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EFFECTS OF EXERCISE AND PHYSICAL ACTIVITY ON HOMOCYSTEINE IN ADULTS: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

GEORGE KELLEY[1] and KRISTI KELLEY[1]

[1]Department of Community Medicine/School of Medicine/West Virginia University, Morgantown, WV, USA

ABSTRACT

Kelley GA, Kelley KS. Effects of Exercise and Physical Activity on Homocysteine in Adults: A Meta-Analysis of Randomized Controlled Trials. ***JEPonline*** 2008;11(5):12-23. The effects of exercise on homocysteine (Hcy), an emerging risk factor for cardiovascular disease, are controversial. The purpose of this study was to use the meta-analytic approach to examine the effects of exercise and physical activity on Hcy in adults. Studies were retrieved by searching computerized databases, cross-referencing, and review of our reference list by authors of eligible studies. Studies were included if they were randomized, controlled exercise and physical activity interventions $\geq$ 4 weeks in adults $\geq$ 18 years of age. Random and fixed-effects models were used to pool results and examine heterogeneity. Five studies representing six outcomes in 167 men and women (88 exercise, 79 control) were included. Overall, nonsignificant exercise minus control group reductions of approximately 8% were found for Hcy (mean, -0.8 µmol/L, 95% confidence interval, -1.9 to 0.4 µmol/L) with statistically significant heterogeneity observed (Q=32.0, p <0.001; I^2=84.4%). When the only statistically significant outcome in overweight/obese adults (mean, -3.0, 95% CI, -3.9 to -2.1 µmol/L) was deleted from the model, no statistically significant heterogeneity was observed (Q=2.7, p=0.61; I^2 <0.0001%) and the pooled results remained non-significant (mean, -0.6, 95% CI, -1.4 to 0.3 µmol/L). Our results suggest that insufficient evidence currently exists to support the role of exercise in lowering Hcy in normal weight adults but that Hcy may be lowered in overweight/obese adults. However, additional research is needed on this topic before any definitive recommendations can be made.

Keywords: Obesity, Physical Fitness, Cardiovascular Disease.

INTRODUCTION

Cardiovascular disease (CVD) is the number one cause of mortality in the United States, accounting for 629,191 deaths in 2006 [1]. While established risk factors for CVD morbidity and mortality include, but are not limited to, conditions such as hypertension and hypercholesterolemia [2], an emerging risk factor for CVD appears to be homocysteine (Hcy) [3]. Homocysteine is an amino acid in the blood in which elevated levels have been shown to increase CVD risk [4-6]. Wald et al. conducted two separate meta-analyses of 12 retrospective and 72 prospective studies and found that a straight line association existed between increasing levels of Hcy and increased CVD events [4]. In addition, Bautista et al., in a meta-analysis of 14 cohort studies, found that elevated levels of Hcy result in moderate increases in the risk of a first-time cardiovascular event, regardless of age and duration of follow-up [5]. Furthermore, it has been estimated that a 1 µmol/L decrease in Hcy can reduce the risk of coronary artery disease by 10% [6]. Exercise and physical activity, low-cost nonpharmacologic interventions that are available to the vast majority of the general public, are recommended for the control of conditions such as hypertension [7] and hypercholesterolemia [8]. However, the results of randomized controlled trials dealing with the effects of chronic exercise and physical activity on Hcy levels in adults have led to equivocal findings [9-14], with four studies reporting no statistically significant reductions in Hcy [9-12], and another two reporting statistically significant reductions [13,14]. Given these divergent findings, the purpose of this study was to use the meta-analytic approach to examine the effects of chronic exercise and physical activity on Hcy levels in adults [15].

METHODS

Data Sources

Studies for potential inclusion in this meta-analysis were retrieved by (1) searching 11 computerized databases (PubMed, EmBase, CINAHL, Sport Discus, Dissertation Abstracts International, Cochrane Central Register of Controlled Clinical Trials, PsychInfo, LILACS, PeDro, ERIC, Web of Science), (2) cross-referencing from retrieved studies, including review articles, and (3) review of our reference list by the corresponding authors of potentially eligible studies included in our list. The search for relevant studies was limited to January 1, 1992 through January 1, 2007. All computer searches were conducted by the first author with the assistance of the second author. While the keywords and terms used varied depending upon the database being queried, one term germane to all searches was “exercise and homocysteine.”

