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Changes in Cardiovascular Disease Risk Factors with Unintentional Versus Intentional Weight Loss: The Coronary Artery Risk Development in Young Adults Study

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Abstract

Background: It is well known that total and intentional weight loss (IWL) are associated with reductions in cardiovascular disease (CVD) risk factors, however, associations with unintentional weight loss (UWL) have not been studied.
Methods: We examined annual changes in blood pressure and lipids associated with UWL versus IWL in 576 participants from the Coronary Artery Risk Development in Young Adults (CARDIA) study who had lost weight over one of two time intervals (*i.e.*, study years 5–7 or 7–10) and reported whether the weight loss was intentional at the end of the interval.
Results: After adjusting for age, sex, race, and field center, an annual weight loss smaller than 6% resulted in small improvements in lipids that were similar regardless of intentionality. When annual weight loss was ≥6%, UWL was associated with less reduction in total cholesterol (−0.2 vs. −10.4 mg/dL), low-density lipoprotein cholesterol (−3.2 vs. −9.4 mg/dL), and triglycerides (−0.5 vs. −19.0 mg/dL) compared with IWL. Intentionality was not associated with the size of changes in blood pressure (systolic blood pressure: −2.7 vs. −2.0 mmHg; diastolic blood pressure: −2.2 vs. −1.3 mmHg) and high-density lipoprotein cholesterol (3.2 vs. 2.7 mg/dL).
Conclusions: Substantial UWL may be accompanied or preceded by other biological changes in this young adult population that alter changes in CVD risk factors that are associated with IWL.

Keywords: unintentional weight loss, cardiovascular disease, risk factors

Introduction

The 1999–2006 National Health and Nutrition Examination Survey (NHANES) data indicated that ~6.2% of adults had lost weight unintentionally in the previous year. This percentage is similar to earlier findings from the NHANES 1976–1980 data that showed a prevalence of 6.9%.[1] Previous studies have shown that unintentional weight loss (UWL) was significantly associated with a 50% or more increase in the risk of cardiovascular disease (CVD) mortality compared with intentional weight loss (IWL).[2,3] Similarly, our group recently reported that compared with weight maintainers, adults 45–70 years of age who lost ≥3% weight over 3 years and were not dieting were at increased risk of incident coronary heart disease and stroke in the subsequent 3 years of follow-up, whereas those who lost weight and dieting were at a similar disease risk.[4] These studies suggested that UWL and IWL may differ in their associations with risks of CVD morbidity and mortality. To our knowledge, no study has examined changes in

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blood pressure and lipids with UWL compared with IWL in adults.

A large number of weight loss trials have shown that IWL in overweight/obese diabetic and nondiabetic adults results in improvements in CVD risk factors.[5–7] Weinsier et al. has shown that improvement in CVD risk factors appear rapidly when adults are in negative energy balance, and this improvement may be driven as much or more by caloric deficit as by reductions in body weight or body fat.[8] It is possible that both intentional and UWL could result in improvements in risk factors. It could seem counterintuitive that UWL, which is known to be associated with increased CVD mortality, would also be associated with improvement in CVD risk factors. However, it is possible that the negative energy balance that causes UWL could result in improvements in metabolic risk factors that may be inadequate to counteract other factors (such as unhealthy behavior, and underlying disease) that increase CVD mortality. Alternatively, UWL may not improve CVD risk factors to the same extent seen with IWL. This study will address this issue by determining if UWL and IWL are associated with different changes in CVD risk factors.

Methods

Study population

We used data from the Coronary Artery Risk Development in Young Adults (CARDIA) study,[9,10] a cohort study that examines the development of CVD in Black and White adults. The baseline examination was conducted in 1985–1986 with 5,115 participants 18–30 years of age from 4 field centers: Birmingham, AL; Minneapolis, MN; Chicago, IL; and Oakland, CA. In each center, a balanced sample was selected in terms of age, sex, race, and education. We used data from examination years 5, 7, and 10, in which intentionality of weight loss was collected and the time intervals between examinations were relatively short. For each participant, weight change and intentionality were established over two time intervals (*i.e.*, years 5–7 and years 7–10). Henceforth, we refer to the beginning of a time interval as time 1, and the end of a time interval as time 2. The Institutional Review Board (IRB) at each field center approved the study and this analysis was approved by the University of North Carolina at Chapel Hill IRB on research involving human subjects.

