Original Article
CLINICAL TRIALS: BEHAVIOR, PHARMACOTHERAPY, DEVICES, SURGERY

Obesity

Influence of a Clinical Lifestyle-Based Weight Loss Program on the Metabolic Risk Profile of Metabolically Normal and Abnormal Obese Adults

Rebecca H. Liu[1], Sean Wharton[1,2], Arya M. Sharma[3], Chris I. Ardern[1] and Jennifer L. Kuk[1]

Objective: It is unclear whether all obese individuals should be prescribed weight loss (WL) treatment. The effect of a clinically significant WL of 5% on metabolic factors among metabolically normal and abnormal overweight and obese (MNO and MAO) individuals was examined.
Design and Methods: The sample included 392 overweight and obese adults from the Wharton Medical Clinic. MAO was defined as having one or more clinically relevant aberrations in glucose, triglycerides, blood pressure (BP), high-density lipoprotein-C, low-density lipoprotein-C, preexisting, or current medication use for metabolic conditions.
Results: Of the 392 patients, 21.2% of the sample was MNO at baseline and 41.3% of the sample attained a 5% WL. Regardless of initial metabolic health status, improvements in most risk factors were observed with a 5% WL in comparison with those who did not lose weight. Even MAO patients who did not achieve a 5% WL still significantly improved BP and cholesterol over the treatment period.
Conclusions: A clinically significant WL is beneficial for the cardiometabolic risk profile of both MNO and MAO. However, a 5% WL is not necessarily required to improve the cardiometabolic risk profile of MAO. Thus, lifestyle-based WL provides beneficial metabolic effects for all overweight and obese individuals, particularly those with significant metabolic aberrations.

Obesity (2013) **21**, 1533-1539. doi:10.1002/oby.20219

Introduction

There has been a growing literature suggesting the presence of a subgroup of obese individuals whom appear to be protected against metabolic and cardiovascular complications, despite having excessive levels of body fat (1-4). These metabolically normal, yet obese (MNOB) individuals exhibit normal blood pressure (BP), high levels of insulin sensitivity, normal blood glucose, and a favorable lipid profile (4,5). Current guidelines for obesity management recommend weight loss (WL) for all obese individuals and overweight individuals with comorbidities. It has been well-established that a 5-10% reduction of initial body weight (BW) can improve metabolic health in metabolically abnormal obese (MAOB) (6-8), however, whether or not WL can further benefit the healthy profile of metabolically normal overweight or obese (MNO) remains unclear. The few studies that have examined the effects of WL in MNOB and MAOB report conflicting results (9-12). Most of the studies reported no measurable effect in the cardiometabolic risk profile of MNOB, whereas one study reported a deterioration in insulin sensitivity following a 10% BW reduction in MNOB subjects (12). As a result, the appropriateness of a prescription of WL for overweight and obese individuals without metabolic risk factors remains controversial, and further research is warranted. Therefore, the purpose of this study was to examine the differential effects of WL on the cardiometabolic risk profile among metabolically normal and abnormal overweight and obese individuals.

Methods and Procedures

Study population and database

We evaluated 392 overweight and obese adults (age 18-88 years) attending the Wharton Medical Clinic (WMC), which is a referral-based specialist clinic designed to educate overweight and obese patients about weight management, and enables patients to implement strategies to improve their health. It operates according to the principles outlined in the National Institutes of Health Clinical Guidelines on the Identification, Evaluation, and Treatment of

[1] School of Kinesiology and Health Science, York University, Toronto, ON, Canada. Correspondence: Jennifer L. Kuk (jennkuk@yorku.ca) [2] The Wharton Medical Clinic, Hamilton, ON, Canada [3] Department of Medicine, University of Alberta, Edmonton, AB, Canada

This research was funded by an industry grant by the Mitacs-Accelerate internship program in partnership with the Wharton Medical Clinic.
Disclosure: R.H.L. held a 6-month internship at WMC, Dr. S.W. is the Medical Director, Drs. J.L.K. and C.I.A. held a research grant from the Mitacs-Accelerate and WMC. Dr. A.M.S. has nothing to declare.
Received: 30 April 2012 **Accepted:** 16 November 2012 **Published online 17 January 2013. doi:10.1002/oby.20219**

