REVIEW ARTICLE

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The Effect of Lifestyle Modification and Cardiovascular Risk Factor Reduction on Erectile Dysfunction

A Systematic Review and Meta-analysis

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Background: Erectile dysfunction (ED) shares similar modifiable risks factors with coronary artery disease (CAD). Lifestyle modification that targets CAD risk factors may also lead to improvement in ED. We conducted a systematic review and meta-analysis of randomized controlled trials evaluating the effect of lifestyle interventions and pharmacotherapy for cardiovascular (CV) risk factors on the severity of ED.

Methods: A comprehensive search of multiple electronic databases through August 2010 was conducted using predefined criteria. We included randomized controlled clinical trials with follow-up of at least 6 weeks of lifestyle modification intervention or pharmacotherapy for CV risk factor reduction. Studies were selected by 2 independent reviewers. The main outcome measure of the study is the weighted mean differences in the International Index of Erectile Dysfunction (IIEF-5) score with 95% confidence intervals (CIs) using a random effects model.

Results: A total of 740 participants from 6 clinical trials in 4 countries were identified. Lifestyle modifications and pharmacotherapy for CV risk factors were associated with statistically significant improvement in sexual function (IIEF-5 score): weighted mean difference, 2.66 (95% CI, 1.86-3.47). If the trials with statin intervention (n=143) are excluded, the remaining 4 trials of lifestyle modification interventions (n=597) demonstrate statistically significant improvement in sexual function: weighted mean difference, 2.40 (95% CI, 1.19-3.61).

Conclusion: The results of our study further strengthen the evidence that lifestyle modification and pharmacotherapy for CV risk factors are effective in improving sexual function in men with ED.

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ERECTILE DYSFUNCTION (ED) IS a highly prevalent global health problem with considerable impact on the quality of life of middle-aged men. Erectile dysfunction is defined as consistent inability to attain or maintain a penile erection of sufficient quality to permit satisfactory sexual intercourse.[1] The Massachusetts Male Aging Study (MMAS),[2] the first large community-based observational survey of men aged 40 to 70 years, estimated a 52% prevalence of ED (17.1% mild, 25.2% moderate, and 9.6% severe). In the similar Health Professionals Follow-up Study,[3] moderate to severe ED was reported by 12% of men younger than 59 years; 22% of men aged 60 to 69 years; and 30% of men older than 69 years. Although the MMAS study was primarily based on a white sample, in the absence of any other population-based rates, the rates obtained from the MMAS study were used to estimate the projected worldwide prevalence of ED. The projection for 2025 shows that a prevalence of over 322 million men will have ED, with the largest projected increases in the developing world, ie, Africa, Asia, and South America.[2]

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Erectile dysfunction shares modifiable risks factors with atherosclerosis and coronary artery disease (CAD), including hypertension, diabetes, dyslipidemia, cigarette smoking, obesity, metabolic syndrome, and sedentary behavior.[4-11] Erectile dysfunction has a high prevalence in individuals with multiple cardiovascular (CV) risk fac-

tors and is an independent predictor of CV events and may serve as the sentinel marker for CV disease (CVD).[4,12-14] The evidence supporting the relationship between ED and CVDs has been continuously increasing in recent years.

Lifestyle factor modification such as diet, exercise, and maintaining an active lifestyle in men has shown improvement in ED.[15-18] Cardiovascular risk factor reduction with pharmacotherapy improves CV events as well as ED.[19,20] However, most of the clinical trials on ED are limited by small sample size, being single-center studies in 1 geographic location. To our knowledge, the effect of both lifestyle interventions and pharmacotherapy for CV risk factors on ED improvement has never been extensively studied. Thus, the aim of this work was to perform a systematic review and a meta-analysis of the findings of published original research articles in which the investigators have assessed the effect of lifestyle modification and pharmacotherapy for CV risk factors on ED.