Study Selection

The inclusion criteria for this study were: (1) randomized controlled trials with a comparative control group, (2) physical activity/exercise (aerobic and/or progressive resistance training) of at least 4 weeks duration as the intervention, (3) studies published and indexed in any language between January 1, 1992 and January 1, 2007, (4) studies published as journal articles, dissertations or master’s theses, (5) adult humans ages 18 years of age and older, and (6) initial and final assessment of homocysteine. The selection of studies was conducted by both authors. We chose 1992 as the starting date for our searches since this was the first year that a reference included the terms exercise and homocysteine [16].

Data Abstraction

Prior to the abstraction of data, a codebook that could hold up to 362 items from each study was developed. The major categories of items that were coded included: (1) study characteristics (for example, year of publication), (2) subject characteristics (e.g., age), (3) Hcy assessment characteristics (for example, time of assessment), (4) training program characteristics (for example, length) and (5) our primary outcome (Hcy). In cases where Hcy was assessed but insufficient data were available for pooling, contact was made with the corresponding author of each study and a

request was made for such. All studies were coded by both authors, independent of each other. The authors then reviewed every item (2172 total) for accuracy and precision. Disagreements were resolved by consensus. Using Cohen's kappa statistic [17], the overall agreement rate prior to correcting discrepant items was 0.89.

Statistical Analyses

Power Estimates

Prior to the statistical pooling of data, a power estimate was generated in order to ensure that an adequate number of Hcy outcomes were available for pooling. Using power estimates designed specifically for meta-analytic datasets (traditional power estimates are not appropriate for meta-analysis) [18], a "medium" effect size of 0.50 [19)] and a random effects variance component of 0.33, the power to detect a statistically significant difference in Hcy at a two-tailed alpha level of 0.05 was 80%. Thus, the number of studies included and the subjects within these studies were sufficient to determine an effect of exercise on Hcy if one existed.

Calculation of Study-Level Effect Estimates for Hcy

The primary outcome in this study was treatment effect differences in Hcy. These were calculated as:

Treatment effect difference = $M_{ei} - M_{ci}$

where M_{ei} is the final minus initial difference in the exercise group and M_{ci} is the final minus initial difference in the control group. Each outcome from each study was then weighted by the inverse of its variance with the variance derived as:

$$\text{Variance} = \frac{(n_{ei} - 1)sd_{ei}^2 + (n_{ci} - 1)sd_{ci}^2}{N_i - 2}$$

where n_{ei} is the sample size for the exercise group, sd_{ei}^2 is the squared standard deviation for the exercise group, n_{ci} is the sample size for the control group, sd_{ci}^2 is the squared standard deviation for the control group, and N_i is the sum of the exercise and control group sample sizes.

For those studies that did not report change outcome standard deviations, these were estimated from initial and final standard deviations using previously developed procedures [20].

Pooled Estimates for Hcy

After calculating treatment effect estimates for Hcy for each outcome from each study, results were pooled. For this meta-analysis, we used a random-effects model [21]. We chose a random-effects model rather then a fixed effects because the former controls for between-study heterogeneity [21]. If the two-tailed 95% confidence intervals generated from the model did not cross zero (0), we considered our results to be statistically significant. Since one study included two separate groups [13] we also ran our analyses with both groups collapsed across that study. Heterogeneity based on a fixed effects model was examined using the *Q* statistic and an alpha value for statistical significance of 0.10 versus 0.05 because this test tends to suffer from low power [22]. In addition, we also examined the consistency of our between study findings for Hcy using I^2 [23]. Generally, I^2 values of 25%, 50%, and 75% are indicative of small, medium, and large amounts of inconsistency [23]. Publication bias was examined using the nonparametric trim and fill approach of Duvall and Tweedie [24] while the sensitivity of our findings was examined by deleting each study from the model once. Study quality was examined using a previously validated and reliable scale in which scores range from 0 to 5 with higher scores representing greater study quality [25]. This scale focuses on the randomization process as well as blinding and the control of withdrawals and dropouts. However,