Overweight and Obesity in Adults (13) and the Canadian Clinical Practice Guidelines for the Treatment of Obesity (6). All patients require family or specialist physician referral to participate in the weight management program. The clinic operates within the Ontario Health Insurance Plan and all services including physician visits, nutritional consultations, exercise prescription, diagnostic testing, standard and indicated blood work, and educational group sessions are provided at no charge to the patient. A sample of 8,579 men and women patients initiating weight management treatment at the WMC between 2008 and 2012 were recruited from three clinical centers located in Hamilton, Burlington and Halton, Ontario consented to be included in this research study. Those who had bariatric surgery ($n = 50$), were <18 years ($n = 5$), had a BMI <25.0 kg/m^2 ($n = 11$) and who attended the clinic for less than 3 months or had less than 3 visits to the clinic ($n = 3,789$) were excluded from the analyses. Individuals with missing BMI ($n = 40$) and who did not have repeat measures of all metabolic parameters (fasting plasma glucose [FPG], triglycerides [TG], BP [systolic-BP and diastolic-BP], high-density lipoprotein-C [HDL-C], low-density lipoprotein-C [LDL-C]) ($n = 4,283$) were also excluded. Patients with extreme values of weight change (<1 percentile or >99 percentile) were considered outliers and excluded from the analyses ($n = 9$) leaving a final sample size of 392 men and women. Due to an error the incorrect informed consent form was used, but written consent was provided for the use of their medical data for research purposes. Patients were informed that their participation would not alter treatment and that they could withdraw consent at any time without influencing their treatment. Access to participants and medical data was facilitated by a research collaboration between WMC and York University. The York University Institutional Review Board approved the study protocols used.

WMC program protocol

At the initial visit, patients completed a comprehensive medical history questionnaire, which included demographics, education level, ethnicity, household income, medications in use, family history, health conditions, health behaviors, and WL history. Trained personnel manually measured patients' BP, height using a wall mounted tape measure (McArthur Medical Sales, Inc., ON) to the nearest 0.1 cm, and BW with MedWeigh MS-2510 Digital High Capacity Platform Scales (Itin Scale Co, Inc., NY) to the nearest 0.1 kg. Thereafter, patients attended an introductory educational workshop that explained the WMC weight management program and the dietary intervention. Afterwards, bariatric educators (BE) provided one-on-one education on nutrition and weight management support by discussing weight goals with patients, educating them on meal planning and implementation, and encouraging resistance and aerobic exercises in their lifestyle under the guidance of a physician. A medical doctor (MD) examined the patient, reviewed the patients' BP results and medical history for obesity-related complications, such as diabetes and sleep apnea, and prescribed medication, if required.

At the second visit, a calorie restricted meal plan of approximately 500-1,000 calories below the patient's baseline daily caloric needs was administered using a calculated RMR (14,15). The measured RMR was performed by indirect calorimetry, using the CardioCoach metabolic cart (Korr Medical Technologies, Inc., UT), using standardized testing procedures. The measured and calculated RMR were used to prescribe the individualized meal plan caloric targets, and RMR measures were repeated at the physician's discretion. The rationale and explanation of the meal plan recommendations were provided in a second educational workshop.

Between the initial and third visit, patients underwent standard blood work, cardiac testing, exercise stress testing, and indirect calorimetry, in no particular order, as indicated by the physician. Blood work was performed at certified medical laboratories using standard procedures and repeated at the discretion of the MD. A baseline electrocardiogram used to assess heart function at rest and during an exercise stress test was completed in most patients. An exercise stress test, when indicated, was ordered prior to any physical activity recommendations to assess cardiorespiratory fitness so that patients could be provided tailored exercise advice and/or to identify those at risk of cardiovascular events with physical activity. At the third visit, a MD reviewed the patients' diagnostic test results to determine other health conditions or reasons for weight issues and to determine if specific testing needed to be repeated or if other testing was required.

