ann. behav. med. (2016) 50:130–146
DOI 10.1007/s12160-015-9739-7

ORIGINAL ARTICLE

# Effect Sizes and Primary Outcomes in Large-Budget, Cardiovascular-Related Behavioral Randomized Controlled Trials Funded by NIH Since 1980

**Veronica L. Irvin, PhD, MPH[1] · Robert M. Kaplan, PhD[2]**

Published online: 27 October 2015


**Abstract**
***Purpose*** We reviewed large-budget, National Institutes of Health (NIH)-supported randomized controlled trials (RCTs) with behavioral interventions to assess (1) publication rates, (2) trial registration, (3) use of objective measures, (4) significant behavior and physiological change, and (5) effect sizes.
***Methods*** We identified large-budget grants (>$500,000/year) funded by NIH (National Heart Lung and Blood Institute (NHLBI) or National Institute of Diabetes & Digestive and Kidney Diseases (NIDDK)) for cardiovascular disease (dates January 1, 1980 to December 31, 2012). Among 106 grants that potentially met inclusion criteria, 20 studies were not published and 48 publications were excluded, leaving 38 publications for analysis. ClinicalTrials.gov abstracts were used to determine whether outcome measures had been pre-specified.
***Results*** Three fourths of trials were registered in ClinicalTrials.gov and all published pre-specified outcomes. Twenty-six trials reported a behavioral outcome with 81 % reporting significant improvements for the target behavior. Thirty-two trials reported a physiological outcome. All were objectively measured, and 81 % reported significant benefit. Seventeen trials reported morbidity outcomes, and seven reported a significant benefit. Nine trials assessed mortality, and all were null for this outcome.
***Conclusions*** Behavioral trials complied with trial registration standards. Most reported a physiological benefit, but few documented morbidity or mortality benefits.

**Keywords** Behavior · Intervention · Cardiovascular · Trial registration · Publication statistics · Effect sizes · Periodicals as topics/statistics · Randomized controlled trials as topics/statistics

## Introduction

Modern approaches to the prevention and management of most chronic diseases, including diabetes and coronary heart disease, require modification of behaviors [1–3]. A few behaviors including physical inactivity, smoking, and poor diet result in four chronic diseases, including cardiovascular disease, that account for 82 % of all noncommunicable disease deaths in the world today [4]. Guidelines for the management of high cholesterol and high blood pressure advise a trial of lifestyle modification before the initiation of medication [5, 6].

Despite their promise, formal behavioral interventions remain underutilized in health care practice. Phillips and colleagues recently reported that primary care patients reported an average of 5.8 unhealthy behaviors and mental health risk factors [7]. Patients wanted to change at least one behavior and to discuss their risks with their physician. Nearly 85 % wanted to change fruit and vegetable consumption, and nearly 80 % wanted to discuss weight management [7]. Even though there is a strong desire for behavioral intervention, formal intervention, beyond mere advice, remains uncommon in medical practice. Even among current smokers, about half were not given advice to quit by their primary care doctors [8].

**Electronic supplementary material** The online version of this article (doi:10.1007/s12160-015-9739-7) contains supplementary material, which is available to authorized users.

✉ Veronica L. Irvin
Veronica.irvin@oregonstate.edu

[1] College of Public Health and Human Sciences, School of Social & Behavioral Health Sciences, Oregon State University, 457 Waldo Hall, Corvallis, OR 97331, USA

[2] Agency for Healthcare Research and Quality, US Department of Health and Human Services, Rockville, MD, USA

A possible explanation for the underutilization of behavioral interventions is the assumption that pharmacological treatments are highly effective, whereas behavioral treatments are less likely to achieve positive outcomes. Systematic reviews, however, show that positive results in pharmacological trials are actually quite rare [9]. Goldacre [10] and Sumner [11] found that media reports of clinical research are often exaggerated, not based on strong research designs, or overgeneralized. Further, for every 5,000–10,000 promising new molecules, only one makes it through all of the review processes required to achieve FDA licensure [12]. Even among the one in 10,000 licensed drugs, lack of efficacy is often discovered in post-marketing studies. A recent analysis of trials funded by the National Heart Lung and Blood Institute (NHLBI) found that evaluated pharmacological treatments were effective in only 40 % of systematic trials [13]. Failure rates were much higher in large-budget randomized controlled trials [9, 13].

These previous analyses have not focused exclusively on behavioral trials, even though behavioral approaches have been evaluated in a significant number of randomized controlled trials [9, 13]. In this article, we consider the evidence for the benefits of behavioral intervention. Specifically, we address three questions: (1) Is there evidence that health behavior can be modified? (2) Does the change produced by behavioral intervention result in physiological change? and (3) Do behavioral interventions affect morbidity and mortality?

In order to address these questions, we need a comprehensive look at the published literature. One difficulty in assessing the literature, however, is that journals favor publication of positive results, and many trials that produce null results are likely to go unpublished [14]. A second challenge is that investigators may have the option of choosing between many outcome measures when they publish their findings, thus inflating the probability of reporting a spurious result [9].

In this analysis, we systematically reviewed large-budget (defined as costs>$500,000 in at least one grant year) randomized controlled trials relevant to cardiovascular disease and funded by the NHLBI or the National Institute of Diabetes & Digestive and Kidney Diseases (NIDDK). Cardiovascular trials were selected because numerous behavioral interventions have been implemented to improve health behaviors that affect cardiovascular health such as nutrition, physical activity, medication adherence, and smoking prevention. The advantage of systematically reviewing grant databases was that we were able to locate funded trials prior to their initiation and determine if there was bias due to non-publication. Further, we were able to use the registration service, ClinicalTrials.gov, to determine whether outcome variables were pre-specified prior to the publication of the trial. Using these safeguards allows us to provide a less biased estimate of the value of behavioral intervention. In interpreting outcomes of large-budget behavioral intervention trials, we considered several factors, including (1) evidence of publication bias, (2) trial registration prior to publication, (3) the use of objective outcome measures, (4) evidence for significant behavior change, (5) evidence for significant physiological change, and (6) effect sizes for change.

## Methods

**Sample of Studies** Our analysis focused on RCTs that involved behavioral interventions funded between 1980 and 2012. We focused on trials that were awarded higher dollar amounts because NHLBI has shown that virtually all of these trials are eventually published, thus eliminating bias due to selective publication [13]. The search process is summarized in a PRISMA diagram (Fig. 1). Two independent searches were conducted—one by the study authors and the second by NHLBI [13]. We searched three different NIH grant databases (QVR, REPORTER, and CRISP) for RCTs that were primarily funded or administered by NHLBI or NIDDK. Because of the relationship between diabetes and cardiovascular disease, several of the cardiovascular, behavioral interventions were administered by NIDDK, such as the Diabetes Prevention Program (DPP) [15] and Look Ahead [3]. We selected the start year of 1980 because study abstracts were more often available in the grant databases after 1980. Inclusion criteria were as follows: RCT for studies from 1980 to 2012; direct costs funded were large enough to require special authorization (>$500,000/ year in at least 1 year of the grant); the word "trial" had to appear in the study abstract; and primary outcome was a cardiovascular risk factor, event, or death. Exclusion criteria included the following: no human subjects protocol required; pediatric studies; animal studies; non-RCTs (e.g., observational, cohort, case control, genetic or proteomics, measurement, basic clinical research); or interventions that were not behavioral (e.g, drugs, supplements, devices, surgeries).

A second independent search was conducted by NHLBI, Division of Cardiovascular Sciences, to identify clinical trials with budgets requiring special authorization funded through 2012 [13]. The NHLBI list allowed us to check our search against an objective criterion. The authors reviewed each discrepant case jointly, and studies became part of this evaluation if there was consensus on their inclusion criteria.

**Identification of Publication** We searched bibliographic databases, PubMed and Google Scholar, as well as publically available grant registries, NIH Reporter and ClinicalTrials.gov, for outcome papers for each grant. Usually, a single paper included results for all the main outcomes. Sometimes two or three papers per trial were needed to obtain results for all primary outcomes or sufficient details to calculate effect sizes. If needed, trial investigators were contacted to clarify the details of the study and which, if any, of their publications matched

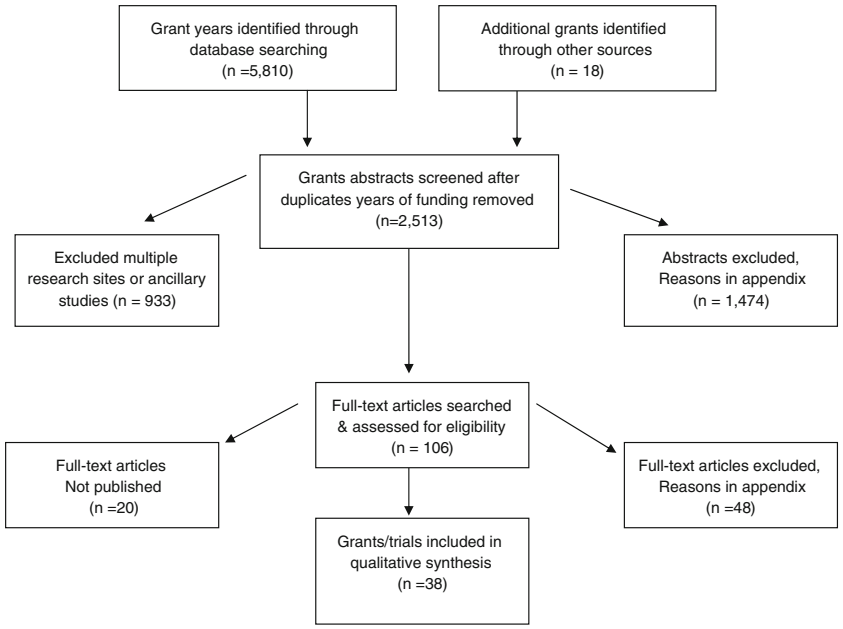


**Fig. 1** PRISMA flow diagram of grant abstracts reviewed, excluded, and retained in final analyses

the grant. We contacted a total of five principal investigators (1) to confirm if the intervention had incorporated a behavior modification, (2) to check if the main outcome had been published, or (3) to clarify the main outcome findings.

**Selection of Behavioral Intervention** For each study, we considered the comparison between a treatment and a control condition. If there were multiple arms in the trial, we analyzed the two arms that had the strongest contrast in terms of dose of the intervention or most different in outcomes following intervention.