Exposures

Weight was measured in light clothing without shoes to the nearest 0.2 pounds using a balance beam scale.[9] Height was measured without shoes to the nearest 0.5 cm using a wall-mounted stadiometer or vertically mounted metal ruler and a metal carpenter's square. In CARDIA years 7 and 10, participants were asked ''at your prior examination, we have that you weighed __ pounds, and at this examination you weigh __ pounds. This represents a change in your weight of __ pounds. Was this weight [gain/loss/stable] intentional?'' For this analysis, participants with a ≥5% reduction in measured weight between time 1 and time 2 (*i.e.*, years 5–7 or years 7–10) were considered to have lost weight.[5] A combination of weight loss and a response of ''yes'' to the intentionality question was defined as IWL, whereas a combination of weight loss and a response of ''no'' was classified as UWL.

Outcomes

Participants were instructed to fast for at least 12 hrs before their clinic examinations at time 1 and time 2.[9] Plasma lipids were determined by the Northwest Lipid Research Laboratory in Seattle at the University of Washington,[9,11] which participated in the Centers for Disease Control and Prevention's lipids standardization program. Total cholesterol and triglycerides were measured enzymatically. High-density lipoprotein cholesterol (HDL-C) was measured by precipitation with dextran sulfate/magnesium chloride. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation[12] only for participants with triglycerides <400 mg/dL. Blood pressure was measured three times at 1-min intervals after a 5-min rest using a Hawksley random zero sphygmomanometer (WA Baum Company, Copiague, NY) on the right arm of a seated participant. The mean of the second and third measures was used for analyses.

Covariates

Age (date of birth), sex, and race were participant reported during the recruitment stage and were confirmed at clinic visits. Education level was based on participant-reported number of years of schooling completed and was categorized as high school or less, some college, or at least college graduate. Smoking status was assessed by self-report and participants were categorized as never smokers, former smokers, or current smokers. Self-reported number of drinks of wine, beer, and liquor consumed per week in the past year was used to calculate daily milliliters of alcohol consumption.[13] Physical activity was evaluated using an interviewer-administered questionnaire that collected the frequency of participation in 13 categories of moderate-to-vigorous exercise during the previous 12 months and expressed in ''exercise units.''[14]

Analytic sample

Approximately 86% ($n = 4\,389$) of the CARDIA participants measured at baseline contributed data for at least one of the two intervals under study [$n = 4\,085$ for interval 1 (*i.e.*, years 5–7), $n = 3\,943$ for interval 2 (*i.e.*, years 7–10)]. Our study focused on 334 participants from interval 1, and 364 participants from interval 2 who were not pregnant, lost 5% or more weight, and had weight measured during the period of study. We excluded participants who were missing intentionality of weight loss ($n = 12$ for interval 1, $n = 32$ for interval 2), missing any relevant CVD risk factor at either time ($n = 21$ for interval 1, $n = 11$ for interval 2), physical activity at time 1 ($n = 3$ for interval 1, $n = 7$ for interval 2), or using medications influencing blood pressure or lipids at time 1 ($n = 11$ for interval 1, $n = 11$ for interval 2). Only two participants reported taking lipid-lowering medications at time 2. We included those two participants in our analyses because inclusion or exclusion of them produced almost identical results. After these exclusions, we found that the majority of participants contributed data to only 1 of the 2 weight loss intervals studied, with just 14 participants eligible to contribute data to both intervals. To avoid within-participant

