts were screened independently by two research assistants. This screening resulted in the exclusion of 29,155 records because they did not



concern cancer survivors or physical activity, or did not report findings from a randomized controlled trial. Assessment of the eligibility of 1,618 full-text records led to the exclusion of 1,490 articles. Reasons for exclusion were (a) publication was a conference abstract ( $n = 418$ ); (b) study did not report a measure of physical activity ( $n = 412$ ); (c) study was not a randomized controlled trial ( $n = 386$ ); (d) duplicate study information was reported (protocol paper, baseline findings, etc.) ( $n = 137$ ); (e) report was not written in English ( $n = 40$ ); (f) study did not involve cancer survivors ( $n = 35$ ); (g) insufficient data were reported or effect size could not be retrieved, even after contacting the authors ( $n = 24$ ); (h) participants were instructed not to exercise outside of the supervised exercise program they were enrolled in, and non-protocol exercise was only assessed as a means of controlling for variability among the sample ( $n = 14$ ); (i) publication could not be located even by professional librarians ( $n = 13$ ); (j) no change techniques could be identified from the intervention description provided ( $n = 9$ ); (k) a crossover-design was used making contamination between conditions likely ( $n = 2$ ). Thus, 128 papers met our inclusion criteria. As some papers reported multiple studies or trials had multiple intervention groups, a total of 138 effect sizes could be computed from these reports. The Supplementary Materials present the characteristics of each study included in the review (Table S2) and the references for the 128 papers.

### ***Analysis Strategy***

We used Cohen's  $d$  as the effect size metric. Effect sizes represent the difference in amount of physical activity at follow-up for the treatment compared to the control condition; larger positive values indicate more effective interventions (i.e., greater physical activity). When multiple indicators of physical activity were reported in a single study, we used each individual effect size to assess the impact of interventions on these different outcomes and also computed

the weighted average effect size within the study to represent the overall study effect. When studies included more than one treatment condition, we divided the sample size for the control group by the number of intervention groups, so as not to “double count” participants (Higgins & Green, 2011). To offer a strong test of the effectiveness of physical activity interventions for cancer survivors, effect sizes were computed using data from (a) the longest follow-up after the intervention, and (b) intention-to-treat analyses if both intention-to-treat and per protocol analyses were reported.

We used STATA Version 14.2 (StataCorp, 2016) to conduct random effects meta-analyses and meta-regressions. We first computed the sample-weighted average effect size and computed heterogeneity statistics ( $Q$ ,  $I^2$ ). Next, we checked for publication bias using the funnel plot and Egger’s regression. Duval and Tweedie’s (2000) trim and fill procedure was used to correct for publication bias. Small sample bias was assessed using the procedure recommended by Coyne, Thombs, and Hagerdoorn (2010): we coded whether or not studies had adequate power (i.e., 55% power to detect a medium-sized effect even when it is present) and regressed effect sizes on this predictor. We also used random effects meta-regressions to test the associations between effect sizes and (a) psychological change techniques, (b) sample characteristics, (c) features of the intervention, and (d) methodological features, including study quality.

***Meta-CART and iterative meta-regression analyses.*** CART is a supervised machine learning algorithm that is fully data-driven. To our knowledge, CART has only been used in one previous meta-analysis in health psychology (Dusseldorp et al., 2014). Importantly, because CART does not take into account intervention-level characteristics (such as sample size) and cannot distinguish between random and fixed effects, we conducted follow-up analyses using

random effects meta-regressions and subgroup analyses. That is, we corroborated the CART findings using procedures that take sample size and random effects into account, and we present the average  $d$ -values for relevant subgroups in the figure representing the tree.

CART analyses were conducted using the publicly available *rpart* package (Therneau, Atkinson, & Ripley, 2015) and the freely available R software (R Core Team, 2012). Table S3 in the Supplementary Materials provides a full description of the analytic procedure, including the R code, used here. Briefly, CART identifies which sets of intervention features maximally predict effect sizes. This is done by iteratively selecting features, which provide the best split of individuals into homologous groups according to their effect sizes. Next, cross-validation is conducted to see how well the model obtained on a subset of individuals (the training set) can predict outcomes for the remaining individuals (the test set). The model was pruned by selecting the final split that provided the best cross-validation results across 1,000 iterations.

Iterative meta-regression analyses (IMRA) were conducted in STATA. When particular factors were significantly associated with effect sizes, we included findings from the subgroup analysis in the figure. We then undertook meta-regressions within both levels of factors that were significant at a previous level, and continued this procedure until no further change techniques or intervention features predicted effect sizes or there were too few tests to permit further analysis ( $k < 4$ ; see Michie et al., 2009).

### ***Coded Variables***

***Categories of change techniques.*** We developed a bespoke taxonomy of categories of psychological change techniques (hereafter “techniques”) designed to change precursors of physical activity. We combined top-down (previous taxonomic research) and bottom-up (in-depth inductive analysis of the empirical studies included in the review) approaches (for

discussion, see Abraham, 2016; Skinner, Edge, Altman, & Sherwood, 2003) and generated a taxonomy comprising 34 distinct techniques (see Table S4 in the Supplementary Materials for definitions of each technique category). Nineteen techniques defined in Abraham and Michie's (2008) taxonomy were found to be relevant, as were 5 techniques defined in a later taxonomy (Michie et al., 2011). An additional 10 techniques were identified from careful assessment of the intervention descriptions provided in papers and included "Establish outcome expectations" (i.e., Encourage participants to expect realistic and positive outcomes of physical activity) and "Provide safety information about physical activity". The presence versus absence of each technique was coded (1 and 0, respectively). Following de Bruin et al.'s (2010) recommendation, techniques were coded for both treatment *and* control conditions.

***Sample, intervention, and methodological characteristics.*** Sample, intervention, and methodological characteristics that could potentially moderate effect sizes were coded from each study (see Table S5 in the Supplementary Materials). Sample characteristics included mean age, gender composition of sample, and average time since cancer diagnosis; intervention characteristics included the source and setting of the intervention, total contact time, as well as modes of delivery; methodological features included whether the control condition was active and aspects of study quality, assessed using the Cochrane Collaboration's Tool for Assessing Risk of Bias (Higgins & Green, 2011).

