The Effect of Weight Loss on C-Reactive Protein

A Systematic Review

Elizabeth Selvin, PhD, MPH; Nina P. Paynter, MHS; Thomas P. Erlinger, MD, MPH


ABSTRACT

Background  Several studies suggest that weight loss reduces C-reactive protein (CRP) level; however, the consistency and magnitude of this effect has not been well characterized. Our objective was to test the hypothesis that weight loss is directly related to a decline in CRP level.

Data Sources  We searched the Cochrane Controlled Trials Register and MEDLINE databases and conducted hand searches and reviews of bibliographies to identify relevant weight loss intervention studies.

Study Selection  We included all weight loss intervention studies that had at least 1 arm that was a surgical, lifestyle, dietary, and/or exercise intervention. Abstracts were independently selected by 2 reviewers.

Data Extraction  Two reviewers independently abstracted data on the characteristics of each study population, weight loss intervention, and change in weight and CRP level from each arm of all included studies.

Data Synthesis  We analyzed the mean change in CRP level (milligrams per liter) and the mean weight change (kilograms), comparing the preintervention and postintervention values from each arm of 33 included studies using graphical displays of these data and weighted regression analyses to quantify the association.

Results  Weight loss was associated with a decline in CRP level. Across all studies (lifestyle and surgical interventions), we found that for each 1 kg of weight loss, the mean change in CRP level was −0.13 mg/L (weighted Pearson correlation, r = 0.85). The weighted correlation for weight and change in CRP level in the lifestyle interventions alone was 0.30 (slope, 0.06). The association appeared roughly linear.

Conclusion  Our results suggest that weight loss may be an effective nonpharmacologic strategy for lowering CRP level.

INTRODUCTION
**Methods**

C-reactive protein (CRP), a nonspecific marker of inflammation, has been implicated in the pathogenesis of chronic diseases including cardiovascular disease, diabetes, and cancer. One of the most important correlates of CRP is adiposity. Large cross-sectional studies have shown that CRP is highly positively associated with measures of adiposity such as body mass index, waist circumference, and waist-hip ratio. Previous studies suggesting that weight loss can reduce CRP levels have been small and have used different interventions to reduce weight. The following study was undertaken to test the hypothesis that weight loss—whether achieved via diet, exercise, or surgical intervention—is directly related to a decline in CRP level and to characterize the magnitude of the association and possible dose-response relation across a broad range of achieved weight loss.

**STUDY IDENTIFICATION**

To characterize the association between weight loss and CRP level, we undertook a systematic review of weight-loss intervention studies that reported measuring CRP. We searched the Cochran Controlled Trials Register and MEDLINE database from 1966 to March 6, 2006, to identify relevant articles and conducted hand searches of review articles and related references. Included studies had at least 1 arm that was exclusively a surgical, lifestyle, dietary, and/or exercise intervention, and the primary goal must have been to study weight loss. We excluded those articles that had nonhuman or no original data, that did not have weight loss as the primary purpose of the intervention, that did not measure CRP, or that had a nonadult study population (ie, participants were younger than 18 years). We also excluded pharmacologic studies to remove the potential confounding effect of drug therapy on the weight loss–CRP relationship. We classified studies as lifestyle interventions if the weight loss intervention included a dietary and/or behavioral modification component (eg, feeding studies or studies that dispensed advice on how to lose weight) or surgical interventions (eg, gastric banding). We also indicated whether a high-sensitivity CRP (hs-CRP) assay was used.

Our search string identified 1521 articles potentially relevant to our study aim, and all abstracts were retrieved for review (Figure 1). Abstracts were reviewed independently by 2 investigators (E.S. and T.P.E.). Differences were resolved by consensus. There were 83
articles retrieved for full-text review based on information in the abstracts and hand searching. Of these, 39 studies were identified as relevant and were abstracted. Data abstraction was conducted independently by 2 investigators (E.S. and N.P.P.), and discrepancies were adjudicated. We contacted the authors of 13 articles for which the mean change in CRP level and/or weight loss could not be abstracted or derived directly from the data available in the published report (all but 6 responded with the requested data). For those studies with multiple publications using data from the same or overlapping study populations, we only abstracted the results from the publication with the largest study population.