At each visit, patients' BP and BW were measured and they attended a lifestyle intervention-related workshop. In addition, patients met with the MD and BE to review medications and to follow-up on any previous or current health conditions, WL progress, exercise regime, and prescribed meal plan. Furthermore, patients were encouraged to perform additional weekly self weigh-ins and to attend additional health education sessions administered by MDs, dietitians, behavioral therapist, and exercise specialists. Approximately, 20 educational sessions on various weight management topics were offered each month.

Data collection

Age, sex, treatment duration, medication use (type 2 diabetes, BP, lipid) and a self-reported physician diagnosis of type 2 diabetes, hypertension and hyperlipidemia were retrieved from patient electronic charts. Anthropometrics measured at baseline were used to calculate BMI as weight in kilograms (kg) per meter (m) squared. At each visit, BW was assessed to track weight changes. Percent weight reduction was calculated using the following equation: [((initial BW - final BW)/initial BW) $\times$ 100]. A clinically significant WL was defined as a 5% and 10% reduction in initial BW.

Definition of metabolically normal and abnormal overweight and obese

The criteria used to define MAO were as follows: fulfilling one or more of the risk factor sets (1) FPG $\geq$7.0 mmol/l (16), doctor diagnosed type 2 diabetes, or medications used to treat high FPG; (2) TG $\geq$2.26 mmol/l (17), doctor diagnosed hyperlipidemia, or medications used to treat high TG; (3) BP: systolic BP $\geq$140 mmHg, diastolic BP $\geq$90 mmHg (18), doctor diagnosed hypertension, or medications used to treat high BP; (4) HDL-C <1.04 mmol/l (17); (5) LDL-C $\geq$4.14 mmol/l (17). Otherwise if none of the risk factor sets were present, the patient was categorized as MNO.

Statistical analyses

Patient characteristics and baseline metabolic variables were presented as means $\pm$ SD stratified by whether a clinically significant WL was attained ($\geq$5% vs. <5%) and health status (MNO and MAO). Group differences in participant characteristics and baseline metabolic values were assessed using an analysis of variance for

TABLE 1 Baseline WMC patient characteristics stratified by 5% WL and metabolic health status

Sample characteristics ($N = 392$)	No 5% WL		5% WL	
	MNO	MAO	MNO	MAO
Prevalence *n* (%)	49 (12.5%)	181 (46.2%)	34 (8.7%)	128 (32.6%)
Age (years)	43.7 ± 9.8	54.7 ± 11.6[a]	52.7 ± 13.7[b]	46.0 ± 12.2
Weight (kg)	102.2 ± 19.4	115.0 ± 27.0[a]	106.6 ± 17.7	112.4 ± 24.5
BMI (kg/m^2)	37.5 ± 6.6	41.2 ± 7.8[a]	39.2 ± 6.1	41.1 ± 7.6
Waist circumference (cm)	111.7 ± 18.9	123.1 ± 17.0[a]	115.3 ± 12.2	120.2 ± 16.4
Treatment time (months)	10.5 ± 9.0	13.6 ± 9.4[a]	16.6 ± 8.6[b]	14.5 ± 7.8
Number of visits	10.4 ± 5.8	14.0 ± 9.9[a]	18.8 ± 12.6[b]	17.0 ± 10.2[c]
Weight loss (kg)	−0.2 ± 3.4	−1.1 ± 3.1	−10.1 ± 4.6[b]	−11.4 ± 5.6[c,d]
Percent weight loss	−0.1 ± 3.3	−0.9 ± 2.7	−9.7 ± 4.8[b]	−10.3 ± 4.8[c]
Baseline metabolic values				
FPG (mmol/l)	5.2 ± 0.6	6.1 ± 1.4[a]	5.2 ± 0.4	6.1 ± 1.5[d]
TG (mmol/l)	1.12 ± 0.47	1.62 ± 0.68[a]	1.14 ± 0.42	1.65 ± 0.81[d]
SBP (mmHg)	118 ± 11	133 ± 14[a]	123 ± 7[b]	134 ± 14[d]
DBP (mmHg)	74 ± 7	79 ± 10[a]	76 ± 7	81 ± 9[c,d]
HDL-C (mmol/l)	1.35 ± 0.25	1.20 ± 0.31[a]	1.42 ± 0.24	1.25 ± 0.35[b]
LDL-C (mmol/l)	2.94 ± 0.59	2.80 ± 1.02	2.97 ± 0.68	2.80 ± 0.97
Sex				
Female	47 (95.9%)	135 (74.6%)	30 (88.2%)	100 (78.1%)
Male	2 (4.1%)	46 (25.4%)	4 (11.8%)	28 (21.9%)