**Identification of Primary Outcomes** For each study, we identified the primary outcome variable for each of the following constructs: behavioral (e.g., diet intake, physical activity, medication adherence, smoking, goal tracking), physiological (e.g., weight, blood pressure, $VO_2$ max, LDL-C), morbidity (e.g., formal disease diagnosis, CVD and CHD events, hospital stays, start of or increased use of medication as a result of disease diagnosis), and all-cause mortality outcomes. In many studies, the primary outcome was identified in the main outcome paper or on ClinicalTrials.gov. When authors discussed multiple primary outcomes, we selected the behavioral, physiological, and morbidity outcome more proximal to the intervention target (e.g., nutrient intake for dietary interventions). For each outcome, we reported whether the instrument used was objective or self-report. We defined objective as measures observed by an impartial third party or device. Primary outcomes identified can be cross-checked between our appendix tables with the original sources in the reference list.

For trials with multiple follow-up periods, we selected the follow-up period after the end of the intensive intervention period for behavior and physiological outcomes and the longest follow-up period for morbidity and mortality outcomes. Post-intervention was chosen because it was the point that we would expect the strongest impact of the behavioral intervention. We chose to include the final follow-up point because it was the most rigorous test of the durability of the intervention.

Sample sizes for populations, mean and standard error (or standard deviations) for outcomes, number of events, and number of deaths for each trial are listed in the appendix tables.

**Additional Variables** We coded the following variables: registration in ClinicalTrials.gov prior to publication, start year (earliest funding noted), publication year of main outcome, and type of comparator (less intense intervention, usual care, or assessment only). We reported the change in primary outcome in original units (e.g., kg, mmHg) between treatment and control group.

**Analysis** Each trial was categorized as showing significant benefit or as having non-significant (null) effects for each type of primary outcome and for total mortality (assuming $p<0.05$ as benefit). Bi-variate analyses were conducted using chi-square with $p<0.05$ as significant to test group differences. When sufficient data were published, we re-calculated effect sizes for the behavioral and physiological outcomes using the effect size calculator developed by the Campbell Collaboration [16].

Effect sizes were derived from the mean, standard deviation, standard error, confidence intervals, or proportions

provided in the outcome paper. The absolute effect sizes for behavioral and physiological outcomes were plotted against one another. We considered an effect size small (0.2), medium (0.5), and large (0.8) for both continuous and proportion calculations [17]. Meta-analyses were conducted separately for the following types of interventions which had a minimum of four studies to pool: single health behavior intervention for nutrition or physical activity, multiple lifestyle interventions incorporating nutrition and physical activity, and blood pressure or heart monitoring trials. Meta-analysis was conducted using STATA-12 using the metan procedure and a random effects model. Studies were weighted by the standard error and then rerun weighted by sample size.

This study was determined exempt from review by the National Institutes of Health, Office of Human Subjects Research.

## Results

A total of 5,828 grant years were identified through our searches (see Fig. 1). We removed multiple years of funding ($n$=3,315) and multiple research sites or ancillary studies of the same grant ($n$=933), which left a total of 1,580 abstracts for review. Using our pre-specified search criteria, we excluded 1,474 grant abstracts (see Appendix Table 1 for specific details). The most common reasons for exclusion included the following: study design was not an RCT, trial was still active, or the focus was not cardiovascular. We searched for main outcome papers for 106 grants; 20 were not found and assumed not published. An additional 48 full-text articles were excluded for not matching search criteria such as not an RCT, or a drug or community trial, or a duplicate with other trials previously identified (details in Appendix Table 1) which left 38 trials with published main outcome papers. Twenty-four trials were uniquely identified in our search. Five trials were found only through the NHLBI search. Nine trials overlapped between the two searches.

Table 1 and Appendix Table 2 list details of the trials included in the review. Approximately 26 % of the studies were funded in the late 1970s and 1980s, another 26 % funded in the 1990s and just under half of the trials were funded in 2000 or later. Sample sizes ranged from 79 to 48,835. Over half of the trials included a multi-factor or lifestyle intervention that included at least two of the following: nutrition or diet, physical activity, and smoking cessation ($n$=18). Nine trials intervened on exercise only ($n$=5) or nutrition only ($n$=4). Other interventions involved blood pressure or heart failure monitoring ($n$=4), improving communication with clinicians ($n$=2), medication adherence ($n$=1), cognitive behavioral therapy ($n$=1), self-management counseling ($n$=1), smoking cessation ($n$=1), or health literacy ($n$=1). Although we were not evaluating the effect of medications, interventions to increase medication adherence and monitoring heart failure were included because they modified a behavior that ultimately leads to optimal exposure of a surgery or drug treatment.

**Publication Bias and Prior Registration** We could not find primary outcome publications for 20 trials. The publication rate was 38 trials out of 58 (38 published, 20 not found published) for a total of 65.5 %. We conducted sub-analyses to compare publication rates among trials that registered with ClinicalTrials.gov prior to publication compared to those that did not pre-register. Prior registration in ClinicalTrials.gov would have only been available for trials active in the year 2000 or later as ClinicalTrials.gov was not launched until 1999 [18]. Eighteen of the 20 unpublished trials and 27 of the 38 included trials received some NIH funding in the year 2000 or later and would have been eligible to register, for a total of 45 trials that should have pre-registered in ClinicalTrials.gov. Overall, three fourths of trials were registered in ClinicalTrials.gov prior to publication (12 of the 18 unpublished trials and 23 of 27 published trials). Pre-specified outcomes were published in all trials that pre-registered (data not shown). Trials that were registered had a higher rate of publication (23 published/35 trials=65 %) than trials that did not prospectively register (4 published/10 trials=40 %), but these rates were not statistically different ($X^2$=1.21, $p$=.27).

**Length of Intervention and Follow-Up** Table 1 lists the range of length of intensive intervention and follow-up periods for each trial. Across all trials, length of intensive intervention ranged between 1 and 60 months and follow-up periods ranged from 3 to 72 months. Table 2 summarizes the durations of the intensive intervention and follow-up periods by type of intervention. The most common length of interventions for exercise and multi-behavior change trial was 6–12 months and for diet trials was 12–14 months. The lengths of follow-up were often longer in the diet and lifestyle interventions than in the exercise and blood pressure monitoring trials. Focusing just on interventions with the potential to change weight (nutrition, physical activity, multi-behavior), over 50 % of single behavior change interventions lasted more than 1 year, whereas less than half of multi-factor interventions lasted longer than 1 year (8 out of 18). Length of total follow-up period (post-baseline) was typically longer in nutrition and multi-factor interventions than in physical activity interventions. All of the nutrition interventions and 12 out of 18 multi-behavior change interventions reported a follow-up period longer than 12 months post-baseline.

**Objective Measurement** Table 2 and Appendix Table 3 list the type of behavior and physiological outcome measured. Superscripts indicate if the measure was objective. Across the 38 trials, only 26 trials reported a behavioral outcome and 11 of these trials (42 %) applied a measure that met the

**Table 1** Selected trial details of the 38 included behavioral interventions

| Trial | Intervention | Comparator | Intervention length (intensive/full) | Participant description | *N* size intervention | *N* size comparator |
|---|---|---|---|---|---|---|
| ACT [22] | Exercise | Brief provider advice | 24 months/ 24 months | Inactive adults (women) | 130 | 133 |
| Be Fit, Be Well [32] | Multi-factor (diet, exercise) | Usual care and education materials | 12 months/ 24 months | Obese patients receiving hypertension treatment | 148 | 166 |
| BPTEACH [33] | Patient education to ask clinicians | Usual care | 6 months | African American hypertensives | 43 | 57 |
| DEER [34][b] | Multi-factor (diet, exercise) | Assessment only | 3 months/ 12 months | Postmenopausal adult women | 43 | 45 |
| DISH [35][c] | Diet for weight control | No medication control | 56 weeks | Participants in previous heart disease trial | 87 | 89 |
| DPP [15, 36][a] | Multi-factor (diet, exercise) | Placebo | 24 weeks/ 2.8 years | Pre-diabetic | 1,079 | 1,082 |
| ENRICHD [37] | Cognitive behavioral therapy | Education materials | 6 months, 9 months | Patients with MI in past 28 days | 1,238 | 1,343 |
| HARP [38] | Med adherence | Cancer control | 6 months | Hypertensive adults | 221 | 213 |
| HART [39] | Self-management counseling | Heart failure education | 12 months | Patients with mild to moderate heart failure | 451 | 451 |
| HCP [40] | Nutrition | Discontinued drug use | 4 years | Participants in previous heart disease trial | 97 | 44 |
| Health Literacy [41, 42][a] | Health literacy | Single session health literacy | 1 months, 12 months | Patients with heart failure | 303 | 302 |
| Help PD [43][d] | Multi-factor (diet, exercise) | Usual care + registered dietician advice | 6 months, 24 months | Pre-diabetic | 151 | 150 |
| HF-ACTION [44][a] | Exercise | Education materials | 3 months, 12 months | Patients with heart failure | 1,159 | 1,172 |
| HOME_BP [45] | Home blood pressure monitor | Home blood pressure monitor and log | 3 months | High-risk African American patients | 221 | 217 |
| HOPP [46] | Smoking cessation | Education materials | 6 months, 7 months | Pregnant smokers | 306 | 297 |
| HPT [47] | Diet (sodium restriction) | Assessment only | 10 weeks, 3 years | Adults with mid-range blood pressure | 196 | 196 |
| Htn Prev [48] | Multi-factor (diet, exercise, sodium) | Usual care | 5 years | Adults with mild hypertension | 102 | 99 |
| ICAN [49] | Multi-factor (diet, exercise) | Usual care | 12 months | Obese, type 2 diabetics | 73 | 71 |
| IN CONTROL [50] | Blood pressure monitor | Usual care | 3 months | Adults with elevated blood pressure | 209 | 212 |
| iReach [23][e] | Multi-factor (diet, exercise) | In person | 6 months | Overweight adults | 158 | 161 |
| Look Ahead [2, 3, 51, 52][a] | Multi-factor (diet, exercise) | Usual care and diabetes education | 6 months, 4 years | Overweight/obese, type 2 diabetics | 2,570 | 2,575 |
| Mediterranean Lifestyle [53–55] | Multi-factor (diet, exercise) | Usual care | 6 months | Post-menopausal women, type 2 diabetics | 163 | 116 |
| MRFIT [56–59] | Multi-factor (smoking, diet) | Usual care | 4 months, 6 years | Men at risk of CHD death but no clinical evidence | 6,428 | 6,438 |
| Optimal Exercise Regimens [60] | Exercise | Assessment only | 12 months | Sedentary adults (men reported here) | 40 | 41 |
| PAD_RF [31] | Patient education to ask clinicians | Attention control | 12 months/ 12 months | Patients with PAD | 97 | 111 |
| PAD Treadmill [61] | Exercise | Assessment only | 6 months | Patients with peripheral artery disease | 51 | 53 |
| POWER [62] | Multi-factor (diet, exercise) remote counseling | Usual care | 6 months, 24 months | Obese adults | 139 | 138 |
| POWER-UP [63] | Multi-factor (diet, exercise) Brief lifestyle counseling | Usual care and quarterly counseling | 12 months, 24 months | Obese adults | 131 | 130 |