since no gold standard currently exists for determining study quality, all scales should be interpreted with extreme caution [26]. Study quality was assessed by both authors, independent of each other. The authors then reviewed every item for accuracy and precision. Disagreements were resolved by consensus. Using Cohen's kappa statistic [17], the overall agreement rate prior to correcting discrepant items was 0.76.

Cumulative meta-analysis, ranked by year, was used to examine changes in Hcy over time [27]. Because of the small number of studies, we did not conduct any other type of subgroup or regression analysis. Descriptive statistics were generated using version 14.0 of SPSS [28] and with the exception of study quality, which was reported as the median, reported as mean ± standard deviation (SD). All meta-analytic analyses and graphs were generated using Comprehensive Meta-Analysis (version 2.2) [29].

RESULTS

Study Characteristics

A description for the selection of studies is shown in Figure 1. Of the 177 studies screened, 6 (3.4%) met our inclusion criteria [9-14]. However, since one study [14] included some of the same subjects as a more recent study [13] we only included data for the more recent study. Thus, a total of five studies representing six outcomes from 167 men and women (88 exercise, 79 control) were included in our meta-analysis [9-13]. The number of outcomes exceeded the number of studies because one study included more than one exercise and control group [13]. A general description of the studies is shown in Table 1. All of the studies were published in English-language journals between 2000 and 2006. Two studies were conducted in either the United States [9,13] or the United Kingdom [10,11] while the other study was conducted in the Netherlands [12]. All of the studies used a parallel-group design. Three studies reported using the analysis-by-protocol approach to analyze their data [10,12,13] while the other two used the intention-to-treat approach or had all subjects complete the study [9,11]. The percentage of dropouts for the three studies that reported such data ranged from 0% to 25% in the exercise groups and 0% to 22% in the control groups [9-11]. Study quality ranged from 1 to 4 (median = 1).

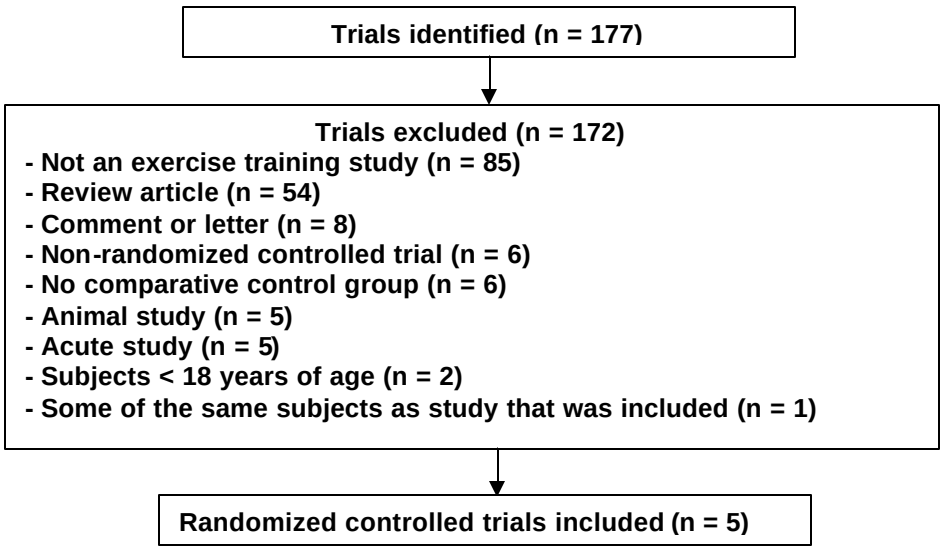

Figure 1. Search results for identifying studies to include in the meta-analysis.