***Reliability of coding.*** Three of the authors (KJ, MEV, HE) independently coded effect sizes ( $k = 27$ , 20% of tests), change techniques ( $k = 20$ , 15% of tests) and sample, intervention, and methodological characteristics ( $k = 25$ , 18% of tests). Coding proved reliable ( $M_{ICC} = 1.00$ ,  $M_{PABAK} = 0.92$ ,  $M_{KAPPA} = 0.96$ ; all ICC, PABAK, and Kappa values were greater than 0.70). Discrepancies were resolved through discussion.

## Results

### *Trial Characteristics*

On average, interventions involved 51 participants in the treatment condition and 43 participants in the control condition ( $SD = 53.68$  and  $52.08$ , respectively). Participants were predominantly white ( $M = 69.0\%$ ) and female ( $M = 73.6\%$ ), and had a mean age of 53.4 years ( $SD = 12.2$ ). Forty-four trials involved survivors with different types of cancer, 66 trials focused on breast cancer survivors only, and the remaining trials targeted survivors of prostate cancer ( $k = 13$ ), colorectal cancer ( $k = 6$ ), and other particular types of cancers ( $k = 9$ ). Participants were undergoing cancer treatment in 43 trials but, on average, recruitment took place 2.95 years after participants' diagnosis ( $SD = 2.24$ ).

The majority of studies came from the USA or Canada ( $k = 83$ ). Interventions were conducted at home ( $k = 91$ ), in hospital/clinic settings ( $k = 41$ ), and/or community centers ( $k = 17$ ), and predominantly involved one-to-one, in-person counseling sessions ( $k = 79$ ) or group counseling sessions ( $k = 46$ ) that were delivered by a physiologist ( $k = 32$ ), a researcher ( $k = 27$ ), or by other professionals ( $k = 54$ ). Most interventions were highly intensive, lasting at least one month and up to six months. The mean number of intervention sessions was 38.67 ( $SD = 46.95$ ), and the average contact time was 39.33 hours ( $SD = 66.28$ ). The number of change techniques used in trials ranged from 1 to 24 ( $M = 8.12$ ,  $SD = 5.19$ ).

Seventy-three trials involved active control conditions that predominantly included education materials. Follow-up periods for interventions ranged from immediate to 4.78 years ( $M = 12.26$  weeks,  $SD = 26.00$ ). The mean attrition rate was 18.34%. Most studies were underpowered according to Coyne et al.'s (2010) criterion ( $k = 83$ ). Study quality assessed via the Cochrane tool was generally good (see Table S6 in the Supplementary Materials). Incomplete

outcome data ( $k = 39$ ) and selective reporting were infrequent ( $k = 10$ ), but so was blinding of participants/personnel ( $k = 1$ ) and outcome assessment ( $k = 34$ ). Random sequence generation ( $k = 83$ ) and allocation concealment ( $k = 79$ ) were common.

### ***Overall Effects of Interventions on Physical Activity Among Cancer Survivors***

The sample-weighted average effect size for 138 physical activity trials was of small-to-medium magnitude ( $d_+ = .35$ ,  $95\%CI = .29$  to  $.41$ ). This effect size equates to 1,149 additional steps per day and 47.16 extra minutes of moderate/vigorous physical activity per week among cancer survivors (based on data from wearable activity monitors presented by Gresham et al., 2018). Table 1 presents effect sizes by type of physical activity and measurement of physical activity. Interventions were similarly effective for moderate/vigorous physical activity, walking, energy expenditure, meeting activity guidelines, and resistance training ( $.28 \leq d_+ \leq .33$ ), but interventions were not effective in reducing sedentary behavior ( $95\%CI = -.08$  to  $.34$ ). Effect sizes were equivalent whether physical activity was measured objectively (e.g., accelerometer data) or via self-reports. There was also no difference in the effect size observed in studies that used an immediate follow-up assessment after the intervention and those using a longer-term follow-up ( $d_+ = .36$  and  $.33$ , respectively).

Figure S1 in the Supplementary materials presents the forest plot of effect sizes. Effects were heterogeneous ( $Q = 345.55$ ,  $p < .001$ ) and heterogeneity was of moderate to high magnitude ( $I^2 = 60.4$ ). Inspection of the funnel plot (see Figure 2) suggested that the observed effects were characterized by publication bias and Egger's regression confirmed that this was the case ( $B = 1.46$ ,  $SE = 0.28$ ,  $p < .001$ ). Trim and fill analysis to correct for publication bias led to the imputation of  $k = 34$  additional effects and yielded an adjusted  $d_+ = .20$  ( $95\%CI = .13$  to  $.27$ ). Eight studies included in the review were unpublished (5.80%). Meta-regression of effect sizes

on publication status (published = 1, unpublished = 0) indicated that the association was not significant ( $B = .19$ ,  $SE = 0.18$ ,  $p = .27$ ).

Meta-regression indicated that the effects were characterized by small sample bias ( $B = -.24$ ,  $SE = 0.07$ ,  $p = .001$ ); whether or not studies were underpowered accounted for 18% of the variance in effect sizes. Studies that were adequately powered according to Coyne et al.'s (2010) criterion exhibited a smaller average effect size ( $d_+ = .23$ ,  $95\%CI = .16$  to  $.30$ ) compared to underpowered studies ( $d_+ = .48$ ,  $95\%CI = .38$  to  $.59$ ).