**Table 1** (continued)

| Trial | Intervention | Comparator | Intervention length (intensive/full) | Participant description | *N* size intervention | *N* size comparator |
|---|---|---|---|---|---|---|
| PREMIER [64] | Multi-factor (diet, exercise, sodium) Established + DASH diet | Education materials and 1-time counseling | 6 months, 18 months | Adults with untreated pre- or stage 1 hypertension | 269 | 273 |
| SCRIP [65] | Multi-factor (diet, exercise, sodium, smoking) | Usual care | 4 years | Adults with atherosclerosis | 145 | 155 |
| SWCP [66][f] | Multi-factor (diet, exercise) | Assessment only | 3 months, 12 months | Moderately overweight (men | 39 | 40 |
| TCYB [67] | Blood pressure monitor | Usual care | 24 months | Hypertensive adults | 159 | 159 |
| TELE-HF [68] | Telemonitoring | Education materials | 180 days | Recently hospitalized for heart failure | 826 | 827 |
| TOHP [69] | Multi-factor (diet, exercise) | Usual care | 14 months, 3–4 years | Recent weight loss participants | 595 | 596 |
| TOURS [70] | Multi-factor (diet, exercise) | Education materials | 12 months | Obese women in rural areas who recently completed lifestyle intervention | 83 | 79 |
| Training level comparison [71] | High-intensity exercise | Low-intensity exercise | 12 months | Male adults with coronary heart disease | 103 | 82 |
| WHI-DM [72][g] | Nutrition personal contact | Education materials | 1 year, 6.1 years | Overweight or obese with hypertension, dyslipidemia | 19,541 | 29,294 |
| WLM [73] | Multi-factor (diet, exercise) | Self-directed maintenance | 30 months | Postmenopausal women | 341 | 341 |

See online Appendix Table 2 for further details. Data in cells are study acronym (see footnote at end), intervention and comparator detail treatment and control arms. Intervention length is described as the intensive period (if any) and the full intervention period. Participant description and sample sizes for both arms. Trial titles from registry or publications for each acronym are provided. Some trials did not provide a short title or acronym; therefore, study authors created a condensed title

*ACT* [22] activity counseling trial, *Be Fit, Be Well* [32] evaluating a blood pressure reduction and weight loss program in a low-income, ethnically diverse population, *BPTEACH* [33] Baltimore partnership to educate and achieve control of hypertension, *DEER* [34] diet and exercise for elevated risk, *DISH* [35] dietary intervention study for hypertension, *DPP* [15, 36] diabetes prevention program, *ENRICHD* [37] enhancing recovery in coronary heart disease patients, *HARP* [38] hypertension and adherence in rural practice, *HART* [39] heart failure adherence and retention randomized behavioral trial, *HCP* [40] hypertension control program, *Health Literacy* [41, 42] health literacy and self-management in heart failure, *Help PD* [43] healthy living partnerships to prevent diabetes, *HF-ACTION* [44] heart failure: a controlled trial investigating outcomes of exercise training (HF-ACTION), *HOME_BP* [45] home-based blood pressure interventions for African Americans, *HOPP* [46] healthy options for pregnancy and parenting, *HPT* [47] hypertension prevention trial, *Htn Prev* [48] primary prevention of hypertension by nutritional-hygienic means, *ICAN* [49] improving control with activity and nutrition, *IN CONTROL* [50] hypertension reduction in inner city Seattle, *iReach* [23] Internet-assisted obesity treatment, *Look Ahead* [2, 3, 51, 52] action for health in diabetes, *Mediterranean Lifestyle* [53–55] effect of the Mediterranean lifestyle program on multiple risk behaviors and psychosocial outcomes, *MRFIT* [56–59] multiple risk factor intervention trial, *Optimal Exercise Regimens* [60] optimal exercise regimens for persons at increased risk, *PAD_RF* [31] reducing risk factors in peripheral arterial disease, *PAD Treadmill* [61] improving functioning in peripheral arterial disease, *POWER* [62] practice-based opportunities for weight reduction, *POWER-UP* [63] practice-based opportunities for weight reduction trial at the University of Pennsylvania, *PREMIER* [64] lifestyle intervention blood pressure control, *SCRIP* [65] Stanford coronary risk intervention project, *SWCP* [66] Stanford weight control program, *TCYB* [67] take control of your blood pressure study, *TELE-HF* [68] Yale heart failure telemonitoring study, *TOHP* [69] trials of hypertension prevention, phase II, *TOURS* [70] treatment of obesity in underserved rural settings, *Training Level Comparison* [71] training level comparison trial, *WHI-DM* [72] Women's Health Initiative randomized controlled dietary modification trial, *WLM* [73] weight loss maintenance randomized controlled trial

[a] For trials with this superscript, we had to extract data from multiple papers

[b] The Deer study had 12-month intervention with the first 3 months intensive but only reported 12-month data

[c] DISH—two intervention arms—weight control and sodium control. Outcomes for weight control arm reported in table. For sodium control arm, behavioral outcome was urinary sodium output which was significantly improved in treatment versus controls and more of the intervention group remained normotensive but not statistically different than controls

[d] Help-PD—intensive intervention was the first 6 months. Main outcome paper reports data every 6 months but conducted statistical analyses for the 18- and 24-month data. Data reported for weight and physiological outcome (glucose) was the adjusted means over 18- and 24-month follow-up

[e] iReach—study authors compared an in-person to an Internet or Internet in-person hybrid study. Authors evaluated how well an Internet delivery would do compared with an in-person version. We coded the in-person arm as the treatment arm and the Internet delivery arm as the control

[f] SWCP was a 12-month intervention with the first 3 months intensive; however, only 12-month data were available in the publication

[g] WHI had an intensive intervention for 12 months and then quarterly contact through the remainder of the year. Behavioral outcomes are reported at 18 months. Physiological outcomes were not published at 12 or 18 months. The closest follow-up to the end of the intensive intervention was at 3 years

definition of objective. Among trials that reported a behavioral outcome ($n$=26), 81.8 % (9 out of 11 trials) reported significant benefit outcomes based on objective assessments, whereas 80.0 % (12 out of 15 trials) reported positive results based on non-objective or self-report assessments. All trials reporting physiologic outcomes ($n$=32) applied objective assessments.

**Significant Outcomes** Table 2 and Fig. 2 report the number of trials that reported a behavior, physiological, clinical morbidity, or mortality outcome and if the finding was statistically significant. Only 26 trials reported a primary behavioral outcome with 21 trials (81 %) reporting a significant benefit. Similarly, 32 of the 38 trials reported a primary physiological outcome, and 81 % of these trials reported a significant benefit for physiologic measures (26 out of 32 trials). Fewer trials measured morbidity outcomes (17 out of the 38 trials), and only seven reported a significant benefit in the clinical outcome for the intervention condition in comparison to the control condition. Only 9 of the 38 studies reported mortality outcomes. All studies that assessed mortality were null.

**Effect Sizes** Table 2 lists the Cohen's $d$ effect sizes that we calculated, as well as the between group differences in original units. Effect sizes could not be calculated for some trials if they did not provide sufficient details in their publications (refer to Appendix Table 3 for listing of effect sizes). About half (14 out of 25 trials) produced small effect sizes for behavioral change (Cohen's $d$ between 0.2 and 0.5), and approximately a quarter ($n$=6) reported medium effect sizes (Cohen's $d$ larger than 0.5) and one fifth ($n$=5) large effects (Cohen's $d$ larger than 0.8) [16]. Approximately three fourths of trials produced small effect sizes (23 out of 30 trials), and 20 % (6 out of 30 trials) produced moderate effect sizes in their primary, physiological outcomes. Example of small to medium changes in original trial units includes changes in weight from 1 to 5.4 kg and changes in blood pressure from 1.5 to 9.4 mmHg.

We plotted the effect sizes of the primary behavioral outcome at post-test ($x$-axis) against the effect sizes of the primary physiological outcome at post-test (Fig. 3). Each circle on the figure represents one trial, and a solid colored circle indicates a significant benefit observed for both the behavioral and physiological outcome. Figure 3 displays 20 trials that report sufficient data to calculate effect sizes for both behavioral and physiological outcomes. The slope of the best fitting line is fairly flat (slope=−0.11). The majority of the trials (80 %) report a significant benefit for both the change in behavior and physiology; however, many of these effects fall within the small level as defined by Cohen (between 0.2 and 0.5).

The analysis was repeated using only weight as the physiological outcome because weight was the most common physiological outcome reported across all trials (Fig. 4). For this analysis, we combined trials that analyzed weight as either the primary or secondary outcome ($n$=15). Physiological effect sizes shown in Fig. 4 may not appear in Fig. 3 of all primary physiological effect sizes. We again see high concordance with 87 % of the trials reporting a significant benefit in the behavior and weight outcomes. We observed a stronger relationship between the data points (slope=0.33), and more of the trials reported moderate to large effects in weight change ($n$=10).

**Meta-Analysis of Effect Size of Single Versus Multiple Behavior Interventions** We conducted a meta-analysis of trials by type of intervention for the following sub-groups: (1) single behavior change interventions targeting blood pressure and heart monitoring interventions, (2) single behavior change interventions targeting nutrition or physical activity, and (3) multiple behavior change interventions of nutrition, physical activity, or smoking. Although four blood pressure and heart monitoring studies were pooled, these studies did not consistently report a behavior and physiological change. Only one trial reported the behavior change (adherence), and only two reported blood pressure. We compared the effect size and number of significant primary outcomes for single versus multiple behavior interventions that modified nutrition and physical activity (Table 3). The mean effect size for the primary physiological outcome was larger in multi-behavior interventions (0.48 effect size) as compared with single behavior interventions (0.34 for physical activity or 0.03 for diet only). The mean effect size for weight change was two to five times higher for multi-behavior change interventions (0.74 effect size) as compared to single behavior change interventions (0.08 for physical activity or 0.14 for diet only).

We coded trials as having a significant benefit in change in weight and change in their primary physiological outcomes. Among interventions that modified a single behavior (nutrition or physical activity), seven out of nine (78 %) reported a significant benefit in their primary physiological outcome, and four out of six (67 %) reported a significant benefit in weight as either a primary or secondary outcome. All of the multiple behavior change interventions reported a significant benefit in their primary physiological outcome, and 94 % reported a significant benefit in weight (either as primary or secondary outcome).