Subject Characteristics

Baseline characteristics of the subjects are shown in Table 2. As can be seen, age, BMI, and Hcy levels were similar between the exercise and control groups. Three studies that met our criteria included both men and women [9,12,13], one was limited to women [10], and the other was limited to men [11]. For those studies that included women, two were limited to postmenopausal women [12,13], one was limited to premenopausal women [10], and the other included both pre and postmenopausal women [9]. Two studies reported that none of the subjects were taking any drugs that could affect Hcy levels [10,11] while three reported that none of the subjects smoked cigarettes

Table 1. Characteristics of included studies.

Study (Year)	Subjects	Intervention	Hcy Assessment
Araiza et al. (2006)[9]	30 sedentary men and women (age range 33 to 69 years) with type 2 diabetes assigned to either a physical activity (n = 15) or control (n = 15) group.	Increase the number of steps walked to at least 10,000 per day, 5 or more days per week, for 6 weeks. Number of steps taken increased by 69% (M ± SD = 10,410 ± 4,162).	Automated immunoassay in the morning after fasting.
Boreham et al. (2005)[10]	15 young (M ± SD = 18.8 ± 0.7 years of age), sedentary women assigned to an exercise (n = 8) or control (n = 7) group.	2 to 5 bouts of progressive stair climbing on stairs, five days per week, up to approximately 11 minutes per day, for 8 weeks (one session per week supervised). Compliance ranged from 75% to 95% (M = 88%).	High performance liquid chromatography after a 12-hour overnight fast and 60 hours after the last stair climbing session.
Cooper et al. (2000)[11]	13 sedentary but healthy males 28 to 40 years of age assigned to either an exercise (n = 6) or control (n = 7) group.	30 minutes of unsupervised walking, at least 5 days per week, for 6 weeks. Mean compliance was 64%.	High performance liquid chromatography after a 6 hour fast and not exercising for at least 48 hours.
de Jong et al. (2000)[12]	60 sedentary, frail elderly men and women ≥ 70 years of age assigned to either an exercise (n = 30) or control (n = 30) group.	17 weeks of supervised exercise, 2 times per week for 45 minutes per session. Emphasis on the use of walking, stooping and chair stands for the development of muscle strength, coordination, flexibility, speed and endurance.	Non-fasting at noon.
Vincent et al. (2006)[13]	49 older adults 60 to 72 years of age assigned to one of 4 groups: normal weight (n = 10) or overweight/obese (n = 19) exercise; normal weight (n = 10) or overweight/obese (n = 10) control.	24 weeks of progressive resistance training, 3 times per week, 50-80% of 1 RM. Subjects performed 1 set of 8 to 13 repetitions using 13 different exercises. Compliance was ≥ 85%.	High performance liquid chromatography after an overnight fast.

Notes: Data presented limited to those groups from each study that met our inclusion criteria; Hcy, homocysteine; Number of subjects includes the final number of subjects in which Hcy measures were available; M, mean; SD, standard deviation; RM, repetition maximum.

[10,11,13]. None of the studies reported any change in diet that could have affected Hcy levels or that subjects were exercising regularly prior to taking part in the study. One study was limited to subjects with Type 2 diabetes [9] while another study included a separate exercise and control group that was overweight or obese [13]. None of the studies reported any statistically significant exercise minus control group changes in body composition, i.e., percent body fat, lean body mass. However, two studies did report statistically significant exercise minus control group increases in maximum

oxygen consumption in $ml \cdot kg^{-1} \cdot min^{-1}$ [10,13], one of which used progressive resistance training as the intervention [13]. In relation to dietary intake, one study reported normal baseline levels of folic acid, vitamin B_6 and vitamin B_{12} in the exercise and control groups with no statistically significant changes observed over the duration of the study [12]. Blood vitamin concentrations of folate, red blood cell folate, and vitamin B_{12} were also assessed with no significant changes observed over the course of the study [12]. One study reported no statistically significant changes in red blood cell folate or vitamin B_{12} over the study period [11].

Table 2. Baseline characteristics of subjects.