### ***Meta-Regression of Effect Sizes on Change Techniques***

Table S7 in the Supplementary Materials indicates the frequency of use of change techniques in both the treatment and control conditions. The most frequently deployed techniques in treatment conditions were: Prompt specific goal setting (78.3%,  $k = 108$ ), Prompt self-monitoring of behavior (58.7%,  $k = 81$ ), Prompt intention formation (47.8%,  $k = 66$ ), and Prompt barrier identification (45.7%,  $k = 63$ ). Only 6 techniques were used in  $k \geq 4$  tests for control conditions; the techniques used most often were Prompt specific goal setting (15.9%,  $k = 22$ ), Prompt self-monitoring of behavior (8.7%,  $k = 12$ ), and Provide information on consequences (8.0%,  $k = 11$ ). Meta-regressions of effect sizes on techniques used in the control and treatment conditions are presented in Tables S8 and S9 in the Supplementary Materials. Using Prompt specific goal setting in the control condition was associated with a smaller intervention effect ( $B = -.25$ ,  $SE = .09$ ,  $p = .006$ ) and explained 7.9% of the variance. Use of Prompt barrier identification in treatment conditions was associated with a smaller intervention effect ( $B = -.14$ ,  $SE = .07$ ,  $p = .05$ ,  $R^2 = .06$ ). Interventions that involved supervised exercise sessions, on the other hand, were associated with greater effectiveness ( $B = .20$ ,  $SE = .07$ ,  $p = .005$ ) and this characteristic explained 9.5% of the variance in effect sizes.

***Meta-Regression of Effect Sizes on Sample, Intervention, and Methodological Features***

Interventions that deliberately targeted participants who were overweight or engaged in little physical activity had larger effect sizes ( $B = .15$ ,  $SE = .07$ ,  $p = .03$ ,  $R^2 = .03$ ; see Table S5 in the Supplementary Materials). Consistent with this finding, higher mean BMI of study participants was also associated with larger effects ( $B = 4.90$ ,  $SE = 2.32$ ,  $p = .04$ ,  $R^2 = .04$ ). Age was negatively associated with effect size ( $B = -.007$ ,  $SE = .003$ ,  $p = .03$ ,  $R^2 = .04$ ), and there was a marginally significant association between effect size and the percentage of minority participants in the sample sizes ( $B = .003$ ,  $SE = .001$ ,  $p = .053$ ,  $R^2 = .10$ ); there were larger effect sizes in samples with a greater proportion of minority participants. The type of cancer (e.g., breast vs. colorectal), stage of cancer, cancer treatment status (currently in treatment vs. not), or treatment type (e.g., chemotherapy) were not associated with effect sizes (see Table S10 in the Supplementary Materials).

Several intervention features predicted effect sizes. Interventions set in community centers and other settings (i.e., not home, clinic, or other community settings) were associated with larger effects ( $B = .20$  and  $.36$ ,  $SE = .10$  and  $.17$ ,  $R^2 = .05$  and  $.06$ , respectively,  $p = .05$ ). Interventions delivered by mail and interventions involving self-complete or tailored workbooks exhibited smaller effects compared to other modes of delivery ( $B = -.18$  and  $-.29$ ,  $SE = .08$  and  $.10$ ,  $R^2 = .08$  and  $.12$ ,  $ps < .03$ ). Intervention contact time explained more than one-fifth of the variance in effect sizes ( $R^2 = .21$ ); greater contact time was associated with increased effectiveness ( $B = .002$ ,  $SE = .001$ ,  $p = .01$ ).

One methodological feature was associated with effect sizes: active control conditions predicted smaller effects of interventions ( $B = -.16$ ,  $SE = .07$ ,  $p = .02$ ,  $R^2 = .05$ ). Risk of bias was not related to effect sizes (see Table S11 in the Supplementary Materials).



***Meta-CART and Iterative Meta-Regression Analyses***

We first conducted CART analysis with the continuous effect size data as the outcome variable. However, as Dusseldorp et al. (2014) also observed, cross-validation indicated that the results were unstable for this outcome, meaning that the prediction errors obtained with cross-validation did not improve with addition of features in the model. We therefore followed Dusseldorp et al.'s (2014) lead and used a dichotomous outcome created by taking a median split of the effect sizes. Here, results became stable. Cross-validation analysis indicated that the first split resulted in the fewest classification errors and distinguished supervised exercise programs and unsupervised programs (see Figure 3). Meta-regression and subgroup analyses confirmed this split and indicated that supervised programs exhibited a larger effect than unsupervised programs ( $d_+ = .49$  vs.  $.26$ ).

We supplemented the meta-CART analysis with iterative meta-regression analyses to determine whether any change techniques or intervention features predicted effect sizes for supervised programs or unsupervised programs (see Table S12 in the Supplementary Materials for regression coefficients). One characteristic, intervention contact time, was associated with larger effect sizes for supervised programs. Effect sizes for trials above and below the median contact time ( $Mdn = 24$  hours) were  $d_+ = .69$  and  $.36$ , respectively. Further meta-regression analyses within high and low levels of contact time revealed no other significant predictors of the effectiveness of supervised programs.

Five characteristics predicted effect sizes for unsupervised programs. Inclusion of prompting barrier identification ( $d_+ = .19$  vs.  $.34$ ) and providing a self-complete or tailored workbook ( $d_+ = .09$  vs.  $.29$ ) both reduced the effectiveness of unsupervised programs. Greater contact time ( $d_+ = .42$  vs.  $.23$ ), targeting overweight or sedentary participants ( $d_+ = .35$  vs.  $.20$ ),

and establishing outcome expectations ( $d_+ = .51$  vs.  $.22$ ), on the other hand, were each associated with larger intervention effects.

There were also significant predictors within the different levels of targeted sample and contact time for unsupervised programs. When overweight and sedentary participants were deliberately targeted in interventions, then providing feedback on performance ( $d_+ = .19$  vs.  $.50$ ) and assessing motivational readiness ( $d_+ = .16$  vs.  $.48$ ) were associated with *lower* effect sizes. Failing to use graded tasks ( $d_+ = .39$  vs.  $.21$ ), assigned goals ( $d_+ = .34$  vs.  $.18$ ), self-monitoring ( $d_+ = .34$  vs.  $.14$ ), and use of barrier identification ( $d_+ = .17$  vs.  $.38$ ) or a tailored workbook ( $d_+ = .09$  vs.  $.30$ ) were each associated with reduced effectiveness of interventions above the median contact time. One technique, establishing outcome expectations, increased the impact of high-contact interventions and led to the largest effect size observed in the review ( $d_+ = .70$ ).