## Discussion

Our review of NHLBI/NIDDK-funded RCTs addresses three important questions: (1) Can health behavior be modified? (2) Does the change produced by behavioral intervention result in physiological change? and (3) Do behavioral interventions affect morbidity and mortality?

**Table 2** Trial outcomes for 38 randomized controlled trials of behavioral interventions

| Trial | Behavior outcome | Effect size (95 % CI) | Group difference in original units | Primary physiological outcome | Effect size (95 % CI) | Group difference in original units | Morbidity | Mortality |
|---|---|---|---|---|---|---|---|---|
| ACT [22][a] | Met activity recommendations[N, S] | 0.4 (0.03, 0.77) | 25.7 versus 14.3 % | $VO_2$ (ml/min)[B, O] | 0.32 (0.08, 0.57) | 80.7 ml/min | NR | NR |
| Be Fit, Be Well [32] | Medication adherence scale[B, S] | 0.38 (0.13, 0.63) | 0.85 units different on medication adherence scale | Weight[B, O] | 0.25 (0.01, 0.50) | 1.05 kg | NR | NR |
| BPTEACH [33] | NR | NR | NR | Systolic blood pressure[N, O] | 0.22 (0.18, 0.61) | 9.44 mmHg | NR | NR |
| DEER [34] | Caloric intake[B, S] | 0.48 (0.07, 0.91) | 172 kcal/day | LDL-C[B, O] | 0.62 (0.19, 1.05) | 12 mg/dl | NR | NR |
| DISH [35][b] | NR | NR | | Weight[B, O] | 0.83 (0.48, 1.2) | 3.5 kg | Normotensive without drugs—benefit | NR |
| DPP [15, 36] | Energy intake[B, S] | 0.23 (0.15, 0.32) | 201 kcal/day | Weight[B ,O] | 0.81 (0.73, 0.90) | 5.4 kg | Diagnosis of diabetes—benefit | NR |
| ENRICHD [37] | Depression[B, S] | 0.33 (0.25, 0.41) | 2.8 points on Beck Depression | NR | NR | NR | Fatal or non-fatal myocardial infarction—null | Yes—null |
| HARP [38] | Pill count[N, O] | 0.04 (−0.16, 0.25) | 2 % more adhered | NR | NR | NR | NR | NR |
| HART [39] | Sodium[N, S] | 0.31 (0.14, 0.49) | 10 % more met goal | Systolic blood pressure[N, O] | 0.11 (−0.01, 0.24) | 2.6 mmHg | Heart failure or hospitalization—null | Yes—null |
| HCP [40] | Sodium[B, O] | 1.12 (0.72, 1.5) | 1,839 mg/day | Diastolic blood pressure[B, O] | 0.22 (0.14, 0.58) | 1.5 mmHg | Normotensive without drugs—benefit | NP |
| Health Literacy [41, 42] | Self-care behavior[B, S] | 0.56 (0.38, 0.73) | 1.4 points on self-care scale | NR | NR | NR | Hospitalizations—null | Yes—null |
| Help PD [43][c] | NR | NR | NR | Glucose mg/dl[B, O] | 0.44 (0.22, 0.67) | 4.35 mg/dl | Diagnosis of Diabetes—null | NR |
| HF-ACTION [44][d] | 6 min walk[B, O] | 0.32 (0.2, 0.41) | 14 m | $VO_2$ (ml/kg/min)[B, O] | 0.34 (0.25, 0.42) | 0.4 mL/kg/min | CV event or hospitalization—null | Yes—null |
| HOME_BP [45] | NR | NR | NR | Blood pressure control[N, O] | 0.09 (−0.15, 0.33) | 25 % of tx had bp control versus 22 % con | NR | NR |
| HOPP [46] | Smoking[B, S] | 0.22 (0.03, 0.41) | 9 % remained abstinent | NR | NR | NR | NR | NR |
| HPT [47] | Sodium[B, O] | 0.32 (0.11, 0.53) | 5.5 mmol | Blood pressure[N, O] | 0.21 (0.0, 0.42) | 1.7 mmHg | Hypertension—benefit | NP |
| Htn Prev [48] | Sodium[B, O] | 0.63 (0.33, 0.99) | 700 mg/day | Blood pressure[B, O] | 0.31 (0.03, 0.60) | 2 mmHg | Hypertension—benefit | NR |
| ICAN [49] | NR | NR | NR | Weight[B, O] | 0.42 (0.09, 0.75) | 3.0 kg | NR | NR |
| IN CONTROL [50] | Completed FU appointment[B, O] | 0.42 (0.16, 0.66) | 65.1 versus 46.7 % | NR | NR | NR | NR | NR |

**Table 2** (continued)

| Trial | Behavior outcome | Effect size (95 % CI) | Group difference in original units | Primary physiological outcome | Effect size (95 % CI) | Group difference in original units | Morbidity | Mortality |
|---|---|---|---|---|---|---|---|---|
| iReach [23][e] | Diet (kcal)[N, O] | 0.03 (−0.18, 0.25) | 18 kcal | Weight (kg)[B, O] | 0.36 (0.14, 0.58) | 2.1 kg | NR | NR |
| Look Ahead [2, 3, 51, 52][f] | Physical activity (kcal/week) [B, S] | 0.34 (0.29, 0.40) | 768.9 kcal/week | Change in METS from sub-max treadmill[B, O] | 0.59 (0.53, 0.64) | 15.1 METS | Composite of cardiovascular events—null | Yes—null |
| Mediterranean Lifestyle [53–55] | Adherence to Mediterranean diet scale[B, S] | 0.77 (0.52, 1.02) | 0.86 point increase with possibly scale range 0–7 | Weight (kg at 6 months)[B, O] | 0.35 (0.11, 0.59) | 1.77 kg | NR | NR |
| MRFIT [56–59][g] | Smoking cessation[B, O] | 0.66 (0.59, 0.72) | 31 versus 12 % quit rate | Blood pressure (diastolic)[B, O] | 0.41 (0.38, 0.45) | 3.8 mmHg | Definite, fatal AMI—null | Yes—null |
| Optimal Exercise Regimens [60] | NR | NR | NR | $VO_2$ max (mL/kg/min)[B, O] | 0.58 (0.14, 1.03) | 2.0 ml/kg/min | NR | NR |
| PAD_RF [31] | Increased dose or use of medication[B, O] | 0.94 (0.61, 1.27) | 53.8 versus 17.5 % | LDL-C[B, O] | 0.36 (0.08, 0.63) | 10.5 mg/dl | NR | NP |
| PAD Treadmill [61] | 6 min walk (m)[B, O] | 0.69 (0.29, 1.08) | 36.2 m | Brachial artery flow (mm)[B, O] | 0.22 (−0.16, 0.61) | 0.06 mm | NR | NR |
| POWER [62] | NR | NR | NR | Weight[B, O] | 0.89 (0.63, 1.16) | 4.5 kg | Hospitalizations—null | NP |
| POWER-UP [63] | NR | NR | NR | Weight[N, O] | 0.16 (0.08, 0.40) | 1.1 kg | NR | NP |
| PREMIER [64] | Fruit and vegetable intake[B, S] | 0.78 (0.59, 0.97) | 2.5 servings/day | Blood pressure (systolic)[B, O] | 0.47 (0.30, 0.64) | 4.3 mmHg | NP | NR |
| SCRIP [65] | % Kcal fat[B, S] | 1.09 (0.82, 1.36) | 7.8 % kcal fat | Minimal diameter change[B, O] | 0.30 (0.05, 0.55) | 0.069 mm | Hospitalizations—benefit | Yes—null |
| SWCP [66] | Energy intake[B, S] | 0.92 (0.45, 1.38) | 2,213 kJ/day | CHD risk (using Framingham equations)[B, O] | 1.11 (0.64, 1.58) | −22.4 events/ 1,000 persons | NR | NR |
| TCYB [67],[h] | NR | NR | NR | Blood pressure controlled[B, O] | NR | 11 % more of tx group had controlled blood pressure | NR | NP |
| TELE-HF [68] | NR | NR | NR | NR | NR | NR | Readmission—null | Yes—null |
| TOHP [69],[i] | NR | NR | NR | Blood pressure (systolic)[B, O] | NR | −2.7 mmHg | Onset of hypertension—benefit | NR |
| TOURS [70] | Self-monitoring records[B, O] | 0.32 (0.01, 0.63) | 29 more days of self-monitoring | Weight regain[B, O] | 0.43 (0.12, 0.74) | 2.5 kg | NR | NR |
| TLC [71] | NR | NR | Attendance | $VO_2$ max (mL/kg/min)[N, O] | 0.38 (−0.2, 0.77) | 0.8 ml/kg/min | NR | NR |

**Table 2** (continued)

| Trial | Behavior outcome | Effect size (95 % CI) | Group difference in original units | Primary physiological outcome | Effect size (95 % CI) | Group difference in original units | Morbidity | Mortality |
|---|---|---|---|---|---|---|---|---|
| WHI-DM [72] | % fat intake$^{B, S}$ | 1.51 (1.49, 1.53) | 10.7 % | Blood pressure (diastolic)$^{B, O}$ | 0.03 (0.01, 0.05) | −0.31 mmHG | Fatal and non-fatal CHD, CVD, stroke—null | Yes—null |
| WLM [73][j] | % Kcal$^{N, S}$ | NR | NR | Weight$^{B, O}$ | 0.27 (0.12, 0.42) | 1.5 kg | NR | NR |

Primary outcomes and effect sizes for trials included in review. See Online Appendix Table 3 for further details. Data in cells are the primary outcome, calculated absolute effect sizes, and reported change in original trial units for the behavioral, physiological, and weight outcomes. Superscripted letters represent whether measure was objective or self-reported and whether outcome was a significant benefit or null. For morbidity outcomes, we include the specific outcome measure and whether null or significant benefit. If the trial was powered to analyze all-cause mortality, we included whether there was a significant benefit or not. Trial titles from registry or publications for each acronym are provided. Some trials did not provide a short title or acronym; therefore, study authors created a condensed title. A total of 38 trials are included. Each type of outcome (behavior, weight, physiology, morbidity, and mortality outcomes) should total to 38. Each trial was categorized as reporting a significant benefit or null finding or not reported/not powered for each type of outcome. Behavior, weight, and physiological outcomes were reported at the end of the intensive intervention. Morbidity and mortality outcomes were reported at the longest follow-up period available