METHODS

DATA SOURCES

A comprehensive search of several computer-assisted databases was conducted (from each database's inception to August 2010, English language, any population). The databases included Ovid MEDLINE, Ovid Medline In-Process & Other Non-Indexed Citations, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials, and Scopus. Computer searches used combinations of medical subject headings or other key words (ie, *impotence*, *erectile dysfunction*, *impotence*, *obesity*, *hyperlipidemia*, *dyslipidemia*, *hypertension*, *diabetes mellitus*, *smoking*, *metabolic syndrome*, and *insulin resistance*). Limiting the searches to randomized controlled trials and similar studies produced a list of 1943 references. In addition, the reference lists of the retrieved articles were reviewed to identify eligible studies. The relevance of studies was assessed with a hierarchical approach on the basis of title, abstract, and the full manuscript.

STUDY SELECTION

Inclusion criteria were randomized controlled trials with follow-up of at least 6 weeks of lifestyle modification or pharmacotherapy for CV risk factors. Erectile dysfunction was measured with the International Index of Erectile Dysfunction (IIEF-5) questionnaire[21] using IIEF-score change as a continuous variable. Exclusion criteria were lack of randomization, lack of control group, and follow-up of less than 6 weeks. Observational studies, review articles, and articles not published in English were also excluded.

QUALITY ASSESSMENT AND DATA EXTRACTION

Study quality was independently assessed (by B.P.G. and M.M.C.) according to the Delphi consensus criteria[22] for quality assessment of randomized clinical trials. The criteria were treatment allocation, similarity of groups at baseline with respect to the most important prognostic indicators, eligibility criteria, blinding (persons giving treatment, patients, care provider, and persons assessing outcome measure), percentage lost to follow-up, measures of variability presented for, and intention-to-treat analysis.

Data were abstracted independently by 2 reviewers (B.P.G. and M.M.C.) who reached consensus on all details. Of the initial 1943 studies extracted through the database search strategy, 27 studies were included on the basis of exclusion criteria. Both reviewers then agreed to exclude 21 of these studies on the basis of following criteria: review/consensus articles (n=7), observational (n=10), no control group (n=2), and no CV risk factor reduction intervention (n=2). Six studies were selected for systematic review and meta-analysis after an agreement was reached between the 2 reviewers. Of the 6 studies, 4 studies analyzed lifestyle intervention, and 2 studies analyzed statin intervention and association with ED. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard[23,24] was followed during all phases of the design and implementation of the present analysis. MOOSE guidelines[25] and QUOROM guidelines[26] were followed. From each trial, demographic data and global risk factors of CV risk factors were recorded.

DATA EXTRACTION

The following characteristics were extracted from the original reports with a standardized data extraction form and included in the meta-analysis: first author, year of publication, design of the study (clinical trial), planned intervention, inclusion criteria, sample size before and after randomization, mean age and demographic information of participants, health status, follow-up duration, and effect size measurements (ie, mean difference). Two investigators (B.P.G. and M.M.C.) collected the relevant reports, while 1 of us (M.M.C.) independently reviewed the published data, and disagreements were resolved by consensus. The outcome of interest was ED score based on the IIEF-5.

STATISTICAL ANALYSIS

Weighted mean differences with 95% confidence intervals (CIs) were calculated using a random effects model for net change in IIEF-5 score. We quantified heterogeneity using the I^2 statistic, which describes the proportion of heterogeneity in results across studies that is not due to chance or random error. And I^2 values less than 25% and greater than 50% reflect small and large heterogeneity, respectively.[27] Clinical trials analyzing lifestyle intervention alone and CV risk factor reduction strategy were analyzed separately. We assessed the heterogeneity in study results by using the I^2 index. We conducted metaregression to determine whether the length of study follow-up affected the changes observed in IIEF-5 score. Publication bias was assessed by the Egger regression test and by visually inspecting funnel plots. Analyses were conducted using Comprehensive Meta-analysis, version 2 (Englewood, New Jersey).