### Discussion

This meta-analysis addressed two questions: How effective are interventions in promoting physical activity among cancer survivors, and what combination of intervention strategies leads to improved effectiveness? Our quantitative synthesis addressed these questions using a database of 138 RCT tests that included more than 13,000 participants. We found that interventions to promote physical activity among cancer survivors are effective; the sample-weighted average effect size was  $d_+ = .35$ . Although correcting for publication bias and small sample bias reduced  $d_+$ , the effect size remained significantly different from zero and of meaningful magnitude ( $d_+ \geq .20$ ). Thus, physical activity interventions for cancer survivors are as, or more, effective than physical activity interventions for general population samples (Abraham & Graham-Rowe, 2009; Michie et al., 2009).

It is notable that this positive effect emerged in the context of several commendable features of the primary research studies. Physical activity was measured objectively in 29% of tests ( $k = 40$ ), the mean attrition rate was modest (18.34%), and study quality assessed via the Cochrane tool was generally good. Moreover, effect sizes for objective and self-report outcomes were similar ( $d_+ = .32$  vs.  $.35$ , respectively). It is also worth noting that interventions proved effective for cancer survivors irrespective of cancer stage, type of cancer, type of treatment, and time since diagnosis. Our findings also indicated that higher BMI was associated with *greater* intervention effectiveness and interventions that deliberately targeted participants who are overweight or sedentary were especially effective. These results underline the value of physical activity interventions for all cancer survivors (e.g., Mustian et al., 2012), and suggest that targeting those with greatest need, that is, overweight or sedentary survivors, facilitates effectiveness.

To answer the second question – what combination of intervention strategies lead to improved effectiveness – we made efforts to use both best-practice and innovative methods. We followed de Bruin et al.'s (2011) best-practice guidance and coded change techniques in control conditions as well as treatment conditions. Prompt specific goal setting in control conditions was significantly (negatively) associated with effect sizes. The significance of this technique could have been missed if we had analyzed change techniques in treatment conditions only, whereas the present findings suggest that prompt specific goal setting should be deployed in physical activity interventions for cancer survivors.

Two innovative methods to identify change techniques and intervention features that predict effectiveness were the use of meta-CART analysis and a novel extension of this technique, iterative meta-regression analysis (IMRA). Whereas the single previous meta-CART

analysis only examined combinations of change techniques as predictors of effect size (Dusseldorp et al., 2014), here we examined how change techniques and intervention features together could be combined. Moreover, because meta-CART analysis could identify only a single split (i.e., supervised vs. unsupervised programs), and this finding had to be confirmed with meta-regression analyses (to take sample size and random effects into account), we used IMRA to test further possible splits beyond the single split that was generated by meta-CART. IMRA offered a richer picture of how intervention strategies combine to predict effectiveness than was afforded by meta-CART on its own.

In particular, IMRA indicated that increased contact time served to magnify the effect of supervised programs. IMRA also identified several splits for unsupervised programs. Greater contact time again enhanced impact, as did targeting overweight or sedentary participants. Thus, the overall effect of targeting overweight or sedentary samples accrued from unsupervised programs. Prompting barrier identification and providing a self-complete/tailored workbook both reduced intervention effects. A previous meta-analysis indicated that prompting barrier identification reduces self-efficacy (Ashford, Edmunds, & French, 2010), which would explain the negative effect of this technique. It is not clear why providing a workbook was counterproductive. Workbooks could make physical activity seem difficult and could undermine intrinsic motivation. However, primary research is needed to test these possibilities. In the meantime, we do not recommend providing workbooks for unsupervised programs.

The effectiveness of unsupervised programs with longer contact time was also contingent upon not using prompt barrier identification or providing a workbook. However, effectiveness also depended upon setting graded tasks, intervention personnel assigning a physical activity goal to participants, and prompting self-monitoring of behavior. Effect sizes for longer

unsupervised programs were substantially reduced when these three techniques were not deployed. It is also notable that established techniques such as set graded tasks and prompt self-monitoring of behavior only emerge as important when particular intervention features are already in place (i.e., when the program is unsupervised and involves greater contact time).

IMRA identified one split for shorter unsupervised programs and two splits for unsupervised programs that targeted overweight or sedentary participants. In each case, findings indicated that interventions would benefit from *not* deploying particular change techniques. Providing general encouragement that was not contingent upon specified behaviors or standards of performance was counterproductive for short unsupervised programs. Providing feedback on performance and assessing motivational readiness were both contra-indicated when unsupervised programs targeted overweight or sedentary participants. It is possible that assessing readiness and providing feedback could undermine motivation for physical activity among overweight or sedentary cancer survivors (see Harkin et al., 2016).

Establishing outcome expectations emerged as a key predictor of the effectiveness of unsupervised programs, and proved especially beneficial when intervention contact time was longer. Establishing outcome expectations was defined as “encouraging participants to imagine or expect realistic and positive outcomes of physical activity” and differs from both provide information on consequences and enhance enjoyment – two techniques that did not predict effect sizes – in its emphasis on favorable but feasible consequences of physical activity. Emphasizing realistic outcomes could serve to prevent over-ambitious goal setting or enable participants to better handle setbacks or lapses. The findings observed here for establishing outcome expectations also echo recent primary research demonstrating that physical activity intentions that are better aligned with expectations are translated into action more effectively (Avishai,

Conner, & Sheeran, 2018). The precise mechanisms by which outcome expectations promote physical activity remain to be determined, however, and this constitutes an important avenue for future research. At the same time, establishing outcome expectations would seem to be a key ingredient for increasing physical activity in unsupervised programs.

Limitations of the present review and the database upon it rests must also be considered. Even though the literature search was conducted in October 2016, we started with 32,626 records. However, only 138 tests qualified for inclusion in the meta-analysis. Given the importance of physical activity for both physical and psychological outcomes, further tests are needed. It is also the case that most studies concerned survivors with breast cancer and survivors in the wake of treatment. Additional tests of patients who are still in treatment and those with prostate and colon in particular, are warranted (see Table S10). Follow-up periods were generally short ( $M = 12$  weeks) and longer-term follow-ups would be desirable. Further tests would permit more fine-grained analyses of the role of feedback (type, quality, quantity, timing) that could not be undertaken in the present review.