	Exercise (n=6)		*Control (n=6)*	
Variable	***Age***	***Range***	***Age***	***Range***
Age (years)	52.5 ± 22.1	19-77	54.1 ± 23.9	19-79
BMI (kg/m^2)	25.6 ± 3.7	21-30	26.5 ± 4.2	22-34
Hcy (µmol/L)	9.9 ± 3.5	7-17	9.8 ± 3.9	7-17

Notes: N, number of outcomes; M ± SD, mean ± standard deviation; Range, mean between group ranges; BMI, body mass index; Hcy, homocysteine.

Homocysteine Assessment

Data for assessment of Hcy from each study is shown in Table 1. Four of the five studies reported the assessment of Hcy after fasting [9-11,13] while two reported that subjects avoided exercise for at least 48 hours prior to the assessment of Hcy [10,11]. Three studies reported the assessment of Hcy in the morning [9,10,13] while another reported assessment in the afternoon [12]. Reliability data for the assessment of Hcy was reported by three studies [11-13]. One study did not report the exact method used to assess Hcy [12].

Table 3. Initial and final homocysteine data (µmol/L) from each study.

		Initial	Final	Difference		Initial	Final	Difference
Study (Year)	**N**	**M ± SD**	**M ± SD**	**M ± SD**	**N**	**M ± SD**	**M ± SD**	**M ± SD**
Araiza et al. (2006)[9]	15	9.1 ± 4.80	8.9 ± 3.6	-0.2 ± 2.2	15	8.3 ± 2.4	8.8 ± 2.8	0.5 ± 1.2
Boreham et al. (2005)[10]	8	7.04 ± 1.7	6.7 ± NA	-0.35 ± 0.7	7	7.2 ± 2.5	7.2 ± NA	0.04 ± 0.9
Cooper et al. (2000)[11]	6	9.7 ± 1.8	10 ± 2.1	0.3 ± 0.5	7	10.1 ± 1.0	10 ± 0.5	-0.07 ± 1.1
De Jong et al. (2000)[12]	30	16.8 ± 7.0	17.3 ± NA	0.5 ± 2.4	30	19.5 ± 7.8	19.8 ± NA	0.3 ± 5.6
Vincent et al. (2006)[13]								
- Normal Weight	10	7.8 ± 2.7	7.1 ± 3	-0.7 ± 1.3	10	9.8 ± 2.9	9.8 ± 3.9	0.0 ± -0.7
- Overweight	19	9.5 ± 2.2	8.8 ± 2.3	-0.7 ± 1.0	10	8.8 ± 3.0	11.1 ± 3.0	2.3 ± 1.2

Notes: N, number of subjects; M ± SD, mean ± standard deviation; NA, not available.

Exercise/Physical Activity Program Characteristics

A description of the exercise and physical activity interventions is also shown in Table 1. Four studies used exercise [10-13], defined as planned movement [30], as the intervention, while one used physical activity [9], defined as any bodily movement that increases energy expenditure [30], as the intervention. Three studies used aerobic types of exercise/physical activity as the intervention [9-11], one used progressive resistance training [13] and another used a combination of the two [12]. Two studies reported that the exercise and physical activity interventions were unsupervised [9,11], one reported that the sessions were supervised [12], and another reported that the exercise intervention consisted of both supervised and unsupervised exercise [10]. Length of training ranged from 6 to 24 weeks (M ± SD = 14.1 ± 8.6 weeks) while the frequency of training ranged from 2-5 times per week (M ± SD = 3.8 ± 1.3 times per week). Compliance, defined as the percentage of exercise sessions attended, ranged from 64% to 100% (M ± SD = 84.3 ± 13.0%).