RESULTS

A total of 6 clinical trials from 4 countries were identified that met the inclusion criteria and included 740 participants altogether; the details of the search flow and characteristics of the 6 included studies are summarized in **Table 1** and **Table 2** and **Figures 1**, **2**, **3**, and **4** and in the eTable and eFigure (http://www.archinternmed.com). Overall, the studies seemed to have moderate to good methodologic quality. Of the 6 clinical trials, 2 were conducted in Italy,[15,16] 2 in the United States,[17,20] 1 in Nigeria,[18] and 1 in Iran.[19] The included trials were published between 2004 and 2010. A total of 740 participants were randomized in the 6 clinical trials, of whom 374 were randomized to the intervention arms and 366 to the control arms. The

Table 1. Characteristics of Clinical Trials

Characteristic	Esposito et al,[16] 2004	Esposito et al,[15] 2006	Herrmann et al,[20] 2006	Lamina et al,[18] 2009	Wing et al,[17] 2010	Dadkhah et al,[19] 2010
Country	Italy	Italy	United States	Nigeria	United States	Iran
Study duration	24 mo	24 mo	12 wk	8 wk	12 mo	12 wk
Sample size						
Intervention	55	35	8	25	185	66
Control	55	30	4	25	187	65
Inclusion criteria	Obesity and IIEF-5 score <22	Metabolic syndrome and IIEF-5 score ≤21	IIEF-5 score <16	HTN with ED	DM with ED	IIEF-5 score <21
Planned intervention	Exercise and lifestyle change	Mediterranean diet	Atorvastatin	Interval exercise program	Weight loss	Atorvastatin
Lost to follow up, %	6	0	0	14	17.7	10
Quality score[a]	7	3	6	6	7	9
Age, y	43.5	44.3 (6.4)	58.0 (13.0)	62.1 (5.23)	60.7	63.9
BMI, mean (SD)	36.9 (NA)	27.9 (3.5)	NA	24.2 (3.1)	35.3 (NA)	25.7 (NA)
CAD	Excluded	Excluded	NA	Excluded	NA	Included
Hypertension	Excluded	Included	Included	Included	Excluded	Included
DM	Excluded	Excluded	Excluded	Excluded	Included	Included
Current smoker	Excluded	Excluded	Included	Excluded	NA	Included
Laboratory values, mean (SD), mg/dL						
Total cholesterol	213 (NA)	215 (36)	NA	100.5 (38.7)	183.5 (NA)	159.7 (NA)
Triglycerides	169 (NA)	158 (57)	NA	NA	NA	150.4 (NA)
HDL cholesterol	39 (NA)	39 (6)	NA	NA	39 (NA)	45.2 (NA)
LDL cholesterol	140.2 (NA)	140 (19)	139 (16)	NA	108 (NA)	138.1 (NA)
Glucose	110 (10)	NA	NA	103	70.7 (9.9)	103 (NA)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, coronary artery disease; DM, diabetes mellitus; ED, erectile dysfunction; HDL, high density lipoprotein; HTN, hypertension; IIEF-5, International Index of Erectile Dysfunction[21] score; LDL, low density lipoprotein; NA, not available.

SI conversion factors: To convert all types of cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; glucose to millimoles per liter, multiply by 0.0555.

[a] Nine-point Delphi consensus criteria.[22]

numbers of participants in the trials ranged from 12 to 372. The mean age of the patients was 55.4 years, and the range of study duration was from 12 to 104 weeks. All studies demonstrated improvement in ED with lifestyle changes and improvement in lipid parameters.

Meta-analysis of all 6 trials demonstrated that the improvement in CV risk factors was associated with statistically significant improvement in sexual function (IIEF-5 score): weighted mean difference of 2.66 (95% CI, 1.86-3.47). When the clinical trials[19,20] evaluating pharmacotherapy for CV risk factors were excluded (ie, only trials of lifestyle change interventions pooled), the improvement in sexual function was also statistically significant: weighted mean difference, 2.40 (95% CI, 1.19-3.61). Pharmacotherapy targeting CV risk factors also demonstrated improvement in sexual function, with a statistically significant weighted mean difference of 3.07 (95% CI, 1.84-4.30).