## **Conclusion**

Notwithstanding these limitations, the present review indicates that interventions to promote physical activity among cancer survivors are effective, and offers new insights into strategies that are liable to be effective in future interventions. Although there was evidence of publication bias and small sample bias, a substantial literature has accumulated ( $k = 138$ ,  $N = 13,050$ ) and indicates that interventions have at least a small effect ( $d_+ \geq .20$ ) on the amount of physical activity undertaken by survivors. Supervised programs were more effective than unsupervised programs, and longer supervised programs had an effect of medium-to-large magnitude ( $d_+ = .69$ ). Unsupervised programs could be as effective as supervised programs ( $d_+ =$

.70) when there was greater contact time and outcome expectations were established. Further primary research is warranted to corroborate these findings.

### References

- Abraham, C. (2016). Charting variability to ensure conceptual and design precision. *Health Psychology Review, 10*, 260-264. <http://dx.doi.org/10.1080/17437199.2016.1190293>
- Abraham, C. & Graham-Rowe, E. (2009). Are worksite interventions effective in increasing physical activity? A systematic review and meta-analysis. *Health Psychology Review, 3*, 108-144. <https://doi.org/10.1080/17437190903151096>
- Abraham, C., & Michie, S. (2008). A taxonomy of behavior change techniques used in interventions. *Health Psychology, 27*(3), 379-387. <http://doi.org/10.1037/0278-6133.27.3.379>
- Ashford, S., Edmunds, J., & French, D. P. (2010). What is the best way to change self-efficacy to promote lifestyle and recreational physical activity? A systematic review with meta-analysis. *British Journal of Health Psychology, 15*(2), 265–88.
- Avishai, A., Conner, M. T., & Sheeran, P. (2018). *Setting realistic health goals: Antecedents and consequences*. Manuscript under review.
- Ballard-Barbash, R., Friedenreich, C.M., Courneya, K.S., Siddiqi, S.M., McTiernan, A., & Alfano, C.M. (2012). Physical activity, biomarkers, and disease outcomes in cancer survivors: A systematic review. *Journal of the National Cancer Institute, 104*(11), 815-840. <http://doi.org/10.1093/jnci/djs207>
- Bluethmann, S.M., Vernon, S.W., Gabriel, K.P., Murphy, C.C., & Bartholomew, L.K. (2015). Taking the next step: A systematic review and meta-analysis of physical activity and behavior change interventions in post-treatment breast cancer survivors. *Breast Cancer Research and Treatment, 149*, 331-342. <http://doi.org/10.1007/s10549-014-3255-5>

Coyne, J. C., Thombs, B. D., & Hagedoorn, M. (2010). Ain't necessarily so: Review and critique of recent meta-analyses of behavioral medicine interventions in health psychology.

*Health Psychology*, 29(2), 107–116. <http://doi.org/10.1037/a0017633>

Cramp, F., & Bryon-Daniel, J. (2012). Exercise for the management of cancer-related fatigue in adults. *The Cochrane Library*. <http://doi.org/10.1002/14651858.CD006145.pub3>

de Bruin, M., Viechtbauer, W., Schaalma, H. P., Kok, G., Abraham, C., & Hospers, H. J. (2010). Standard care impact on effects of highly active antiretroviral therapy adherence interventions: A meta-analysis of randomized controlled trials. *Archives of Internal Medicine*, 170(3), 240-250.

Dusseldorp, E., van Genugten, L., van Buuren, S., Verheijden, M. W., & van Empelen, P. (2014). Combinations of techniques that effectively change health behavior: Evidence from Meta-CART analysis. *Health Psychology*, 33(12), 1530–1540. [doi:10.1037/hea0000018](https://doi.org/10.1037/hea0000018)

Duval, S., & Tweedie, R. (2000). Trim and Fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*, 56(2), 455-463.  
doi: 10.1111/j.0006-341X.2000.00455.x

Ferrer, R.A., Huedo-Medina, T.B., Johnson, B.T., Ryan, S., & Pescatello, L.S. (2011). Exercise interventions for cancer survivors: A meta-analysis of quality of life outcomes. *Annals of Behavioral Medicine*, 41(1) 32-47. <http://doi.org/10.1007/s12160-010-9225-1>

Fong, D. Y. T., Ho, J. W. C., Hui, B. P. H., Lee, A. M., Macfarlane, D. J., Leung, S. S. K., et al. (2012). Physical activity for cancer survivors: meta-analysis of randomised controlled trials. *British Medical Journal*, 344, e70. <http://doi.org/10.1136/bmj.e70>

Greaves, C. J., Sheppard, K. E., Abraham, C., Hardeman, W., Roden, M., Evans, P. H., & Schwarz, P. (2011). Systematic review of reviews of intervention components associated with



increased effectiveness in dietary and physical activity interventions. *BMC Public Health*, 11(1), 119. <https://doi.org/10.1186/1471-2458-11-119>

Harkin, B., Webb, T. L., Chang, B. P. I., Prestwich, A., Conner, M. T., Kellar, I., Benn, Y., & Sheeran, P. (2016). Does monitoring goal progress promote goal attainment? A meta-analysis of the experimental evidence. *Psychological Bulletin*, 142(2), 198-229.