Table 1. Characteristics of Participants at Time 1

Characteristics	*IWL (n = 293)*	*UWL (n = 283)*
Age at time 1 (years)[a]	31.2 (3.6)	31.3 (3.9)
Male (%)	34.8	43.8
Black (%)	44.4	54.8
Less than high school (%)	28.3	43.5
Current smokers (%)	28.3	40.6
≥10 mL/day alcohol consumption (%)	26.3	38.2
Moderate to vigorous activity score[a]	318 (264)	339 (278)

Participants who lost ≥5% measured weight between time 1 and time 2 (*i.e.*, year 5–7, or year 7–10) were included in the analysis.
[a]Values expressed as mean (SD).
IWL, intentional weight loss; SD, standard deviation; UWL, unintentional weight loss.

correlation, we randomly selected 1 observation from each of those 14 participants for exclusion. The final analytic sample included 576 participants.

Statistical analyses

We used linear regression models to compare the annual change in each CVD risk factor in IWL versus UWL, after adjusting for age at time 1, sex, race, and field center. We also tested the interaction between amount of annual weight change and intentionality for each risk factor. We conducted sensitivity analysis to evaluate the impacts on our results of further adjustment for education level, smoking status, alcohol consumption levels, exercise units, body mass index, cancer status, and diabetic status at time 1, as well as exclusion from the IWL group of those who had bariatric surgery over the study period. When the outcome was blood pressure, use of antihypertensive medications at time 2 was also included as a covariate (antihypertensive use at time 1 was an exclusion criteria). The significance level (α) was set to 0.05. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Table 1 shows the demographic and behavioral characteristics of participants at time 1 in the IWL group and the UWL group. The mean age was 31 years in both groups. The UWL group included a larger proportion of men, Blacks, those who completed less than a high school education, current smokers, and those who consumed ≥10 mL alcohol per day compared with the IWL group. The physical activity score was not very different between the groups stratified by intentionality.

A significant interaction ($P < 0.02$) was detected between annual percent weight loss (continuous variable) and intentionality for annual changes in total cholesterol, LDL-C, and triglycerides, whereas no interaction was detected for other outcomes ($P > 0.1$). Exploratory restricted quadratic splines showed that these interactions appeared to be driven by data from participants with ≥6% annual weight loss. Therefore, we stratified data within intentionality groups into subsets by annual weight loss of <6% and ≥6%.

Table 2 displays weight and CVD risk factors at time 1, and amount of weight loss in the IWL group versus the UWL group, stratified by annual percent weight loss. The UWL group had lower body weight and body mass index at time 1 than the IWL group in both strata. The UWL groups tended to have more favorable levels of lipids compared with the IWL groups, whereas, systolic blood pressure and diastolic blood pressure were very similar between groups. Also, the UWL group lost less weight annually than the IWL group when expressed in kg or percent of body weight. Over the ~2- and 3-year time intervals (study years 5–7 and 7–10), the average annual percent weight loss was 3.5% in the IWL group and 3.1% in the UWL group in the <6% stratum, and 8.0% in the IWL group and 7.8% in the UWL

Table 2. Unadjusted Levels of Weight and Cardiovascular Disease risk Factors at Time 1 and Weight Loss in Groups Defined by Amount and Intentionality of Weight Loss

	Annual weight loss			
	1.3% to <6%		*≥6%*	
Weight or CVD risk factor	*IWL (n = 259)*	*UWL (n = 266)*	*IWL (n = 34)*	*UWL (n = 17)*
Time 1				
Weight (kg)	84.3 (18.5)	74.9 (17.4)[a]	96.5 (21.8)	74.8 (13.3)[a]
Body mass index (kg/m^2)	29.3 (6.1)	25.7 (5.3)[a]	33.7 (6.6)	26.7 (4.7)[a]
Systolic blood pressure (mmHg)	108.9 (11.0)	108.5 (11.9)	109.8 (11.7)	110.9 (11.2)
Diastolic blood pressure (mmHg)	70.0 (9.5)	69.7 (10.8)	69.0 (9.4)	71.2 (9.5)
Total cholesterol (mg/dL)	183.9 (34.6)	179.6 (34.6)	181.4 (26.4)	177.5 (26.7)
LDL-C (mg/dL)	114.8 (31.8)	107.7 (33.1)[a]	115.5 (24.2)	103.5 (27.9)
Triglycerides (mg/dL)	91.2 (56.5)	86.5 (50.3)	94.9 (74.1)	91.9 (52.1)
HDL-C (mg/dL)	50.3 (12.8)	54.1 (16.5)[a]	46.4 (12.3)	55.1 (10.8)[a]
Annual percent weight loss	−3.5 (1.1)	−3.1 (1.1)[a]	−8.0 (2.2)	−7.8 (1.6)
Annual absolute weight loss (kg)	−2.9 (1.2)	−2.3 (1.0)[a]	−7.9 (3.7)	−5.8 (1.4)[a]