Table 2. IIEF-5 Scores of Clinical Trials Before and After Randomization[a]

Source	Before Randomization		After Randomization	
	Intervention	Control	Intervention	Control
Esposito et al,[16] 2004	13.9 (4.0)	13.5 (4.0)	17.0 (5)	13.6 (4.1)
Esposito et al,[15] 2006	14.4 (3.8)	14.9 (3.7)	18.1 (4.0)	15.2 (3.5)
Herrmann[20] et al, 2006	10.2 (7.4)	4.0 (3.6)	18.0 (0.6)	12.3 (12.4)
Lamina et al,[18] 2009	11.5 (5.3)	8.1 (4.0)	15.1 (4.9)	8.90 (4.0)
Wing et al,[17] 2010	17.3 (7.0)	18.3 (7.6)	18.3 (7.6)	18.4 (8.1)
Dadkhah et al,[19] 2010	10.4 (1.1)	10.1 (2.9)	13.9 (3.7)	10.5 (3.3)
Overall	12.9 (4.8)	11.5 (4.3)	16.7 (5.9)	13.2 (5.9)

Abbreviation: IIEF-5, International Index of Erectile Dysfunction.[21]

[a] All data are reported as mean (SD) IIEF-5 scores.

The heterogeneity for lifestyle changes and pharmacotherapy analysis was minimal (I^2 statistics 14% and 22%, respectively), strengthening the inference and validity of the statistical pooling procedures. In metaregression, the length of study follow-up did not impact the effect size ($P=.22$). There was no evidence of publication bias, but this analysis was severely underpowered, with only 6 trials, and so the conclusions about publication bias are unreliable.

COMMENT

The present systematic review and meta-analysis that includes 6 clinical trials demonstrates the beneficial effect of lifestyle intervention along with CV risk factor reduction on ED. The studies were conducted in various geographical locations with different dietary practices and provide more reliable evidence than previously available

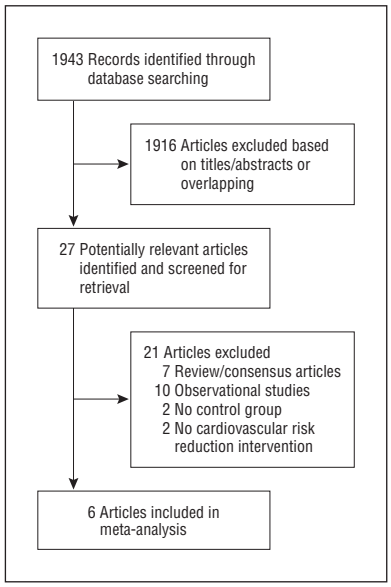

Figure 1. Process of study selection.

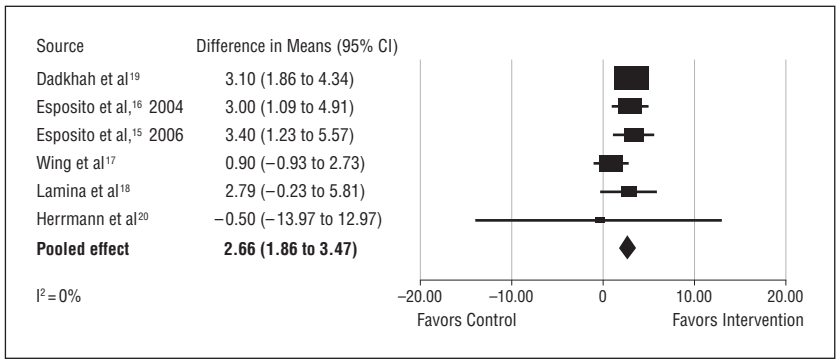

Figure 2. Forest plot shows the standardized difference in means in International Index of Erectile Dysfunction (IIEF-5)[21] score after lifestyle intervention and cardiovascular risk factor reduction.