Higgins, J. P. T., & Green, S. (Eds.). (2011). *Cochrane handbook for systematic reviews of interventions* (Version 5.1.0). Retrieved from <http://www.cochrane-handbook.org>

Jacobs, L. A., & Shulman, L. N. (2017). Follow-up care of cancer survivors: Challenges and solutions. *Lancet Oncology*, 18(1):e19-e29. doi:10.1016/S1470-2045

Meneses-Echávez, J. F., González-Jiménez, E., & Ramírez-Vélez, R. (2015). Supervised exercise reduces cancer-related fatigue: A systematic review. *Journal of Physiotherapy*, 61(1), 3–9. <http://doi.org/10.1016/j.jphys.2014.08.019>

Michie, S., Abraham, C., Whittington, C., McAteer, J., & Gupta, S. (2009). Effective techniques in healthy eating and physical activity interventions: a meta-regression. *Health Psychology*, 28(6), 690-701. <http://dx.doi.org/10.1037/a0016136>

Michie, S., Ashford, S., Sniehotta, F., Dombrowski, S.U., Bishop, A., & French, D. P. (2011). A refined taxonomy of behaviour change techniques to help people change their physical activity and healthy eating behaviours: The CALO-RE taxonomy. *Psychology and Health*, 26(11), 1479-1498. <http://dx.doi.org/10.1080/08870446.2010.540664>

Mishra, S. I., Scherer, R. W., Snyder, C., Geigle, P. M., Berlanstein, D. R., & Topaloglu, O. (1996). Exercise interventions on health-related quality of life for people with cancer during active treatment. (S. I. Mishra, Ed.) (Vol. 339, pp. b3410–460). Chichester, UK: John Wiley & Sons, Ltd. <http://doi.org/10.1002/14651858.CD008465.pub2>

Mustian, K.M., Sprod, L.K., Janelins, M., Peppone, L.J., & Mohile, S. (2012). Exercise recommendations for cancer-related fatigue, cognitive impairment, sleep problems, depression, pain, anxiety, and physical dysfunction: A review. *Oncology & Hematology Review*, 8(2), 81-88. doi:10.17925/OHR.2012.08.2.81

National Cancer Institute (2017). *Statistics*. Retrieved from <https://cancercontrol.cancer.gov/ocs/statistics/statistics.html>

National Cancer Institute. (2017). Cancer survivors and physical activity. Retrieved from [http://progressreport.cancer.gov/after/physical\\_activity](http://progressreport.cancer.gov/after/physical_activity)

Rossi, A., Friel, C., Carter, L., & Garber, C. E. (2017). Effects of theory-based behavioral interventions on physical activity among overweight and obese female cancer survivors: A systematic review of randomized controlled trials. *Integrative Cancer Therapies*, 10, 1534735417734911. <http://doi.org/10.1177/1534735417734911>

Schmitz, K. H., Courneya, K. S., Matthews, C., Demark-Wahnefried, W., Galvão, D. A., Pinto, B. M., et al. (2010). American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors. *Medicine & Science in Sports & Exercise*, 42(7), 1409–1426. <http://doi.org/10.1249/MSS.0b013e3181e0c112>

Schmitz, K. H., Holtzman, J., Courneya, K. S., Masse, L. C., Duval, S., & Kane, R. (2005). Controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. *Cancer Epidemiology, Biomarkers & Prevention*, 14(7), 1588–1595. <http://doi.org/10.1158/1055-9965.EPI-04-0703>

Sheeran, P., Klein, W. M. P., & Rothman, A. J. (2017). Health behavior change: Moving from observation to intervention. *Annual Review of Psychology*, 68(1), 573–600. <http://doi.org/10.1146/annurev-psych-010416-044007>

Skinner, E. A., Edge, K., Altman, J., & Sherwood, H. (2003). Searching for the structure of coping: A review and critique of category systems for classifying ways of coping.

*Psychological Bulletin*, 129, 216–269. doi:10.1037/0033-2909.129.2.216

Speck, R.M., Courneya, K.S., Mäse, L.C., Duval, S., & Schmitz, K.H. (2010). An update of controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. *Journal of Cancer Survivorship*, 4(87), 87-100. <http://doi.org/10.1007/s11764-009-0110-5>

Spencer, J. C., & Wheeler, S. B. (2016). A systematic review of Motivational Interviewing interventions in cancer patients and survivors. *Patient Education and Counseling*, 99(7), 1099–1105. <http://doi.org/10.1016/j.pec.2016.02.003>

Stacey, F. G., James, E. L., Chapman, K., Courneya, K. S., & Lubans, D. R. (2014). A systematic review and meta-analysis of social cognitive theory-based physical activity and/or nutrition behavior change interventions for cancer survivors. *Journal of Cancer Survivorship*, 9(2), 305–338. <http://doi.org/10.1007/s11764-014-0413-z>

Therneau, T., Atkinson, B., & Ripley, B. (2015). *rpart*: Recursive partitioning and regression trees. <http://CRAN.R-project.org/package=rpart>.

Winzer, B. M., Whiteman, D. C., Reeves, M. M., & Paratz, J. D. (2011). Physical activity and cancer prevention: a systematic review of clinical trials. *Cancer Causes & Control*, 22(6), 811–826. <http://doi.org/10.1007/s10552-011-9761-4>

Wolin, K. Y., Ruiz, J. R., Tuchman, H., & Lucia, A. (2010). Exercise in adult and pediatric hematological cancer survivors: an intervention review. *Leukemia*, 24(6), 1113–1120. <http://doi.org/10.1038/leu.2010.54>

Table 1

*Effect Sizes for Physical Activity Outcomes*

Outcome	<i>N</i>	<i>k</i>	<i>d</i>	95% <i>CI</i>	<i>Q</i>	<i>I</i> <sup>2</sup>
All studies	13,050	138	.35	.29 to .41	345.55***	60.4
Type of physical activity						
Moderate/vigorous activity	5,999	63	.29	.21 to .37	126.17***	50.9
Walking	1,279	23	.31	.15 to .48	37.65*	41.6
Energy expenditure	3,122	35	.30	.18 to .42	84.74***	59.9
Meeting activity guidelines	3,234	26	.28	.15 to .41	74.61***	66.5
Sedentary behavior	721	10	.13	-.08 to .34	13.56	33.6
Resistance training	1,379	7	.33	.07 to .58	25.04***	76.0
Measurement of physical activity						
Self-report	11,109	98	.35	.28 to .43	287.14***	66.2
Objective assessment	1,941	40	.32	.20 to .44	58.41*	33.2

*Note.* *N* = number of participants, *k* = number of independent tests, *d* = sample-weighted average effect size, 95%*CI* = 95% confidence interval, *Q* and *I*<sup>2</sup> = homogeneity statistics.