Hcy Outcomes

Data for Hcy for each group from each study is shown in Table 3. Treatment effect changes in Hcy, our primary outcome for this study, are shown in Figure 2. As can be seen, random-effects modeling, which controls for between-study heterogeneity, resulted in a nonsignificant exercise minus control group reduction of approximately 8% in Hcy. This was the result of an approximate 3% decrease in the exercise groups and a 5% increase in the control groups. Similar results were found when data were collapsed across studies versus groups (M, -0.6, 95% CI, -1.4 to 0.3 µmol/L). Using a fixed-effects model, statistically significant heterogeneity was found ($Q = 32.0$, $p < 0.001$; $I^2 = 84.4\%$). When the only statistically significant outcome in overweight/obese adults (M, -3.0, 95% CI, -3.9 to -2.1 µmol/L) was deleted from the model,[13] no statistically significant heterogeneity was observed ($Q = 2.7$, $p = 0.61$; $I^2 = <0.0001\%$) and the pooled results remained non-significant (M, -0.6, 95% CI, -1.4 to 0.3 µmol/L). An examination for publication bias revealed that no such bias existed. Cumulative meta-analysis, ranked by year, consistently resulted in nonsignificant findings, although there has been an increasing trend towards statistical significance as each new study has been added over the years.

DISCUSSION

The overall results of our meta-analysis suggest that exercise and physical activity do not result in statistically significant reductions in Hcy. However, from a clinical perspective, our 0.8 µmol/L reduction in Hcy may be important since a 1.0 µmol/L reduction has been shown to reduce the risk of coronary artery disease by 10% [6]. One of the most interesting findings from our meta-analysis was the fact that the only group in which statistically significant reductions in Hcy occurred was in older, overweight and obese subjects who participated in progressive resistance training [13]. While the authors also found statistically significant reductions in the normal weight group, our weighted results and subsequent 95% confidence intervals did not observe such. Whether our observed changes were a spurious finding or the result of their body weight, type of exercise intervention, the fact that the subjects had probably been sedentary over a long period of time, or some other factor, is not known. One possible explanation may be related to insulin sensitivity. For example, it has been has suggested that since Hcy clearance can be problematic in overweight and obese subjects, particularly those with insulin resistance [31], and that insulin sensitivity is improved as a result of resistance training [32], such improvements may be associated with greater Hcy clearance [13]. For those who are not insulin resistant, reductions in Hcy may be the result of the preservation of muscle amino acids brought about by concentric contractions causing transitory elevations in insulin levels and increased protein synthesis [33]. However, further randomized controlled trials on this topic are warranted before any firm conclusions can be drawn.

While exercise and physical activity should always be recommended because of the numerous cardiovascular and non-cardiovascular benefits that can be derived from such [34], other nonpharmacologic approaches may be more appropriate for lowering Hcy levels. This may include additional intake of such things as folic acid as well as vitamin B_{12} [35]. Additional considerations may include multiple interventions such as exercise and vitamin therapy or exercise and pharmacological therapy.

Meta-analysis, like any other type of review, is limited by the availability of studies and the data reported in those studies. With the former in mind, we offer the following suggestions for future research on this topic. First, only one study included subjects in which the average Hcy levels across all groups was considered elevated [12]. Therefore, it is suggested that future randomized controlled trials focus on subjects with elevated Hcy levels $\geq$ 15 µmol/L since they may derive the greatest benefits [36,37]. Second, since only one study reported complete information on folic acid, vitamin B_6

and vitamin B_{12} intake and these variables may have an important impact on Hcy levels [3], future studies should assess and report such data. Third, given the deleterious effects of overweight and obesity, future randomized controlled trials should focus on representative samples of subjects who are overweight and/or obese. Finally, animal studies may provide important insights into the mechanisms underlying changes in Hcy.