Data presented as the group means ± SD and prevalence (%).
DBP, diastolic blood pressure; FPG, fasting plasma glucose; MAO, metabolically abnormal overweight and obese; MNO, metabolically normal overweight and obese; SBP, systolic blood pressure; TG, triglyceride; WL, weight loss.
[a]Difference by metabolic status within no 5% WL, $P < 0.05$.
[b]Difference by 5% WL within MNO, $P < 0.05$.
[c]Difference by 5% WL within MAO, $P < 0.05$.
[d]Difference by metabolic status within 5% WL, $P < 0.05$.

continuous variables and chi-square tests for categorical variables. Paired *t*-tests were conducted to examine differences from baseline to final visit in metabolic risk, within each metabolic health status by WL group. Thereafter, a repeated measures analysis of covariance was conducted to examine differences by 5% WL within each metabolic risk strata while considering age, sex, BMI, treatment time, and each respective baseline measure (FPG, TG, systolic BP, diastolic BP, HDL-C, or LDL-C). There was no significant WL × sex interaction. Therefore, analyses were collapsed across men and women.

The likelihood of having MNO status or developing an additional metabolic risk factor at follow-up in individuals who did and did not achieve a 5% WL was examined using multivariable logistic regression, with and without adjustment for age, sex, BMI, treatment duration, and the number of metabolic risk factors at baseline. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC).

Results

Sample characteristics

Briefly, the study sample was predominantly female (80%; $n = 312$), middle age (53.6 ± 12.3 years) and class 3 obese (BMI = 40.5 ± 7.6 kg/m^2). On average, patients attended the clinic for 13.8 ± 8.9 months and made 15.0 ± 10.1 visits. About a fifth of the sample (21%; $n = 83$) was MNO at baseline, and more than a third of the sample attained a 5% WL (41.5%; $n = 163$). Among the MNO patients at baseline, only 7 (8%) were overweight and only 14 (4%) of MAO patients at baseline were overweight. Participant characteristics at baseline, stratified by whether they attained a 5% WL are shown in Table 1. Among patients who did not have a 5% WL, MNO patients were younger, weighed less at baseline, had a smaller waist circumference and attended the clinic for a shorter duration in comparison with MAO patients ($P < 0.05$). MNO patients who attained a 5% WL were older, attended and visited the clinic more often and had a higher baseline systolic BP in comparison with MNO who did not lose 5% of their BW ($P < 0.05$). MAO patients with a 5% WL had a higher baseline diastolic BP than MAO who did not attain a 5% WL ($P < 0.05$).

Metabolic health profile and a clinically significant WL

When using clinical cutoffs, 21.2% ($n = 83$) of patients had zero risk factors at baseline and 53.6% ($n = 210$) had zero risk factors at follow-up (Figure 1). Comparatively, when using sub-clinical cutoffs (FPG ≥5.6 mmol/l; TG ≥1.69 mmol/l; BP: systolic BP ≥130 mmHg, diastolic BP ≥80 mmHg; HDL-C: men <1.04 mmol/l, women <1.29 mmol/l; LDL-C ≥3.37 mmol/l), the prevalence of MNO with zero