**Figure 1.** Flow diagram of selection of articles for inclusion.

**DATA ABSTRACTION**

Baseline and postintervention weight (in kilograms) and CRP level (in milligrams per liter) were abstracted from each study. A majority of studies reported mean CRP level at baseline and after intervention. Mean change in CRP level from baseline to post–weight loss intervention was abstracted or derived for each intervention arm. Regardless of the distribution of CRP level at baseline (usually right skewed), changes in CRP level from baseline to the end of follow-up would be expected to follow a roughly normal distribution, especially for those studies with a large sample size. For those studies that only reported median CRP level at baseline and median CRP level at follow-up (ie, did not report the mean of the differences) or did not report baseline or follow-up weight, we contacted the authors to obtain these data. Studies by those authors who did not respond to 3 or more requests for data were included in our qualitative analysis but were excluded from the quantitative analyses.

**STATISTICAL ANALYSIS**

To isolate the effect of weight loss on change in CRP level, we analyzed the mean change in CRP level (milligrams per liter) and the mean weight change (kilograms) comparing the preintervention and postintervention values from each arm (if more than 1) from each included study. That is, we analyzed the effect of weight loss on CRP, regarding each arm as a separate data point. We plotted each intervention arm of all studies separately to assess a possible trend in change in CRP level with change in weight. All analyses were weighted by
sample size under the assumption that larger, more precise studies should have greater influence.

We conducted the analyses stratified by type of intervention: lifestyle (diet and/or exercise) or surgical. To graphically display the relation of weight change to change in CRP level, we used scatter (bubble) plots, with each bubble proportional to the number of participants in the intervention arm. The corresponding weighted regressions of weight change on change in CRP level are displayed on each plot.

We conducted sensitivity analyses to assess the relative influence of large studies and certain groups of studies with particular characteristics. Specifically, we examined the leverage of each study with a study arm population of more than 50 persons and the effect of excluding studies with weight loss interventions that included some form of physical activity. Because no studies reported sex-stratified analyses and most study populations were predominantly female, we were unable to adequately assess a possible interaction by sex.

RESULTS

QUALITATIVE ANALYSIS

All eligible studies are included in the Table, including 33 lifestyle intervention studies and 6 studies of surgical weight loss interventions. These studies were a heterogeneous group, representing study populations from Australia, Austria, Canada, Finland, France, Japan, Italy, Spain, England, and the United States. The majority were small studies, ranging from 13 persons per study arm in the smallest to 199 persons per study arm in the largest study. Most studies were conducted in populations of women, and no studies reported sex-specific results. There were only 6 studies that included 50% or larger male populations. Most studies were conducted in middle-aged populations. In the lifestyle intervention studies, the mean age across arms was 49 years (range, 29-69 years). The participants in the surgical intervention studies tended to be slightly younger (mean age, 40 years; range, 38-43 years). The lifestyle interventions tended to be of relatively short duration, with an average follow-up of 7.5 months across arms (range, 0.5-24 months). The mean follow-up for the surgical intervention studies was 13 months (range, 4-24 months). Among the lifestyle intervention studies, the mean achieved weight change across study arms was −6.2 kg (range, −15.0 to 0.0 kg) and the mean change in CRP level was −0.9 mg/L (range, −2.3 to 0.5 mg/L). Among the surgical intervention studies, the mean weight change was −33.1 kg (range, −44.3 to −23.3 kg), and the mean change in CRP level was −4.5 mg/L (range, −6.6 to −2.3 mg/L). In 6 of the studies, we were unable to abstract or derive mean change in CRP level or mean change in weight, and the authors did not respond to repeated requests.
These studies are included in the Table but were excluded from our quantitative analyses.

Our search identified only 2 studies that included information on weight loss resulting from liposuction and change in CRP level. A liposuction intervention study of 30 obese women that reported a mean weight change of $-3$ kg (95% confidence interval [CI], $-4$ to $-2$ kg) after 6 months showed a corresponding $-0.5$ mg/L change (95% CI, $-1.2$ to $-0.2$ mg/L) in CRP level ($P<.02$). A smaller study compared 15 obese women before and 10 to 12 weeks after liposuction and reported the results separately by normal glucose tolerance ($n=8$) or type 2 diabetes mellitus ($n=7$). The mean weight change in the normal glucose tolerance group was $-6.3$ kg (95% CI, $-8.9$ to $-3.7$ kg), and the mean change in CRP level was $-0.2$ mg/L (95% CI, $-1.1$ to 0.8 mg/L). The mean weight change in the group with type 2 diabetes was $-7.9$ kg (95% CI, $-10.2$ to $-5.6$) with a mean change in CRP of $-0.5$ mg/L (95% CI, $-1.3$ to 0.4). It has been postulated that induction of a negative energy balance may be required to affect inflammatory markers; liposuction may not induce the same metabolic changes as exercise or diet-induced weight loss. While these 2 studies suggest that weight loss resulting from liposuction may result in reductions in CRP level, it is difficult to draw firm conclusions because of the small sample sizes. Liposuction interventions were thus excluded from formal quantitative analysis.