\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .

Figure 1

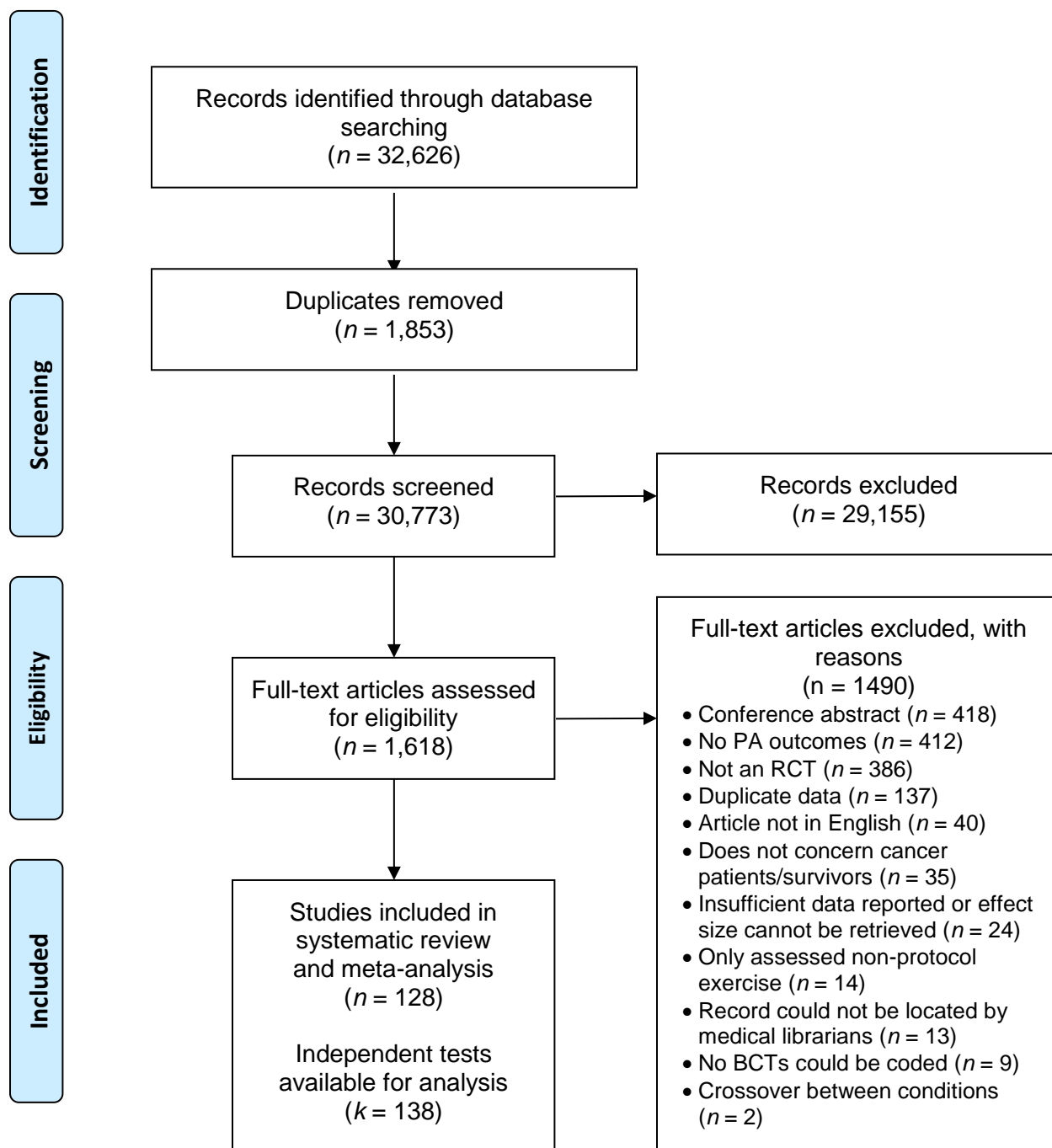
*Flow of Information Through the Phases of the Review*