Participants who lost ≥5% measured weight between time 1 and time 2 (*i.e.*, year 5–7, or year 7–10) were included in the analysis. Values were expressed as mean (SD). Body mass index was calculated as weight in kilograms divided by height in meters squared. Annual weight loss was calculated as (weight at time 2 − weight at time 1)/years between time 1 and time 2. Annual percent weight loss was calculated as annual weight loss divided by weight at time 1.
[a]Significantly different at a significance level of 0.05 level between IWL and UWL by annual weight loss category.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

group in the ≥6% stratum. Absolute annualized weight loss was significantly greater in the IWL group (−7.9 kg) than in the UWL group (−5.8 kg) in the ≥6% stratum.

Figure 1 shows annual changes in CVD risk factors in the IWL group and the UWL group, stratified by annual percent weight loss, adjusted for age at time 1, sex, race, and field center. Among participants who lost less than 6% of weight annually, there was little change in blood pressure, but lipid levels declined for total cholesterol, LDL-C, and triglycerides, and increased for HDL-C. Intentionality of weight loss was not associated with changes in any of the risk factors examined. In contrast, among those with annual weight loss ≥6%, the UWL group experienced smaller declines in total cholesterol, LDL-C, and triglycerides compared with the IWL group. Changes in systolic blood pressure, diastolic blood pressure, and HDL-C were similar by intentionality. All these results were essentially unchanged after additionally adjusting for education level, smoking status, alcohol consumption levels, exercise units, body mass index, cancer status, and diabetic status at time 1. Further adjustment for annual percent or kilograms of weight loss did not result in substantial changes in the results as well. Finally, exclusion from the IWL group of the two participants who had bariatric surgery over the study period essentially had no influence on the results.

Discussion

Our analyses of cohort data from young adults showed that for the majority of participants who lost weight, IWL and UWL were associated with similar improvements in CVD risk factors. However, UWL was associated with less favorable improvements in some risk factors when the annual weight loss was 6% or more (averaging 8% per year). Due to more detrimental levels in some risk factors in the IWL group compared with the UWL group at time 1, regression to the mean could contribute to the differences in improvements in those risk factors. But the role of regression to the mean is unlikely to be primary because no significant differences in improvements between groups were found in the smaller weight loss stratum. In this young population only 10% of our observations in the UWL group had an average annual weight loss that was as large as 6%. It is fair to view this amount of UWL as uncommon in young adults, but nevertheless, worthy of consideration.

Our observational, longitudinal study design allowed for examination of simultaneous changes in weight and changes in risk factors, but it did not allow establishment of causality. It is possible that the differences seen between intentional and unintentional weight change in this study were not related to intentionality *per se*, but to unmeasured factors that differed between intentional and unintentional weight losers. An unmeasured disease condition could be the root cause of changes in risk factors as well as the cause of UWL, with the associations seen here between UWL and CVD risk factors only correlational.