**QUANTITATIVE ANALYSIS**

There were 28 lifestyle intervention studies included in our final analysis, contributing 44 observations (1 per intervention arm). Five surgical interventions contributed 1 observation each to the analysis (each study only had 1 intervention arm). The correlation between mean baseline weight and mean baseline CRP level across all studies is shown in Figure 2; the weighted Pearson correlation ($r$) was 0.76 which is consistent with previous studies. Our main results are presented in Figure 3, where the surgical and lifestyle intervention studies are presented on the same scale to show the change in CRP level for each 1-kg change in weight across the spectrum of weight loss observed in our full population of interventions. The slope of the overall regression line was 0.13, indicating that overall, there is a 0.13-mg/L decline in CRP level for each 1 kg of weight loss (weighted $r = 0.85$). The lines representing the slopes for the lifestyle and surgical interventions separately are also included in Figure 3. In the surgical interventions, the slope for the weighted regression line was 0.16, indicating that for each 1-kg change in weight, there was a corresponding 0.16-mg/L change in CRP level (weighted $r = 0.91$). It is important to note that the interpretation of these results is limited by the very small number of surgical intervention studies. Figure 4 also displays the stratified results for the lifestyle (panel A) and surgical interventions (panel B). Figure 5 shows the range of percentage change in CRP level from baseline across categories of percentage weight change from baseline. The category with the largest weight
changes (>16% from baseline) included all the surgical interventions and no lifestyle interventions.

**Figure 2.** Scatterplot of baseline weight and baseline C-reactive protein (CRP) level in lifestyle and surgical interventions. Each observation is the baseline weight and baseline CRP level in each arm of the included lifestyle intervention studies (circles) and surgical intervention studies (squares). The size of the circles is proportional to the sample size. The sample size–weighted Pearson correlation ($r$) is 0.76.

**Figure 3.** Relationship between change in weight and change in C-reactive protein (CRP) level across all weight-loss interventions (lifestyle and surgical). Circles represent lifestyle interventions and squares represent surgical interventions. The size of the marker (circle or square) is proportional to the sample size and corresponds to the weight of the observation in the regression models. The solid line is the weighted regression line across all interventions. The dashed lines are the within-group weighted regression lines. The weighted Pearson correlation ($r$) is 0.85.
Figure 4. Scatterplots of mean change in weight and mean change in C-reactive protein (CRP) level in the lifestyle interventions (A) and surgical interventions (B). Each observation is the weight change from baseline and corresponding change in CRP level in each arm of the included lifestyle intervention studies. The size of the marker (circle or square) is proportional to the sample size and corresponds to the weight of the observation in the regression model. The solid lines are the sample size-weighted regression lines.

Figure 5. Box plots of percentage change in C-reactive protein (CRP) level from baseline over categories of percentage change in weight from baseline across all included weight loss interventions. The whiskers denote 1.5 x IQR (interquartile range). The single outlier (>1.5 x IQR) is indicated by a dot.

In sensitivity analyses, we found that weighted and unweighted analyses were similar, ie, weighting the analyses according to sample size did not appreciably alter our results but probably resulted in a more precise characterization of the change in slope. Restricting our analysis to studies with moderate to small sample size (<50 participants in each arm) also did not alter our results, suggesting no undue influence by the few relatively large studies. The slope for those interventions with an exercise component was 0.14. The slope for those interventions that had no exercise component was 0.02. This result likely reflects that the interventions that included exercise were more likely to have higher weight loss; indeed, there were 4 dietary (no exercise) interventions that had little or no weight change (weight loss <1 kg).

COMMENT
Weight loss was associated with a decline in CRP level across all types of interventions. We found that for each 1 kg of weight loss, the overall mean change in CRP was –0.13 mg/L per 1-kg loss of weight. We modeled the relationship of CRP to weight loss across a range of achieved weights and found that, on average, the largest changes in weight are likely to produce the highest magnitude of change in CRP level. Indeed, the largest changes in CRP level (–5 to –10 mg/L) were observed in those surgical intervention studies that demonstrated the most pronounced weight change (–30 to –45 kg). While there were only 2 studies of liposuction interventions, the patterns observed and magnitude of effect were similar in these reports.