[a] ACT—behavior effect size calculated from proportions–percent of participants meeting moderate or vigorous physical activity recommendations post-intervention

[b] DISH—two intervention arms—weight control and sodium control. Outcomes for weight control arm are reported in the table. For sodium control arm, behavioral outcome was urinary sodium output which was significantly improved in treatment versus controls and more of the intervention group remained normotensive but not statistically different than controls

[c] Help-PD—intensive intervention was the first 6 months. Main outcome paper reports data every 6 months but conducted statistical analyses for the 18- and 24-month data. Data reported for weight and physiological outcome (glucose) was the adjusted means over 18- and 24-month follow-up

[d] HF action—the main outcome paper reported median and IQR for the behavior (distance walked) and physiological variable (peak oxygen consumption). We calculated effect sizes based on a normal distribution assumption

[e] iReach—study authors compared an in-person to an Internet or Internet in-person hybrid study. Authors evaluated how well an Internet delivery would do compared with an in-person version. We coded the in-person arm as the treatment arm and the Internet delivery arm as the control

[f] Look Ahead—different FU—behavior outcome $VO_2$ and weight reported at 12 months; Cardiovascular events and mortality reported at final follow-up (max 13.5 years, median 9.6 years)

[g] MRFIT—behavior and physiological outcomes reported at 12 months; AMIs reported at 7 years; and mortality reported at original follow-up (max 6 years)

[h] TCYB—insufficient data presented to calculate blood pressure effect sizes

[i] TOHP—insufficient data presented to calculate blood pressure effect sizes

[j] WLM—insufficient data presented to calculate change in percent kcal effect sizes

*NR* not reported, *N* null, *B* significant benefit, *H* harm, *O* objective, *S* self-reported, *ACT* [22] activity counseling trial, *Be Fit, Be Well* [32] evaluating a blood pressure reduction and weight loss program in a low-income, ethnically diverse population, *BPTEACH* [33] Baltimore partnership to educate and achieve control of hypertension, *DEER* [34] diet and exercise for elevated risk, *DISH* [35] dietary intervention study for hypertension, *DPP* [15, 36] diabetes prevention program, *ENRICHD* [37] enhancing recovery in coronary heart disease patients, *HARP* [38] hypertension and adherence in rural practice, *HART* [39] heart failure adherence and retention randomized behavioral trial, *HCP* [40] hypertension control program, *Health Literacy* [41, 42] health literacy and self-management in heart failure, *Help PD* [43] healthy living partnerships to prevent diabetes, *HF-ACTION* [44] heart failure: a controlled trial investigating outcomes of exercise training (HF-ACTION), *HOME_BP* [45] home-based blood pressure interventions for African Americans, *HOPP* [46] healthy options for pregnancy and parenting, *HPT* [47] hypertension prevention trial, *Htn Prev* [48] primary prevention of hypertension by nutritional-hygienic means, *ICAN* [49] improving control with activity and nutrition, *IN CONTROL* [50] hypertension reduction in inner city Seattle, *iReach* [23] Internet-assisted obesity treatment, *Look Ahead* [2, 3, 51, 52] action for health in diabetes, *Mediterranean Lifestyle* [53–55] effect of the Mediterranean lifestyle program on multiple risk behaviors and psychosocial outcomes, *MRFIT* [56–59] multiple risk factor intervention trial, *Optimal Exercise Regimens* [60] optimal exercise regimens for persons at increased risk, *PAD_RF* [31] reducing risk factors in peripheral arterial disease, *PAD Treadmill* [61] Improving functioning in peripheral arterial disease, *POWER* [62] practice-based opportunities for weight reduction, *POWER-UP* [63] practice-based opportunities for weight reduction trial at the University of Pennsylvania, *PREMIER* [64] lifestyle intervention blood pressure control, *SCRIP* [65] Stanford coronary risk intervention project, *SWCP* [66] Stanford weight control program, *TCYB* [67] take control of your blood pressure study, *TELE-HF* [68] Yale heart failure tele-monitoring study, *TOHP* [69] trials of hypertension prevention, phase II, *TOURS* [70] treatment of obesity in underserved rural settings, *Training Level Comparison* [71] training level comparison trial, *WHI-DM* [72] Women's Health Initiative randomized controlled dietary modification trial, *WLM* [73] weight loss maintenance randomized controlled trial

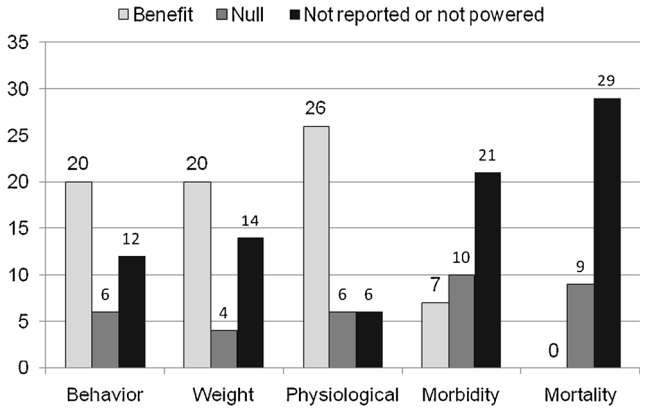


**Fig. 2** Number of behavioral intervention trials that reported a benefit or null finding for their primary behavior, weight, physiological, morbidity, and mortality outcomes

Can behavior be modified? It is commonly believed that health behavior is difficult to modify. Many practitioners have become skeptical about the effectiveness of behavioral alternatives for the management of cardiovascular risk factors [19]. Our review suggests that the great majority of behavioral trials do, indeed, demonstrate a positive benefit. Further, most behavioral trials are pre-registered in the ClinicalTrials.gov service, and the primary outcome variable is specified in advance. This assures that investigators are not selecting positive outcomes from among many alternatives in a post hoc fashion. Behavioral intervention researchers are conforming to high methodological standards.

Our results are consistent with a variety of other analyses. For example, a recent evidence synthesis for the US Preventive Services Taskforce (USPSTF) considered the benefits and harms of behavioral counseling interventions to prevent cardiovascular disease (CVD) for persons with established risk factors [20]. After considering 49 trials in meta-analysis, they concluded that behavioral interventions to improve lifestyle resulted in reductions in total cholesterol low-density lipoprotein, blood pressure, fasting glucose, diabetes, and adiposity [20].

Do behavioral changes result in physiological changes? Our review suggests that behavioral intervention often results in physiological changes including reductions in weight, blood pressure, and serum cholesterol. Overall,

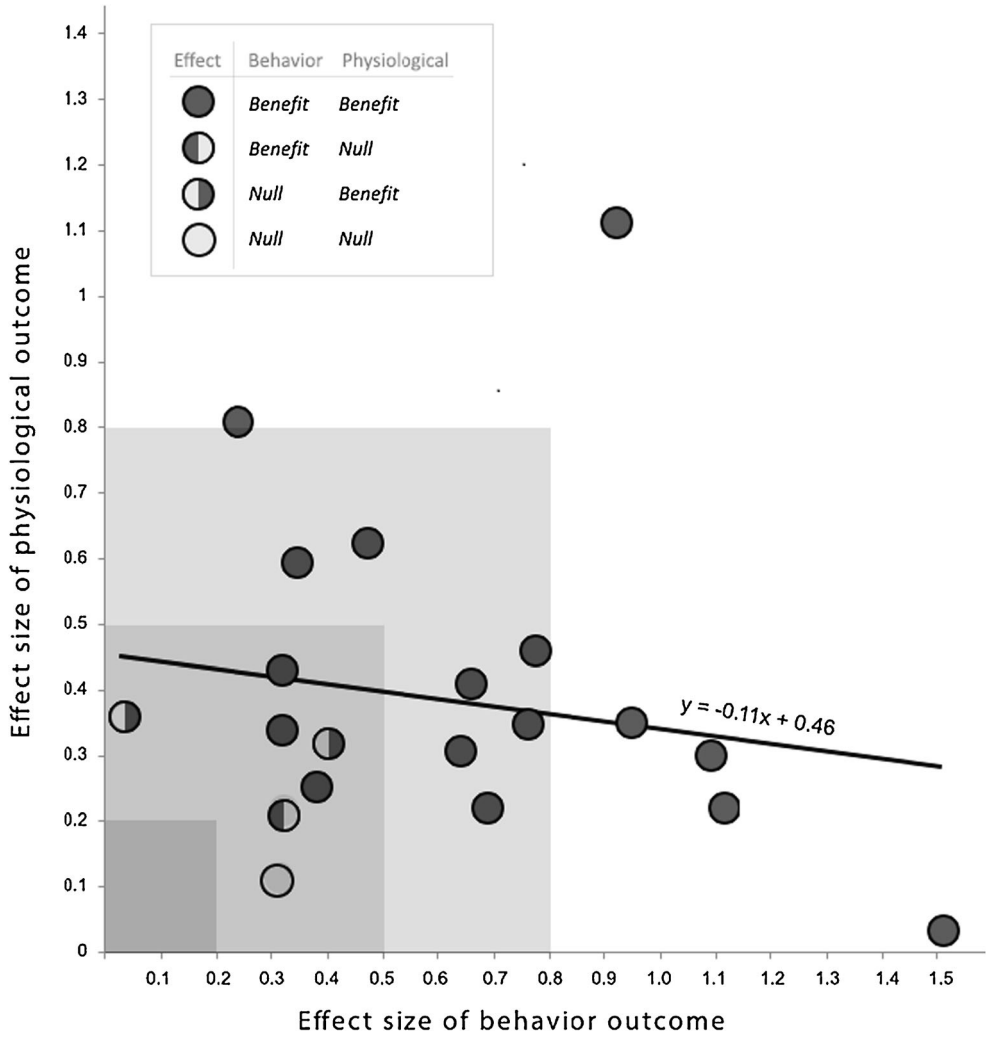


**Fig. 3** Scatterplot and best-fit line of the effect size of the change in the behavioral outcome (*x*-axis) against the effect size of change in the physiological outcome (*y*-axis). *Each circle* represents one trial with *dark-colored circles* representing significant benefit. *Dark shading* represents effect sizes under 0.2, *medium shading* represents small effect sizes (Cohen's *d* between 0.2 and 0.5), *lighter shading* represents medium effect sizes (Cohen's *d* between 0.5 and 0.8), and *no shading* represents large effect sizes (Cohen's *d* greater than 0.8)