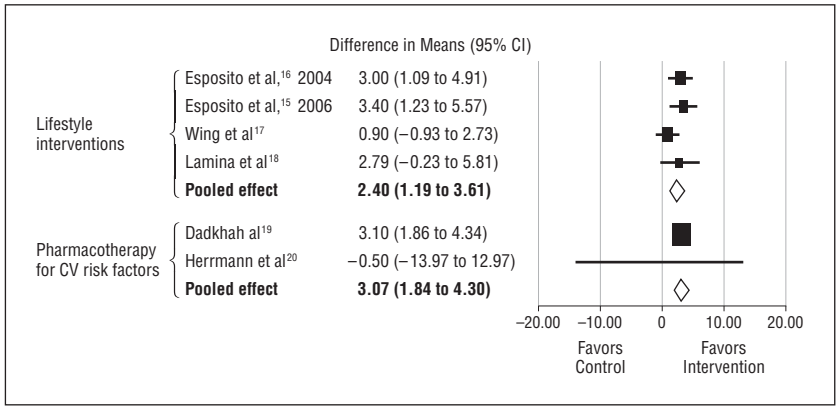

Figure 3. Forest plot shows the standardized difference in means of International Index of Erectile Dysfunction (IIEF-5)[21] score after lifestyle intervention only and pharmacotherapy for cardiovascular (CV) risk factors.

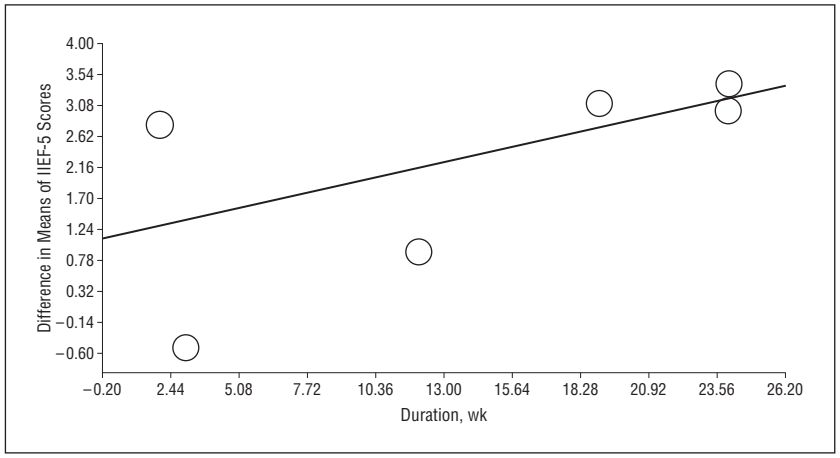

Figure 4. Regression of duration on difference in means of International Index of Erectile Dysfunction (IIEF-5)[21] score for the 6 included studies.

on the effect of lifestyle intervention on ED. To our knowledge, this is the first work that has systematically assessed through meta-analysis the effect of lifestyle interventions and CV risk factor reductions on ED. The results of the present meta-analysis add to and strengthen existing knowledge that healthy dietary habits and increased physical activity are important components of health to improve quality of life in men by improving sexual health.

In our meta-analysis, we identified 6 clinical trials that studied different ethnic populations and evaluated different physiological bases for the intervention. After applying the rigorous inclusion criteria, we pooled the studies and got a larger sample size of 740 to get more robust results. The effect of ED change was measured with the IIEF-5 score, which represents the sum of ordinal responses to 5 items with a minimum score of 5 and maximum score of 25 points (normal erectile function, 22-25; mild ED, 17-21; mild to moderate ED, 12-16; moderate ED, 8-11; and severe ED, ≤7). The results of the 6 trials show improvement in IIEF-5 score by 2.7 points. A separate analysis of clinical trials with lifestyle intervention only and clinical trials with pharmacotherapy targeting CV risk factors only demonstrated pooled IIEF-5 score improvement of 2.4 and 3.1 points, respectively. The minimal clinically important difference (MCID) in the erectile function domain is accepted to be a 4-point improvement in IIEF-5 score.[28] However, the MCID varies significantly according to the baseline ED severity (mild ED, 2.0; moderate ED, 5.0; and severe ED, 7.0 points improvement in IIEF-5 score). Therefore, the results of this analysis regarding the pooled IIEF-5 score improvement of 2.7 points might not translate into clinically important differences for moderate and severe ED. Nevertheless, the overall weighted mean difference of 2.7 in IIEF-5 score improvement is consistent with significant improvement in mild ED and lesser improvement in more advanced ED.