The overall magnitude of effect observed in our study is similar to results from small individual studies that examined possible linear associations between weight loss and change in CRP level resulting from dietary and lifestyle changes in individual participants. There were 3 studies in our review that reported Pearson correlations for the linear relation between change in CRP level and change in weight among the individual participants in the study: Heilbronn et al, in a 3-month study of a very-low-fat diet in obese women in Australia, reported a correlation of 0.27; Tchernof et al, in a small study of 24 obese women who were on a very-low-calorie diet for 14 months, reported a correlation of 0.44; and Dansinger et al, in a low-intensity effectiveness study comparing the popular Atkins, Zone, Weight Watchers, and Ornish diets among a sample of US men and women (n <30 in each intervention arm), reported an overall correlation of 0.37.

Adipose tissue may be directly involved in the production and regulation of inflammatory cytokines that induce CRP production, and it has been suggested that inflammation may represent one of the mechanisms by which lifestyle changes and weight loss reduce the risk of cardiovascular disease. Several findings over the last decade suggest that weight loss could directly lead to reductions in CRP levels. In particular, adipocytes produce cytokines that regulate CRP production. Interleukin 6, a key proinflammatory cytokine and principal regulator of hepatic CRP production, may be particularly important in mediating the increases in CRP levels associated with greater adiposity. Thus, a reduction in body weight is likely to have important consequences for circulating levels of CRP.

We found that intervention studies that achieved weight loss through a variety of approaches were associated with significant reductions in CRP levels. The effect of weight loss on CRP levels in diverse populations across a wide range of achieved weight loss has not been previously quantified. The similar association observed across all types of lifestyle interventions and across surgical studies is consistent with the hypothesis that it is weight loss per se that is driving the change in CRP level. Previous studies have hypothesized that exercise or physical fitness may have a direct effect on CRP independent of any change in weight. While many cross-sectional observational studies have shown associations of physical activity and inflammatory markers including CRP, most exercise intervention studies (without weight loss) have found no association (or associations only in post hoc subgroup analyses). However, because our primary hypothesis was related to weight loss, we did not review studies of exercise interventions that did not also aim to achieve...
reductions in weight. Further studies are needed to fully characterize a possible effect of exercise on CRP level that is independent of weight loss.

By abstracting data from previously published studies, we were able to characterize the continuous relationship between weight loss and CRP and summarize the association in a large, diverse population of individuals. Regardless of the type of intervention imposed, CRP levels declined, on average, when weight loss was achieved. The relation appeared roughly linear.

The present study has several important limitations. Our analysis is essentially an "ecologic" approach because we did not have information on individual participants. In our analyses, we analyzed each intervention arm as a separate data point. While we would expect groups within studies to be more similar than groups across studies, the groups were nonoverlapping, and this does not affect our point estimates. The limitations of this study largely reflect the limitations of the literature, including high rate of loss to follow-up in many weight loss studies, short duration of the studies, and incomplete reporting of data. Publication bias is also a concern. It is possible that weight loss intervention studies that measured CRP and showed significant decreases in both weight and CRP level were more likely to be published than similar studies that did not find significant differences before and after the intervention.

Important strengths of this study include the identification of a large number of studies with heterogeneous populations. Sensitivity analyses allowed us to evaluate the relative influence of individual and subgroups of studies on our estimates. We found that the relationship observed was robust across subgroups analyzed. Most published weight loss intervention studies have been small, and individual results have varied. Summarizing data from many studies allowed us to more precisely estimate the effect of weight loss on change in CRP level compared with any single previous study. In addition, combining results within and across studies allowed us to characterize the relationship between weight loss and CRP across a broad range of achieved weight loss and change in CRP level.

This study demonstrates that weight loss is associated with a decline in CRP level across the range of weight loss interventions. There have been few large, controlled studies that have rigorously assessed the effect of weight loss on CRP level. Our results extend the findings of previous nonsystematic and qualitative reviews of the literature on weight loss and inflammation and suggest that weight loss may be an effective nonpharmacologic strategy for lowering CRP level.

AUTHOR INFORMATION

Correspondence: Elizabeth Selvin, PhD, MPH, Department of Epidemiology and the Welch
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Author Contributions: Dr Selvin and Ms Paynter both had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Selvin and Erlinger. Acquisition of data: Selvin, Paynter, and Erlinger. Analysis and interpretation of data: Selvin, Paynter, and Erlinger. Drafting of the manuscript: Selvin, Paynter, and Erlinger. Critical revision of the manuscript for important intellectual content: Selvin, Paynter, and Erlinger. Statistical analysis: Selvin and Paynter. Study supervision: Erlinger.

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Author Affiliations: Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, and Welch Center for Prevention, Epidemiology, and Clinical Research, The Johns Hopkins University, Baltimore, Md (Dr Selvin and Ms Paynter), and Department of Internal Medicine, University of Texas Medical Research, Austin (Dr Erlinger).

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