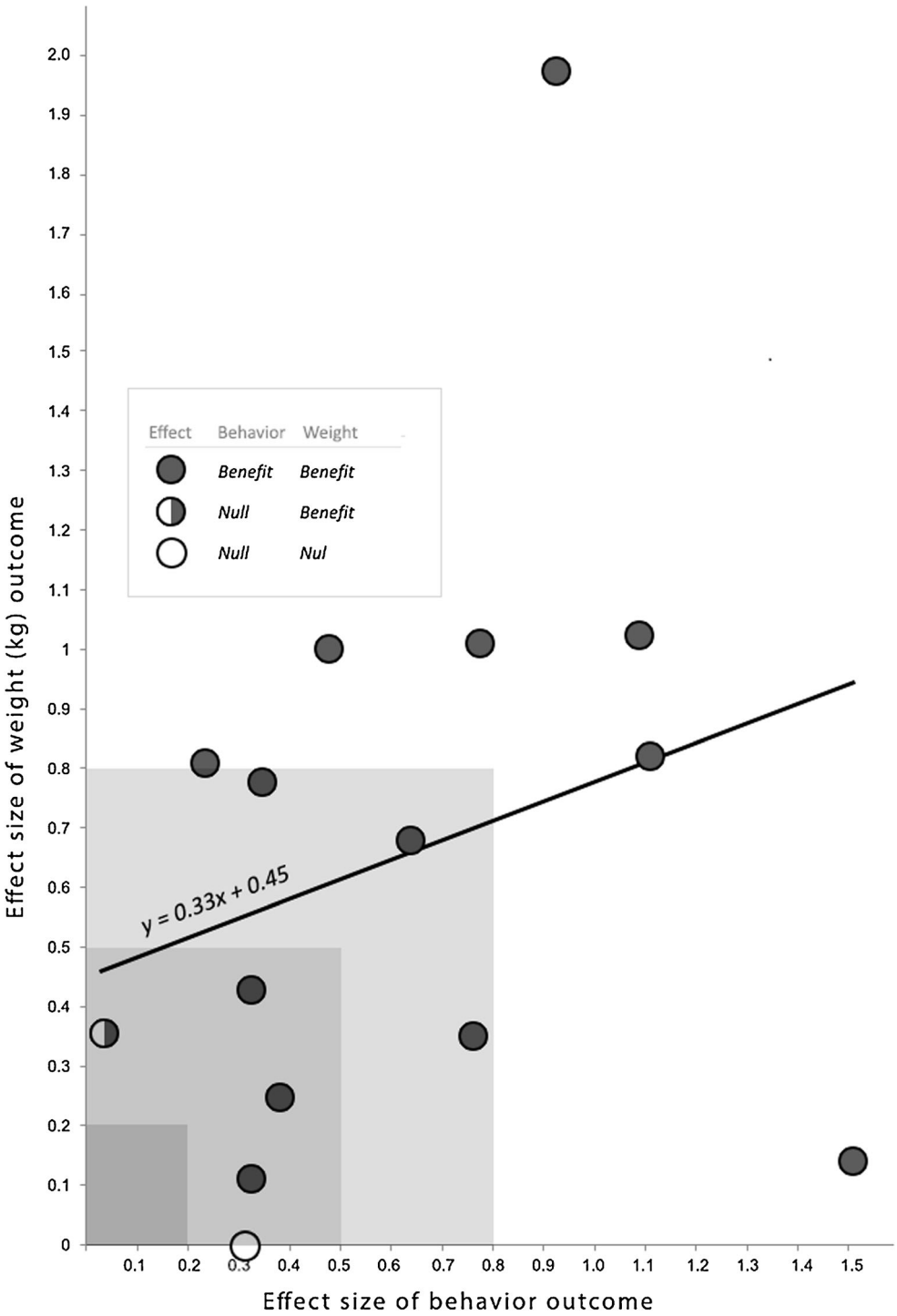


**Fig. 4** Scatterplot and best-fit line of the effect size of the change in the behavioral outcome (*x*-axis) against the effect size of change in the weight outcome (*y*-axis). *Each circle* represents one trial with *dark-colored circles* representing significant benefit. *Dark shading* represents effect sizes under 0.2, *medium shading* represents small effect sizes (Cohen's *d* between 0.2 and 0.5), *lighter shading* represents medium effect sizes (Cohen's *d* between 0.5 and 0.8), and *no shading* represents large effect sizes (Cohen's *d* greater than 0.8)

there was a high degree of concordance between behavioral and physiological outcomes. Both types of measures were reported in 20 of the 38 trials. Among these trials, 80 % reported a benefit for both behavior change and physiologic change (16 of 20 trials). Few studies report data on the relationship between behavior change and physiological change. More consistent reporting of the target behavior change and its relationship to changes on physiological and health outcome variables is needed. Future interventions should test and publish mediational analyses between their behavior change and physiological outcomes. These mediational analyses would provide a better understanding of the mechanisms that did or did not produce the intended physiological change.

**Table 3** Summary table of number of significant benefits and effect sizes achieved and length of intervention and follow-up period by type of behavioral intervention

| Type of intervention | Blood pressure monitoring | Nutrition only | Physical activity only | Multi-behavior change |
|---|---|---|---|---|
| Number of trials | 4 | 4 | 5 | 18 |
| Reported behavioral outcome | 1 | 3 | 3 | 13 |
| Significant behavior benefit (*N*) | 1 | 3 | 2 | 11 |
| Behavior change effect size from meta-analysis | 0.42 | 0.15 | 0.34 | 0.53 |
| Reported physiological outcome | 2 | 4 | 5 | 18 |
| Significant physiological benefit (*N*) | 1 | 3 | 4 | 18 |
| Physiological change effect size from meta-analysis | 0.09 | 0.03 | 0.34 | 0.48 |
| Reported weight outcome | 0 | 4 | 2 | 17 |
| Significant weight benefit (*N*) | N/A | 4 | 0 | 16 |
| Weight change effect size from meta-analysis | N/A | 0.14 | 0.08 | 0.74 |
| Reported morbidity | 1 | 4 | 1 | 8 |
| Significant morbidity benefit (*N*) | 0 | 3 | 1 | 4 |
| Reported mortality | 1 | 1 | 1 | 3 |
| Significant mortality benefit (*N*) | 0 | 0 | 0 | 0 |
| Range of duration of intensive intervention period (months) | 3–24 | 2.5–48 | 3–24 | 3–60 |
| Mode (most common) length (months) | 3 | 12–14 | 6–12 | 6–12 |
| Range of length of total follow-up (months) | 3–24 | 14–72 | 6–24 | 6–72 |
| Mode (most common) length (months) | 6 | 12–14 | 12 | 12 |

Tables in cells reflect sub-group analysis of the behavioral intervention trials by their specific focus of the intervention—blood pressure monitoring, nutrition only, physical activity only, multi-factor, or lifestyle interventions. The multi-factor interventions had to include at least two of the following behavior change targets—nutrition, physical activity, and smoking. We report the number of trials for each type of intervention and the number who reported and who found significant benefits for behavior, physiological, morbidity, or mortality outcomes. We also include the effect size that we calculated from the meta-analysis of effect sizes from each type of intervention. Effect sizes above are weighted by sample size. Please note that the effect sizes were quite different for the nutrition intervention trials for standard error versus weighted by sample size because of the large sample size of the WHI trial. For the nutrition only interventions, effect sizes for the behavioral outcome were 0.98 when weighted by standard error and 0.15 when weighted by sample size; for the physiological outcome were 0.28 when weighted by standard error and 0. 03 when weighted by sample size; and for the weight outcome were 0.35 when weighted by standard error and 0.14 when weighted by sample size

Measurement tools may be inadequate to clearly document behavioral change. For instance, most nutritional measures were collected via self-report, which has known measurement error due to participant recall, knowledge, and reactivity [21]. It might be argued that the goal of behavioral intervention is to affect physiological outcomes. Thus, movement of a physiological parameter might be the best evidence that the behavioral treatment was successful. However, in some trials, there were changes on physiological measures despite null effects for behavior change [22, 23]. We do not know whether the results from these trials were (1) because there was high measurement error for the behavioral measures or (2) because the physiological outcomes were affected through a non-behavioral pathway.

Do behavioral interventions affect morbidity and mortality? The goal of most health interventions is to improve health outcomes, including functioning, quality of life, and longevity. In examining this literature, we note that many of the behavioral trials evaluated outcomes in terms of risk factors or behavior changes. Very few of the trials evaluated long-term outcomes including mortality or clinical morbidity. This is in contrast to many of the large pharmaceutical trials that focus attention on changes in cardiovascular mortality or all-cause mortality [9]. Thus, it could be argued that behavioral trials are not being held to the same rigorous standard as are evaluations of pharmaceutical and surgical interventions. However, pharmaceutical interventions often modify a risk factor but report no benefit on the primary health outcomes [9].

The finding that behavioral trials typically do result in significant improvements in risk factors suggests that we need more trials that take the evaluation to the next level. Future trials might include more evaluations of long-term health outcomes. Less than half of multi-factor, lifestyle interventions included in our review reported a follow-up period greater than 1 year. In order to measure clinical events or morbidity, longer length of follow-up is required. Maintenance studies are needed to determine if these small to moderate physiological effects are maintained post-treatment and if these effects are sufficient to reduce cardiovascular events.

These trials will need to be large in order to assure sufficient statistical power to evaluate the null hypothesis. Unfortunately, powering behavioral trials to detect mortality effects will require a major change in the size of trials. For example, cholesterol-lowering medications are believed to be one of the most effective instruments for reducing likelihood of death from cardiovascular disease. In the very influential Coronary Primary Prevention Trial [24], 1.6 % of participants taking cholesterol lowing medications died over a 7-year follow-up in comparison to 2 % of participants in the control group. To have a 90 % chance of detecting a difference between groups would require more than 23,000 subjects per group. In the original Physician's Health Study [25] on the effects of aspirin to prevent deaths from myocardial Infarction, there were 5 deaths per 11,000 who were randomly assigned to take aspirin in comparison to about 18 deaths per 11,000 physicians who took placebo. In order to prospectively plan for a 90 % chance of detecting an effect this size at the 0.05 alpha level, 16,000 subjects per group would be required.

As these calculations demonstrate, finding a significant treatment effect for mortality often requires enormous sample sizes. Typically, sample size requirements may be many levels of magnitude larger than is current practice in behavioral trials. In the 38 trials included in this review, the majority of trials included samples sizes of several hundred combining both study arms. Only four trials reported more than 1,000 participants/group and only two trials more than 5,000 participants/group. Future investigations may need to consider much larger sample sizes to demonstrate the benefits of behavioral interventions.