Therapies currently used for the treatment of ED include oral therapy with phosphodiesterase type 5 (PDE-5) inhibitors, which are highly effective in the treatment of ED, showing IIEF-5 score improvements of 7 to 10 points using different classes of PDE-5 inhibitors at maximum doses.[29] However, we demonstrate that CV risk factor reduction improves ED even in men who are not responsive to PDE-5 inhibitors. In our current meta-analysis, 3 of 6 clinical trials (240 men [35%]) demonstrated concurrent use of PDE-5 inhibitors. In a separate meta-analysis of these 3 clinical trials,[17,19,20] lifestyle interventions and pharmacotherapy with statins demonstrated IIEF-5 improvement of 2.1 points (95% CI, 0.22-3.95) (eFigure). Our findings suggest that CV risk factor reduction provides incremental benefits in ED well beyond that achieved with the use of PDE-5 inhibitors. This finding is an important implication in the current clinical practice, where PDE-5 inhibitors are the mainstay of therapy for ED, and many patients may be prescribed PDE-5 inhibitors prior to evaluation of CV risk factors. Adoption of lifestyle modifications and CV risk factor reduction will provide incremental benefit regardless of PDE-5 inhibitor use.

There are several reasons to recognize ED as an early modifiable risk factor for CV disease. There is an average lead time between manifestation of ED and CAD presentation of 2 to 5 years.[30-32] Erectile dysfunction is an early marker of CAD and also an independent risk factor for CV mortality and morbidity.[14,33,34] Sexual health is an important indicator of quality of life for men, and decrease in sexual function may be an early manifestation of developing components of CV risk factors. Men with ED represent a specific population that may be motivated to adapt a healthy lifestyle to improve sexual health. The patients with ED provide an opportunity to screen for CV risk factors. Most men may recognize dysfunction in their sexual health early, in contrast to risk factors for CVD, which are often recognized late after much of the irreversible vascular damage may have occurred. By creating increased awareness that ED may be an early manifestation of underlying cardiac disease, men could seek medical attention early for evaluation of CV risk factors. Increased awareness of ED association with coronary risk factors may provide an opportunity for early identification of risk factors modifiable with lifestyle interventions and thus avoid adverse effects of pharmacologic therapy. Erectile dysfunction detection in the primary health clinic may provide an opportunity for early adoption of a healthy lifestyle to improve the overall health of men.

Several mechanisms may explain the improvement in ED brought about by lifestyle interventions that optimize diet and increase physical activity targeting weight loss. The studies included in our meta-analysis evaluated different pathophysiologic mechanisms for improvement in ED by lifestyle intervention and pharmacologic intervention. The specific role of dietary changes alone was further demonstrated by Esposito et al,[15] who analyzed high consumption of a Mediterranean diet. A diet rich in whole grain, fruits, vegetables, legumes, walnuts, and olive oil was associated with improvement in ED with metabolic syndrome. Subjects who ate a Mediterranean diet demonstrated a mean (SD) increase of 3.0 (0.6-5.2) in IIEF-5 score and improvement in endothelial function and C-reactive protein levels. Reduction in the proinflammatory state and modulation of the cytokine milieu by Mediterranean diet was a possible mechanism in improvement in endothelial function and ED.

Physical activity was significantly inversely associated with ED. Men who ran for nearly 90 minutes per week or did rigorous outdoor activity for 180 minutes per week had a 30% reduced risk of developing ED.[35] Esposito et al[16] demonstrated the beneficial effect on ED by a 4.0-point improvement in IIEF-5 score, amelioration of both endothelial dysfunction and markers of systemic vascular inflammation by weight loss, and increasing physical activity by 114 minutes in a randomized controlled trial of 110 obese men in a 2-year study. However, results of the study were not generalizable owing to the limitations of it being a single-center study that excluded patients with diabetes and involved very frequent contact with study participants resulting in improved compliance. Lamina et al[18] demonstrated improvement in IIEF-5 score by 3.6 points in the exercise group compared with the sedentary group (–0.85) in older patients (aged 50-70 years) with hypertension after 8 weeks of interval exercise. The proposed underlying mechanism for improving ED was reduction in markers for inflammation with regular, long-term physical training and interval training. The study also excluded patients with diabetes and obese patients (body mass index [BMI], >30), therefore limiting generalizability (BMI is calculated as weight in kilograms divided by height in meters squared). Other limiting factors were small sample size (n=50), single-center study, and patients taking methyldopa for hypertension.