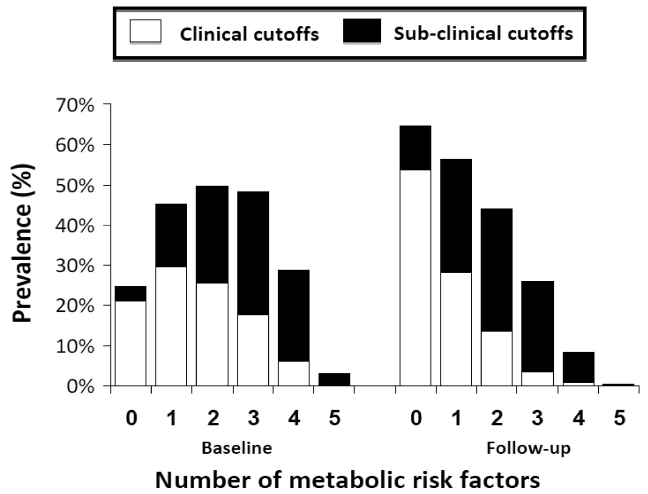

FIGURE 1 Prevalence of number of metabolic risk factors at baseline and following treatment.

risk factors was only 3.6% (n = 14) of patients at baseline and increased to 11.2% (n = 44) of patients following treatment.

Attaining a 5% WL was not associated with a significantly different risk of attaining a MNO status following treatment compared with those who did not attain a 5% WL ($P > 0.05$; Table 2). However, patients with a 5% WL were 35% less likely to develop an additional metabolic factor at follow-up (unadjusted OR = 0.65, 0.44-0.96) as compared with those who did not lose weight. This association remained significant after adjusting for age, sex, BMI, treatment time, and the number of high risk factors at baseline (OR = 0.65, 0.42-1.00, $P = 0.05$). Similar results of attaining MNO status and developing an additional risk factor at follow-up with a 5% WL were observed when only MAO at baseline were considered (data not shown).

Cardiometabolic risk factors with and without a clinically significant WL

Both MNO and MAO patients who attained a 5% WL, significantly improved most of their metabolic risk factors from baseline to final visit, particularly MAO ($P < 0.05$; Figure 2). MAO patients who did not achieve a clinically significant WL improved systolic BP, HDL-C, and LDL-C with treatment ($P < 0.05$). Conversely, MNO patients who did not achieve a clinically significant WL observed an increase in their TG levels with treatment ($P < 0.05$). MNO patients with a 5% WL had a significantly greater improvement in TG (5% WL: -0.03 ± 0.07 vs. 0.14 ± 0.07 mmol/l, $P < 0.01$) and HDL-C (5% WL: 0.08 ± 0.03 vs. -0.015 ± 0.03 mmol/l, $P < 0.01$) than MNO patients who did not lose weight even after adjusting for age, sex, BMI, treatment time, and each respective baseline measure (FPG, TG, BP, HDL-C, or LDL-C). In the adjusted model, MAO individuals with a 5% WL had a significantly greater improvement in FPG (5% WL: -0.16 ± 0.09 vs. 0.07 ± 0.09 mmol/l, $P = 0.04$), TG (5% WL: -0.19 ± 0.05 vs. -0.02 ± 0.05 mmol/l, $P = 0.002$), systolic BP measures (5% WL: -8 ± 1 vs. -4 ± 1 mmHg, $P = 0.006$), diastolic BP measures (5% WL: -4 ± 1 vs. -2 ± 1 mmHg, $P = 0.007$), and HDL-C (5% WL: 0.05 ± 0.01 vs. 0.02 ± 0.01 mmol/l, $P = 0.05$), relative to MAO individuals who did not lose weight.

Discussion

The primary finding of this study is that a clinically relevant WL of 5% of initial BW resulted in significant improvements in MNO and MAO metabolic profiles. Interestingly, even MAO patients who did not achieve a 5% WL still significantly improved several metabolic risk factors despite not losing a clinically relevant amount of BW. Our metabolic improvements of 8 mmHg in systolic BP and 2 mmHg in diastolic BP are related to a 15-39% theoretical reduction in CVD mortality (19), while our HDL-C increase of 0.08 mmol/l is associated with a theoretical 8% reduction in CVD mortality in men and women (20). These findings demonstrate the beneficial health effects of using lifestyle-based modifications to resolve metabolic risk factors for overweight and obese individuals, particularly those with significant metabolic aberrations.