**Effect Size** The effect sizes of the behavior and physiological outcomes were predominantly in the range as the small ($d$= 0.2) to medium ($d$=0.5) levels [17]. Because so few trials analyzed changes in morbidity and mortality, we do not know if these effects sizes are large enough to invoke a clinically meaningful change in morbidity. If small or medium effect sizes are achieved, we do not know how well they are maintained or if a sustained small effect would produce morbidity changes equivalent to larger, short-term physiological effects. Future interventions might test the clinical outcomes achieved with smaller physiological and behavioral changes sustained long term. For interventions that target high-risk populations, larger changes in effect size in both the behavior and physiological outcomes might be needed to achieve clinical outcomes. Instead of powering trials for a moderate effect size, trials might estimate Cohen's $d$=1 which would equate to about a change in one standard deviation between treatment and control groups.

We conducted a sub-analysis of interventions that targeted a single behavior change (nutrition or physical activity or heart monitoring) as compared with interventions targeting multiple behavior or lifestyle changes. Effect sizes achieved with multiple behavior change interventions were larger than those achieved with single behavioral targets. In a recent review, Nigg and Long found the majority of interventions with older adults focused only on one behavior change [26]. Our sample of trials included twice as many multi-behavior change interventions as compared to single behavior change interviews.

**File Drawer and Selective Reporting** Null and negative results may be less likely to be published in comparison to positive results. This selective non-reporting is known as "file drawer" bias. The trend toward study preregistration may help address this problem because it allows identification of all studies that are launched. Knowing the denominator of studies will allow better estimates of the rate of non-reporting. Gordon et al. [13] conducted a review of NHLBI-funded trials and noted that 64 % of trials that cost more than $5 million dollars were published within 12 months, 91 % within 30 months, and 97 % within 48 months of the grant end date. Behavioral interventions (not restricting the sample to over $5 million) were less likely to be published than non-behavioral interventions, with only 11 % published at 12 months, 48 % at 30 months, and 72 % at 48 months following the grant end date. Gordon et al. did not report publication rates for behavioral interventions costing over $5 million [13]. In our analysis, approximately 65 % of behavioral trials were published. We used an end date of December 2012, which only allowed some studies about 18 months to publish prior to our analyses. Lower publication rate among behavioral trials might be attributed to the type of outcomes reported. Previous analyses have shown that trials that report a clinical-event end-point were more likely to be published than trials that did not [13]. Less than half of trials in our analysis reported a clinical, morbidity outcome. Publication rates might improve if behavioral interventions were powered for and reported clinical outcomes (like hospitalization or formal disease diagnosis).

Over three fourths of behavioral trials funded since 2000 were registered prospectively with ClinicalTrials.gov. All reported their pre-specified primary outcomes. Thus, our results are not clearly explained by selective reporting of primary outcomes. The rate of registration is high considering behavioral interventions are not required to register with ClinicalTrials.gov [18]. A recent review of behavioral RCTs published in several leading behavioral health journals found that the majority of behavioral intervention trials did not register and did not adequately declare primary and secondary outcomes [27]. The Milette review did not differentiate by source of funding [27]. In our data, trials that registered had a higher rate of publication than trials that did not register, although this difference was not statistically significant. Investigators of behavioral interventions may be registering in order to publish in certain journals or because of a requirement of their sponsor. NIH now requires all funded trials to register

[28]. Better estimates of the rate of non-reporting are expected in the future.

**Limitations** Our evaluation has a significant number of limitations. First, we concentrated only on large-budget NHLBI and NIDDK trials. Clearly, this is a small fraction of all of the behavioral trials in the literature. Ultimately, only 38 studies met the inclusion criteria, and it is legitimate to ask how representative these 38 studies are of all behavioral trials. We must emphasize that this group of studies is the population of studies that met the inclusion criteria. It is true that all of these were studies funded through the peer review system. But, we did not arbitrarily eliminate studies. One of the strengths of the study is that we knew the population of studies that were funded prior to publication. In addition, the USPSTF recently reviewed a wide range of behavioral trials and came to similar conclusions [20].

A second concern is that we evaluated only large trials. We focused on large trials because they were more likely to be registered, and we had a better opportunity to rule out bias due to non-publication [13]. On the other hand, these large funded trials are likely to be atypical. Additional work using a more representative sample of trials is in order.

A third concern is that we focused on studies done in the USA, a country with a unique health care system and a unique research funding structure. The reason for focusing on US studies was that we were able to access NIH grant databases of funded studies. This is important because access to the population of funded studies allowed us to avoid biases associated with selective non-publication of normal or negative results.

A fourth concern is that behavioral medicine investigators sometimes recruit participants who do not have elevated scores on a target variable. As a result, there is less room for change because of floor effects [29]. A meta-analysis by Schneider and colleagues [30] found that distress prior to an intervention explained as much as half of the variability between studies on treatments for anxiety and depression. Many studies showed modest or no effects of intervention when baseline distress was low. Floor effects are important. On the other hand, most of the behavioral interventions are used for population-based prevention and may need to focus on non-clinical populations. The USPSTF, which serves as the basis for US clinical prevention policy, typically excludes studies where patients are selected because they have high scores on a target variable. The reason is that the USPSTF wants the results to generalize to the primary care population who receive preventive services because they do not have elevated scores or diagnosed diseases. The role of clinical versus population study group must be carefully considered in designing and generalizing from studies.

Lastly, systematic reviews can now be registered, but we were unaware of registration services when we began our analysis in the fall of 2011. One registration service is Prospero which was developed in 2011, but the founding principles were not released until May 2014 (see http://www.crd.york.ac.uk/PROSPERO/). We do support registration of reviews and would have used this service had we been aware of it when we began our work. We recognize that registration reduces biases, promotes transparency of methods, and avoids potential duplication. To facilitate the replication of our work by others, the tables in the paper and the detailed online Supplemental Materials report the PRISMA diagram, the number of results returned and excluded, and raw numbers and RR used in calculations. We support replication and encourage others to reproduce our findings.

In summary, behavioral factors play an important role in the etiology and pathogenesis of major cardiovascular conditions. Our review of large-budget NHLBI- and NIDDK-funded behavioral trials suggests that the great majority produce positive outcomes in terms of behavioral change and modification of cardiovascular risk factors. The common belief that behavior cannot be changed is not supported by this review or by a related meta-analysis conducted for the USPSTF [20]. In contrast, the majority of NHLBI trials evaluating pharmaceutical interventions produce null results [13], and the number of positive morbidity or mortality outcomes in drug trials has declined since 2000 [9]. Behavioral interventions have fewer negative side effects than drugs, and behavior change might lead to cascading benefits with other related health behaviors. Behavioral interventions show promise with significant benefits to behavior and physiological outcomes. More research is needed to test the maintenance of these changes and to determine if these physiological changes are sufficient to lengthen and improve quality of life.

**Conflict of Interest and Ethical Adherence** Manuscript submitted to Annals of Behavioral Medicine
Study authors: Veronica L. Irvin & Robert M. Kaplan
Study title: Effect Sizes and Primary Outcomes in Large Behavioral Randomized-Controlled Trials Funded by NIH Since 1980

**Funding Source** This research was conducted while both authors were affiliated with the Intramural Research Program of the National Institutes of Health, Clinical Center, Department of Rehabilitation Medicine. Dr. Irvin was a post-doctoral fellow with the National Institutes of Health. The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the National Institutes of Health or the US government.

**Conflict of Interest** Both authors were with National Institutes of Health at the time of data analysis—Dr. Kaplan as an employee and Dr. Irvin as a post-doctoral fellow. There was no official grant funded by NIH to conduct these analyses. Dr. Irvin is now Assistant Professor at Oregon State University and Dr. Kaplan is now Chief Scientific Officer at the Agency for Healthcare Research and Quality. There are no other conflicts of interests to report.

**Ethical Adherence** This study was determined exempt from review by the National Institute of Health, Office of Human Subjects Research (NIH OHSRP no. 11648 PI: Kaplan).