Figure 2

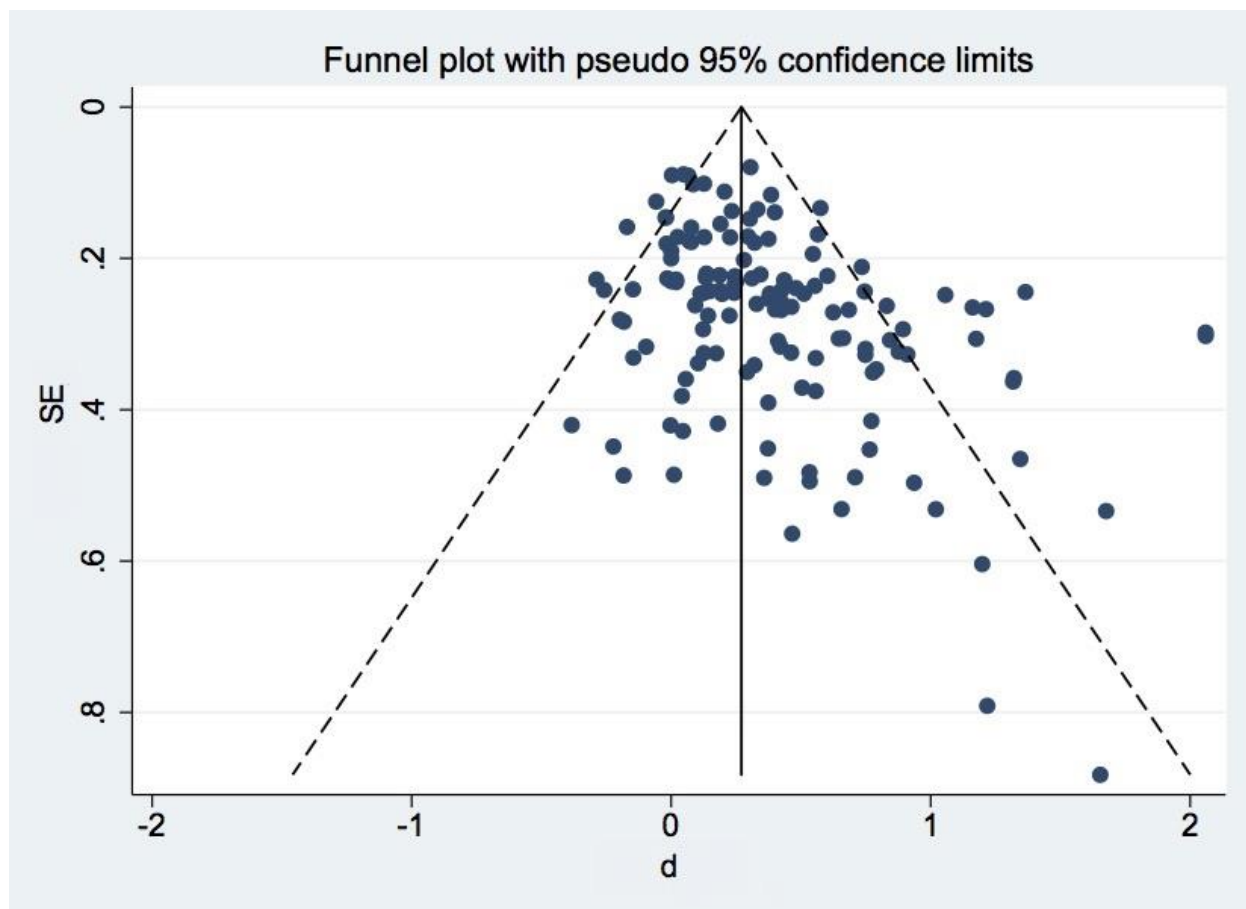
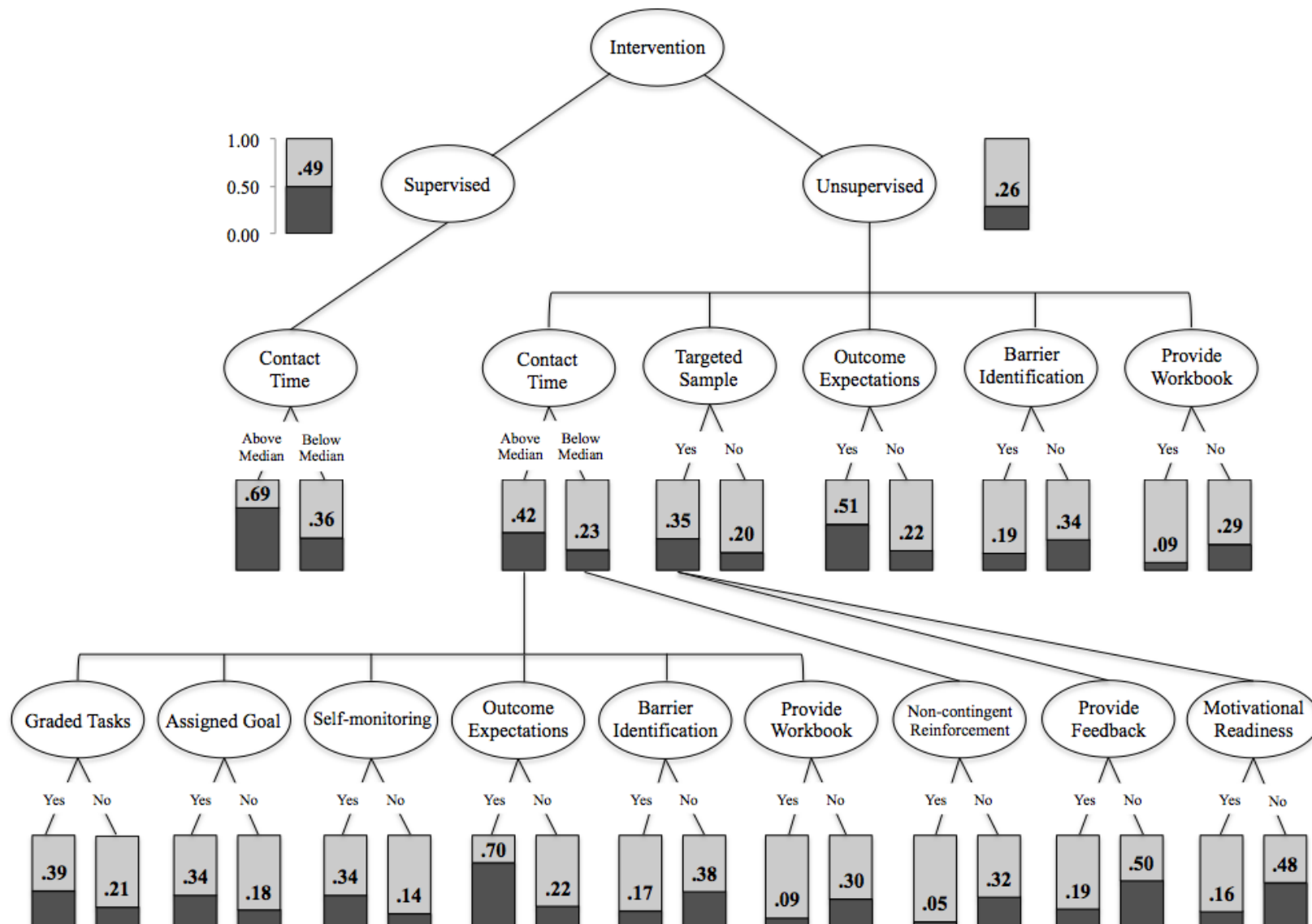
*Funnel Plot of Effect Sizes*

Figure 3. *Meta-CART and Iterative Meta-Regression Analyses*

## PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8-9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8-9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Materials
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9-12
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9-12, Supplementary



			Materials
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	12, Supplementary Materials
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	9-10

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10-11
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplementary Materials
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Materials
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14, Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-17, Figure 3, Supplementary Materials
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13, 16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	15-17

<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-21
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).