UWL is generally recognized to be caused by loss of appetite related to impending disease or existing disease. Unhealthy lifestyles and psychological stress could also cause UWL.[15] Underlying causes of UWL could influence CVD risk factors directly and indirectly. For example, smoking can suppress appetite and cause negative energy balance. The latter can further result in UWL and decreases

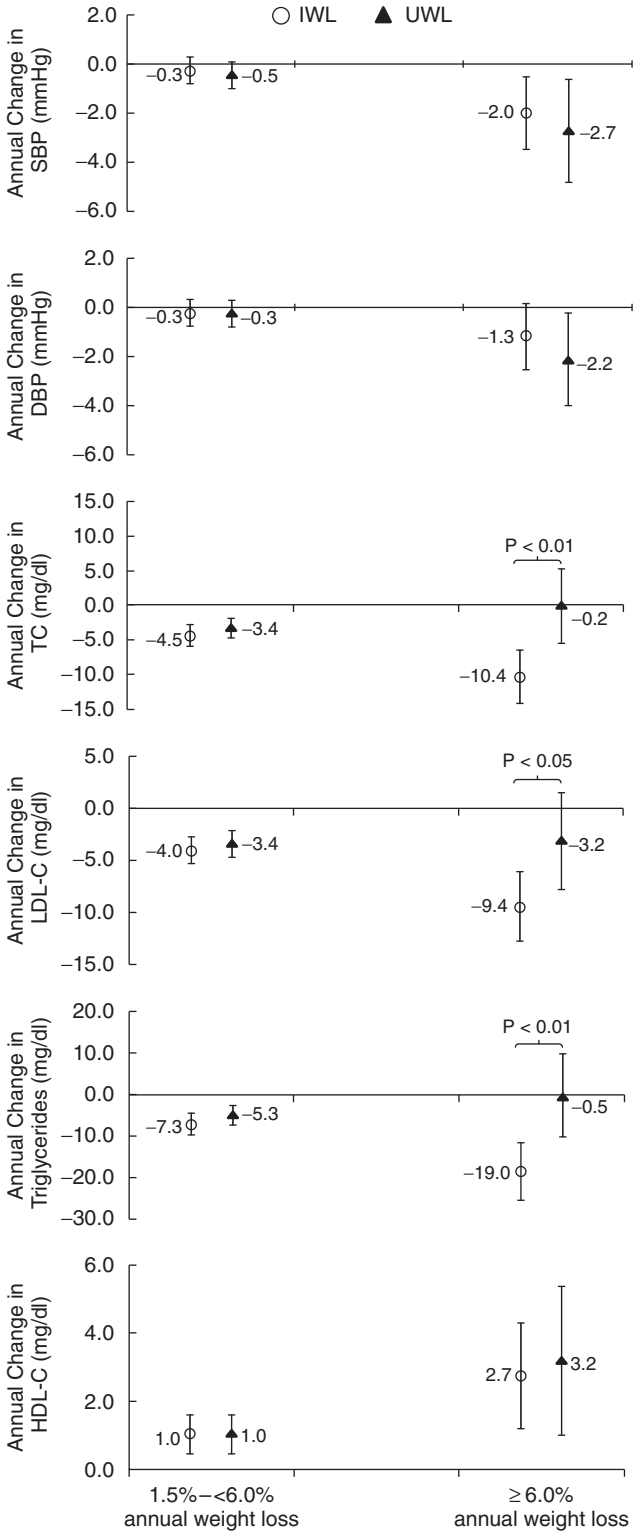

FIG. 1. Comparison of annual changes in cardiovascular disease risk factors between IWL and UWL stratified at 6% of annual weight loss. Participants who lost ≥5% measured weight between time 1 and time 2 (*i.e.*, year 5–7, or year 7–10) were included in the analysis. Values were adjusted for age at time 1, sex, race, field center. IWL, intentional weight loss; UWL, unintentional weight loss; TC, total cholesterol; DBP, diastolic blood pressure; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

in CVD risk factors.[16] On the other hand, smoking can result in increase in CVD risk factors through other pathways.[17,18] The change in a CVD risk factor is the net effect of the direct and the indirect influences of smoking. In our study, a 6% or more annual weight loss may indicate that the underlying causes of UWL were more severe than were the causes of UWL of less weight. Thus, those severe causes had relatively strong associations with CVD risk factors, including deleterious changes (*i.e.*, direct influence) in total cholesterol, LDL-C, and triglycerides. In contrast, the underlying cause of negative energy balance, that is IWL, could be dieting and/or increased physical activity that may improve CVD risk factors. As a result, the declines in those CVD risk factors associated with UWL were smaller than the decreases associated with IWL. Therefore, a large magnitude of UWL could be used as an indicator for early detection of severe underlying causes.