## References


1. Fisher EB, Fitzgibbon ML, Glasgow RE, et al. Behavior matters. *Am J Prev Med*. 2011; 40: e15-30.
2. Neiberg RH, Wing RR, Bray GA, et al. Patterns of weight change associated with long-term weight change and cardiovascular disease risk factors in the Look AHEAD Study. *Obesity (Silver Spring)*. 2012; 20: 2048-2056.
3. Look ARG, Wing RR, Bolin P, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013; 369: 145-154.
4. World Health Organization. Non-communicable diseases. Available at http://www.who.int/mediacentre/factsheets/fs355/en/. Accessibility verified July 3, 2015.
5. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014; 129(25 Suppl 2): S49-73.
6. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014; 129(25 Suppl 2): S1-45.
7. Phillips SM, Glasgov RE, Bello G, et al. Frequency and prioritization of patient health risks from a structured health risk assessment. *Ann Fam Med*. 2014; 12: 505-513.
8. Kaplan RM, Morgan G. *Providers advice concerning smoking cessation: Evidence from the medical expenditures panel survey.* San Antonio: Presented at the annual meeting of the Society of Behavioral Medicine; 2015.
9. Kaplan RM, Irvin VL. Likelihood of null effects of large NHLBI clinical trials has increased over time. *PLOS One*. 2015; 10(8): e0132382.
10. Goldacre B. Preventing bad reporting on health research. *BMJ*. 2014; 349: g7465.
11. Sumner P, Vivian-Griffiths S, Boivin J, et al. The association between exaggeration in health related science news and academic press releases: retrospective observational study. *BMJ*. 2014; 349: g7015.
12. Pharmaceutical Research and Manufacturers of American. PhRMA 2012 Industry Profile. Available at http://www.phrma.org/sites/default/files/159/phrma_industry_profile.pdf. Accessibility verified July 3, 2015.
13. Gordon D, Taddei-Peters W, Mascette A, et al. Publication of trials funded by the National Heart, Lung, and Blood Institute. *N Engl J Med*. 2013; 369: 1926-1934.
14. Easterbrook PJ, Gopalan R, Berlin J, Matthews DR. Publication bias in clinical research. *The Lancet*. 1991; 337: 867-872.
15. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002; 346: 393-403.
16. Cambell Collaboration. David B. Wilson. Practical meta-analysis effect size calculator. Available at http://www.campbellcollaboration.org/escalc/html/EffectSizeCalculator-SMD8.php. Accessibility verified July 6, 2015.
17. Cohen J. A power primer. *Psychol Bull*. 1992; 112: 155-159.
18. Zarin DA, Tse T. Moving toward transparency of clinical trials. *Science*. 2008; 319: 1340-1342.
19. Lovshin JA, Drucker DJ. Metabolic disease puts up a fight: Are diet and exercise helpful for the heart? *Nat Med*. 2013; 19: 1216-1217.
20. Lin JS, O'Connor E, Evans CV, et al. Behavioral counseling to promote a healthy lifestyle in persons with cardiovascular risk factors: A systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2014; 161(8): 568-578.
21. National Cancer Institute. Dietary assessment primer. Available at http://dietassessmentprimer.cancer.gov/learn/. Accessibility verified July 3, 2015.
22. Writing Group for the Activity Counseling Trial Research G. Effects of physical activity counseling in primary care: The Activity Counseling Trial: A randomized controlled trial. *JAMA*. 2001; 286: 677-687.
23. Harvey-Berino J, West D, Krukowski R, et al. Internet delivered behavioral obesity treatment. *Prev Med*. 2010; 51: 123-128.
24. No authors. The lipid research clinics coronary primary prevention trial results. 1. Reduction in incidence of coronary heart-disease. *JAMA*. 1984; *251*:351-364.
25. No authors. Hennekens CH: Preliminary report: Findings from the aspirin component of the ongoing physicians' health study. *N Engl J Med*. 1988; *318*:262-264.
26. Nigg CR, Long CR. A systematic review of single health behavior change interventions vs multiple health behavior change interventions among older adults. *TBM*. 2012; 2: 166-179.
27. Milette K, Roseman M, Thombs BD. Transparency of outcome reporting and trial registration of randomized controlled trials in top psychosomatic and behavioral health journals: A systematic review. *J Psychosom Res*. 2011; 70: 205-217.
28. National Institutes of Health. HHS and NIH take steps to enhance transparency of clinical trial results. Available at http://www.nih.gov/news/health/nov2014/od-19.htm. Accessibility verified July 6, 2015.
29. Linden W, Satin JR. Avoidable pitfalls in behavioral medicine outcome research. *Ann Behav Med*. 2007; 33: 143-147.
30. Schneider S, Moyer A, Knapp-Oliver S, et al. Pre-intervention distress moderates the efficacy of psychosocial treatment for cancer patients: A meta-analysis. *J Behav Med*. 2010; 33: 1-14.
31. McDermott MM, Reed G, Greenland P, et al. Activating peripheral arterial disease patients to reduce cholesterol: A randomized trial. *Am J Med*. 2011; 124: 557-565.
32. Bennett GG, Warner ET, Glasgow RE, et al. Obesity treatment for socioeconomically disadvantaged patients in primary care practice. *Arch Intern Med*. 2012; 172: 565-574.
33. Johnson W, Shaya FT, Khanna N, et al. The Baltimore Partnership to Educate and Achieve Control of Hypertension (The BPTEACH Trial): A randomized trial of the effect of education on improving blood pressure control in a largely African American population. *J Clin Hypertens (Greenwich)*. 2011; 13: 563-570.
34. Stefanick ML, Mackey S, Sheehan M, et al. Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol. *N Engl J Med*. 1998; 339: 12-20.
35. Langford HG, Blaufox MD, Oberman A, et al. Dietary therapy slows the return of hypertension after stopping prolonged medication. *JAMA*. 1985; 253: 657-664.
36. Delahanty LM, Pan Q, Jablonski KA, et al. Genetic predictors of weight loss and weight regain after intensive lifestyle modification, metformin treatment, or standard care in the Diabetes Prevention Program. *Diabetes Care*. 2012; 35: 363-366.
37. Berkman LF, Blumenthal J, Burg M, et al. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA*. 2003; 289: 3106-3116.
38. Martin MY, Kim YI, Kratt P, et al. Medication adherence among rural, low-income hypertensive adults: A randomized trial of a

multimedia community-based intervention. *Am J Health Promot*. 2011; 25: 372-378.
39. Powell LH, Calvin JE Jr, Richardson D, et al. Self-management counseling in patients with heart failure: The heart failure adherence and retention randomized behavioral trial. *JAMA*. 2010; 304: 1331-1338.
40. Stamler R, Stamler J, Grimm R, et al. Nutritional therapy for high blood pressure. Final report of a four-year randomized controlled trial—The Hypertension Control Program. *JAMA*. 1987; 257: 1484-1491.
41. DeWalt DA, Schillinger D, Ruo B, et al. Multisite randomized trial of a single-session versus multisession literacy-sensitive self-care intervention for patients with heart failure. *Circulation*. 2012; 125: 2854-2862.
42. Baker DW, Dewalt DA, Schillinger D, et al. The effect of progressive, reinforcing telephone education and counseling versus brief educational intervention on knowledge, self-care behaviors, and heart failure symptoms. *Journal of Cardiac Failure*. 2011; 17(1): 789-796.
43. Katula JA, Vitolins MZ, Morgan TM, et al. The Healthy Living Partnerships to Prevent Diabetes study: 2-year outcomes of a randomized controlled trial. *Am J Prev Med*. 2013; 44: S324-332.
44. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009; 301: 1439-1450.
45. Pezzin LE, Feldman PH, Mongoven JM, et al. Improving blood pressure control: Results of home-based post-acute care interventions. *J Gen Intern Med*. 2011; 26: 280-286.
46. McBride CM, Curry SJ, Lando HA, et al. Prevention of relapse in women who quit smoking during pregnancy. *Am J Public Health*. 1999; 89: 706-711.
47. Hypertension Prevention Trial Research Group. The Hypertension Prevention Trial: Three-year effects of dietary changes on blood pressure. *Arch Intern Med*. 1990; 150: 153-162.
48. Stamler R, Stamler J, Gosch FC, et al. Primary prevention of hypertension by nutritional-hygienic means. Final report of a randomized, controlled trial. *JAMA*. 1989; 262: 1801-1807.
49. Wolf AM, Conaway MR, Crowther JQ, et al. Translating lifestyle intervention to practice in obese patients with type 2 diabetes: Improving Control with Activity and Nutrition (ICAN) study. *Diabetes Care*. 2004; 27: 1570-1576.
50. Krieger J, Collier C, Song L, Martin D. Linking community-based blood pressure measurement to clinical care: A randomized controlled trial of outreach and tracking by community health workers. *Am J Public Health*. 1999; 89: 856-861.
51. Pi-Sunyer X, Blackburn G, Brancati FL, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: One-year results of the LOOK AHEAD trial. *Diabetes Care*. 2007; 30: 1374-1383.
52. Eight-year weight losses with an intensive lifestyle intervention: The LOOK AHEAD study. *Obesity (Silver Spring)*. 2014; *22*:5-13.
53. Toobert DJ, Glasgow RE, Strycker LA, et al. Biologic and quality-of-life outcomes from the Mediterranean Lifestyle Program: A randomized clinical trial. *Diabetes Care*. 2003; 26: 2288-2293.
54. Toobert DJ, Glasgow RE, Strycker LA, et al. Long-term effects of the Mediterranean lifestyle program: A randomized clinical trial for postmenopausal women with type 2 diabetes. *Int J Behav Nutr Phys Act*. 2007; 4: 1.
55. Toobert DJ, Strycker LA, Glasgow RE, Barrera M Jr, Angell K. Effects of the mediterranean lifestyle program on multiple risk behaviors and psychosocial outcomes among women at risk for heart disease. *Ann Behav Med*. 2005; 29: 128-137.
56. Multiple Risk Factor Intervention Trial Research Group. Multiple risk factor intervention trial. Risk factor changes and mortality results. *JAMA*. 1982; 248: 1465-1477.
57. Multiple Risk Factor Intervention Trial Research Group. Coronary heart disease death, nonfatal acute myocardial infarction and other clinical outcomes in the Multiple Risk Factor Intervention Trial. *Am J Cardiol*. 1986; 58: 1-13.
58. Benfari RC. The multiple risk factor intervention trial (MRFIT). III. The model for intervention. *Prev Med*. 1981; 10: 426-442.
59. Neaton JD, Broste S, Cohen L, et al. The multiple risk factor intervention trial (MRFIT). VII. A comparison of risk factor changes between the two study groups. *Prev Med*. 1981; 10: 519-543.
60. King AC, Haskell WL, Taylor CB, Kraemer HC, DeBusk RF. Group- vs home-based exercise training in healthy older men and women. A community-based clinical trial. *JAMA*. 1991; 266: 1535-1542.
61. McDermott MM, Ades P, Guralnik JM, et al. Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: A randomized controlled trial. *JAMA*. 2009; 301: 165-174.
62. Appel LJ, Clark JM, Yeh HC, et al. Comparative effectiveness of weight-loss interventions in clinical practice. *N Engl J Med*. 2011; 365: 1959-1968.
63. Wadden TA, Volger S, Sarwer DB, et al. A two-year randomized trial of obesity treatment in primary care practice. *N Engl J Med*. 2011; 365: 1969-1979.
64. Appel LJ, Champagne CM, Harsha DW, et al. Effects of comprehensive lifestyle modification on blood pressure control: Main results of the PREMIER clinical trial. *JAMA*. 2003; 289: 2083-2093.
65. Haskell WL, Alderman EL, Fair JM, et al. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease. The Stanford Coronary Risk Intervention Project (SCRIP). *Circulation*. 1994; 89: 975-990.
66. Wood PD, Stefanick ML, Williams PT, Haskell WL. The effects on plasma lipoproteins of a prudent weight-reducing diet, with or without exercise, in overweight men and women. *N Engl J Med*. 1991; 325: 461-466.
67. Bosworth HB, Olsen MK, Grubber JM, et al. Two self-management interventions to improve hypertension control: A randomized trial. *Ann Intern Med*. 2009; 151: 687-695.
68. Chaudhry SI, Mattera JA, Curtis JP, et al. Telemonitoring in patients with heart failure. *N Engl J Med*. 2010; 363: 2301-2309.
69. Stevens VJ, Obarzanek E, Cook NR, et al. Long-term weight loss and changes in blood pressure: Results of the Trials of Hypertension Prevention, phase II. *Ann Intern Med*. 2001; 134: 1-11.
70. Perri MG, Limacher MC, Durning PE, et al. Extended-care programs for weight management in rural communities: The treatment of obesity in underserved rural settings (TOURS) randomized trial. *Arch Intern Med*. 2008; 168: 2347-2354.
71. Kim JR, Oberman A, Fletcher GF, Lee JY. Effect of exercise intensity and frequency on lipid levels in men with coronary heart disease: Training Level Comparison Trial. *Am J Cardiol*. 2001; 87: 942-946. **a943**.
72. Howard BV, Van Horn L, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: The Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006; 295: 655-666.
73. Svetkey LP, Stevens VJ, Brantley PJ, et al. Comparison of strategies for sustaining weight loss: The weight loss maintenance randomized controlled trial. *JAMA*. 2008; 299: 1139-1148.