There has been growing evidence to support the presence of a subset of ‘‘healthy obese" individuals who appear to be protected against metabolic and cardiovascular complications, despite having excessive levels of body fat. However, there has been conflicting data concerning the future health risk of this subgroup of obese individuals. It is unclear whether all obese individuals should be prescribed WL treatment and whether all obese will uniformly benefit from WL treatment. To date, there are only a few studies that have compared the effects of WL in MNOB and MAOB subjects (9-12). Two studies observed that despite similar WLs among MNOB and MAOB by diet or exercise, only MAOB had significant improvements in the lipid profiles, with no measurable effect on cardiometabolic risk measures of MNOB subjects (9,10). Similarly, an exercise and diet intervention by Janiszewski and Ross (11), demonstrated greater metabolic improvements in MAOB patients in comparison with MNOB patients, independent of sex. The final study, a 6-month energy restricted diet intervention, by Karelis et al. (12) also resulted in a 26% improvement in MAOB; however, unlike the previous studies that report no effect of WL in MNOB, this study demonstrates an unfavorable 13% deterioration in insulin sensitivity in MNOB individuals. This is the lone study to unexpectedly suggest a potentially harmful effect of WL for MNOB. This study is the largest to date to examine the differential effects of WL in MNO and MAO using a behavioral lifestyle WL

TABLE 2 Likelihood of MNO profile at follow-up by WL status

	OR (95% CI) unadjusted	OR (95% CI) adjusted
MNO profile following treatment		
No 5% WL	1.00	1.00
5% WL	1.36 (0.91-2.04)	1.29 (0.80-2.10)
One more risk factor following treatment		
No 5% WL	1.00	1.00
5% WL	0.65 (0.44-0.96)	0.65 (0.42-1.00)

Adjusted for sex, age, BMI, treatment duration, and the number of high risk factors.
MNO, metabolically normal overweight and obese; OR, odds ratio; WL, weight loss.