Our study found that UWL was associated with some favorable changes in CVD risk factors, and previous studies have shown that weight maintenance was associated with detrimental[19–21] or no[22] changes in those risk factors. Thus, it is reasonable to speculate that UWL is associated with more favorable changes in CVD risk factors compared with weight maintenance. This is inconsistent with previous studies that UWL is associated with similar[23] or increased[2–4] risk of CVD compared with weight maintenance. There are several possible explanations. One is analogous to the direct and indirect effects of underlying causes of UWL. Direct effects of underlying causes of UWL on CVD mortality could counteract or outweigh the indirect beneficial effect of weight loss on CVD risk through risk factor changes. Another possible explanation is that weight loss might have not been maintained. Analysis of participant-reported data from 1999 to 2006 NHANES data indicated that among American adults who had ever been overweight or obese, the proportion having maintained ≥5% weight loss for 1 year or longer was 36.6%.[24] However, this study did not distinguish IWL and UWL.

Many previous cohort studies examined changes in CVD risk factors associated with weight loss. However, due to lack of information on intentionality, those studies did not distinguish IWL and UWL and found that total weight loss was associated with improvements in those risk factors. Our findings suggest that when annual weight loss is less than 6%, the use of total weight loss may not reduce the validity of the results in young adults. In contrast, when annual weight loss is 6% or more, the use of total weight loss may underestimate the extent of the decreases in several risk factors. Since those who annually lost ≥6% of weight unintentionally only account for 3% of weight losers in our sample of relatively healthy young adults, inclusion of UWL may have little impact on the results. In our study, the initial CVD risk factors in the UWL group were slightly more favorable than those risk factors in the IWL group. Previous studies conducted in adults ≥45 years of age found that the UWL group was more likely to report poor health status compared with the IWL group.[2,25] It is likely that the underlying causes of UWL in healthy young adults are different from causes in adults who are older or poorer in health. Further study is needed to examine whether our results remain true in those who are older or poorer in health.

Use of data collected with strict quality control is a strength of our study. Furthermore, most previous studies have been conducted in adults ≥40 years of age.[2,23,26–29] Ours is among the first studies of UWL in young adults. Our study has limitations. The cutpoint of 6% annual weight loss used in this study to form subgroups was data driven because there is a dearth of information on which to base an *a priori* cutpoint. We admit this cutpoint may not have generalizability to other cohorts. The sample size for those who annually lost ≥6% of weight was small, however, statistically significant associations were found for some risk factors. Weight was measured in 2- to 3-year intervals and mathematically converted to annual change. Changes assessed annually may have been somewhat different. Furthermore, the causes of UWL were not studied here, and need to be examined in future work. Finally, intentionality was participant reported and not free of recall bias. Nevertheless, self-report is likely to be the best available method to measure intentionality in observational studies.

Our study is the first to examine the association of UWL with changes in CVD risk factors. We found that in young adults, unintentional loss of a moderate amount of weight improves CVD risk factors to an extent similar to that seen with IWL. It was only with relatively large amounts of annual weight loss that differences between UWL and IWL emerged. It remains to be seen whether a similar phenomenon would be found in middle aged and older adults. Underlying causes that result in a large amount of UWL could partially counteract the effect of negative energy balance on total cholesterol, LDL-C, and triglycerides. Thus, investigators should consider distinguishing IWL and UWL in observational studies that examine causes and consequences of weight loss, especially when weight loss is large.

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Author Disclosure Statement

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