In a larger trial, Wing et al[17] examined the effect of weight loss with intensive lifestyle intervention on ED in 372 older patients with type 2 diabetes. The participants were recruited from 5 sites within the United States and randomly assigned to intensive lifestyle intervention (ILI) or to the control group that received diabetes support and education (DSE). The ILI group had close encounters with the researchers to achieve a 7% reduction in weight loss over a 1-year follow-up period. Physical activity was recommended to gradually increase to 175 minutes/wk of moderate activity. The study concluded that weight loss intervention produced small improvements and preservation of erectile function relative to controls. The small improvement in erectile function compared with other studies was owing to the greater impairment of neurogenic and endothelium-mediated relaxation of smooth muscle among the diabetic population, therefore limiting the reversibility of diabetic ED.

The current meta-analysis includes studies that explored the effect of statins on ED. Herrmann et al[20] initially demonstrated a 7.8-point IIEF-5 score improvement after treatment with atorvastatin for 12 weeks in a randomized controlled

placebo trial with a small sample size (n=12) and poor response to sildenafil citrate. The result of the study was also influenced by a single outlier patient in the placebo group who had an increase in IIEF-5 score from 9 to 29.

In a similar analysis, Dadkhah et al[19] undertook a larger study with 131 men with ED who did not respond to sildenafil citrate and who were randomized to 40 mg of atorvastatin vs placebo. After 12 weeks, the total IIEF-5 score improved by 3.5 points along with a 47% reduction in serum level of low-density lipoprotein cholesterol. Atorvastatin effects independent of lipid-lowering effects such as antiproliferative, antithrombotic, and anti-inflammatory activities were the proposed mechanisms for improved endothelial mechanism for added benefit in patients with severe ED.

The present study has certain limitations that warrant consideration. The number of included participants is fairly small, and only 6 studies were included in this review. Publication bias remains a possibility. However, despite the differences across the studies in lifestyle intervention, we found minimal statistical heterogeneity for lifestyle changes and pharmacotherapy analysis (I^2=14% and I^2=22%, respectively), which suggests a similar effect across trials. This consistent effect justifies conducting a meta-analysis, which will increase the precision of the measured treatment effect and produce a pooled estimate with narrower confidence intervals leading to more confidence in the treatment effect.

The duration of the analyzed studies was short, from 8 weeks to 24 months, which limits the evaluation of long-term impact on ED and limits additional implications of lifestyle intervention on CV mortality and morbidity. However, this should not limit the potential importance of lifestyle intervention as a public health policy globally in the light of increasing evidence that a healthy lifestyle is a crucial component for disease prevention, risk factor reduction, and ultimately reduced mortality and morbidity.

The contribution of the current meta-analysis becomes more important in the prevailing epidemic of sedentary lifestyle and obesity. Our study not only points out the paucity of literature in this area, despite ED being a global issue, but also highlights the role of lifestyle changes in perhaps preventing this condition, decreasing the need for pharmaceuticals, and providing the added benefit of CV risk reduction. The strengths of this study include the comprehensive literature search, bias protection measures such as reviewing the duplicate literature review, and the analytical techniques that allowed the pooling of outcomes across 6 randomized controlled trials of good methodologic quality. The trials had wide geographic variety and varying patient characteristics that serve to improve generalizability of inferences. We recognize that more studies are needed to test the various nonpharmacologic and pharmacologic interventions. Our study is an attempt to highlight the need for such large-scale trials. Thus, we hope that in addition to critically appraising the evidence, we have provided an estimate of the effect of lifestyle changes on ED that is as close to the truth as possible (with available data).

In summary, this study further strengthens the evidence of improvement in ED and maintenance of sexual function with lifestyle intervention and CV risk factor reduction. Men with ED provide an opportunity to identify CV risk factors and initiate lifestyle changes. Lifestyle interventions focused on modifiable health behaviors may be a safe strategy to improve ED and reduce CV risk factors.

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