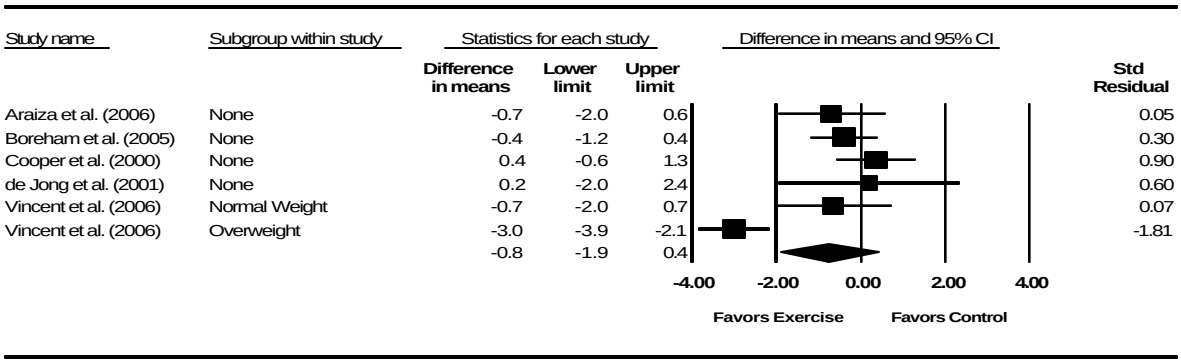

Figure 2. Forest plot for exercise minus control group (treatment effect) changes in Hcy. The black squares represent the point estimates while the lines represent the lower (left) and upper (right) 95% confidence intervals. The size of the black boxes for each outcome represents the weighted mean for that outcome. The overall weighted mean difference is shown by the middle of the diamond while the left and right extremes of the diamond represent the corresponding 95% confidence interval. Std Residual is the standardized residual for each respective outcome.

While the interpretation of our results may be limited because of the heterogeneity of our included studies in terms of such things as population characteristics, age, and type of exercise, it is important to realize that combining studies that are different is the very essence of meta-analysis [38]. However, while we included studies that used different types of exercise interventions across different subject characteristics (age, body weight, etc.), we only included randomized controlled trials because it is the only way to control for confounders that are not known or measured as well as the fact that nonrandomized controlled trials tend to overestimate the effects of healthcare [39,40]. Consequently, we were unable to explore the relationship between selected variables and changes in Hcy because of the small number of studies that met our inclusion criteria. For example, recent research has shown that increased plasma Hcy levels are associated with older age, male gender, cigarette smoking, coffee consumption, high blood pressure, an unfavorable lipid profile, high creatinine levels, impaired renal function, and levels of C-reactive protein [41]. Given these associations, future studies should consider these factors when examining the effects of physical activity and exercise on Hcy. In addition, physical exercise has a different impact on metabolic and hemodynamic parameters based on frequency, intensity, duration, compliance to the exercise protocol, and type of activity performed. In our current meta-analysis, we included both aerobic and/or progressive resistance training studies. However, since aerobic exercise places more of a volume load on the heart and progressive resistance exercise places more of a pressure load [42], the subsequent adaptations that occur as a result of these interventions may have differing effects on Hcy levels. Alternatively, the level of intensity associated with different modes of training may effect changes in Hcy. Thus, it may be that those interventions in which maximum oxygen consumption increased might interact with changes in Hcy. Unfortunately, because of the small number of studies

that met our inclusion criteria, we were unable to examine for these potential covariates as well as other potential covariates such as age, gender, and various co-morbidities. Future studies should consider these factors when designing physical activity and exercise intervention studies aimed at determining their effects on levels of Hcy.

Finally, while the focus of our study was on Hcy and our positive results were limited to overweight/obese adults, it is important to realize that exercise affords cardioprotection in both normal weight as well as overweight and obese adults [43]. For example, elevated levels of myocardial heat shock proteins associated with higher intensity physical activity have been shown to provide myocardial protection against ischemia-reperfusion injury [43].

CONCLUSIONS

Our results suggest that insufficient evidence currently exists to support the role of exercise in lowering Hcy in normal weight adults but that Hcy may be lowered in overweight/obese adults. However, a need exists for additional, well-designed, randomized controlled trials before any definitive recommendations can be made.

Address for correspondence: Kelley, GA, DA, Professor and Director, Meta-Analytic Research Group, School of Medicine, Department of Community Medicine, PO Box 9190, Robert C. Byrd Health Sciences Center, Room 2350-A, West Virginia University, Morgantown, West Virginia, USA 26506-9190. PHONE: 304-293-6279; FAX: 304-293-5891; Email: gkelley@hsc.wvu.edu.

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