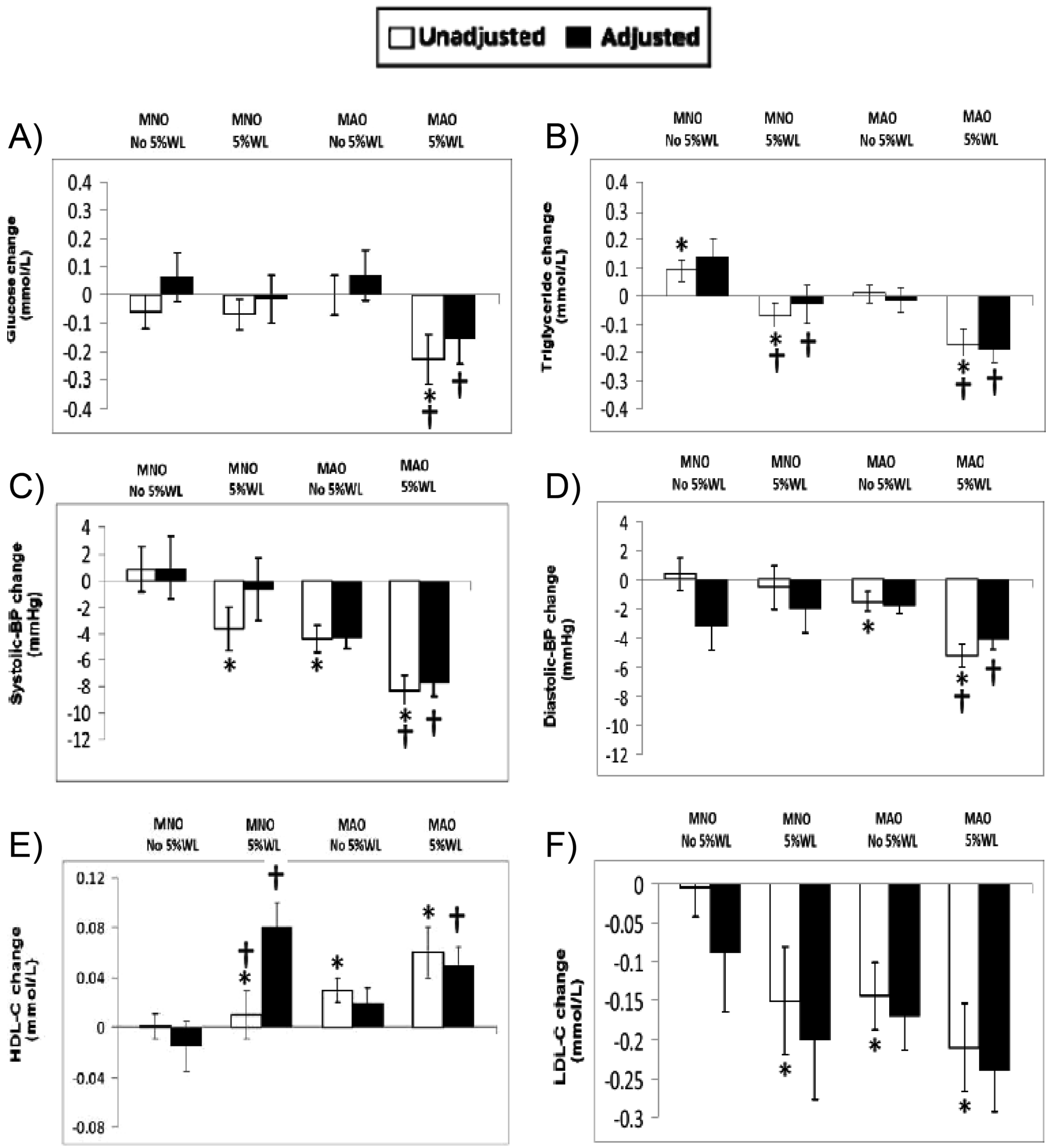

FIGURE 2 (**A**–**F**) Metabolic parameter changes in MNO and MAO subjects in response to presence and absence of 5% WL: (**A**) glucose, (**B**) triglycerides, (**C**) systolic BP, (**D**) diastolic BP, (**E**) HDL-C, and (**F**) LDL-C. Adjusted for baseline metabolic parameter, sex, age, BMI, and treatment duration. MNO, metabolically normal overweight and obese; MAO, metabolically abnormal overweight and obese; WL, weight loss; BP, blood pressure. *Significantly different within group change from baseline, $P < 0.05$. †Significantly different from no 5% WL within metabolic strata, $P < 0.05$. There were no significant WL × metabolic strata interactions for all metabolic parameters, $P > 0.05$.

approach. While our results are similar to previous studies in that we observed marked improvements in the MAO profile, our study extends previous observations, and suggests that lifestyle modification is beneficial for improving metabolic risk regardless of whether a clinically relevant WL of 5% was achieved. To this end, our findings are in line with the clinical treatment guidelines that support WL as beneficial for overweight and obese patients, regardless of their current metabolic health status.

Currently, there is no standardized definition for MNOB. Some authors use sub-clinical thresholds based on the National Cholesterol Education Program's Adult Treatment Panel III metabolic syndrome criteria (1,2,4), while others use insulin sensitivity cutoffs (3,21) to define MNOB. As a result, the prevalence of MNOB can vary greatly from as many as 30-40% of the obese population (2,3,22-25) to as few as 6% depending on the definition used (1). In this study, we used clinical accepted cutoffs to define metabolic health status. If we had used sub-clinical cutoffs, the prevalence of MNO would have been drastically reduced (3.6% vs. 21.2% at baseline). Using clinically relevant cutoffs to describe MAO ensured that these individuals were clearly at increased risk for negative outcomes and could benefit from WL. However, this also meant that our MNO may not have been at optimal health as even subclinical elevations in FPG, BP, LDL-C, and HDL-C have been reported to be associated with increased mortality risk (26). Nevertheless, this approach was more in line with the recommendations of the NHLBI Guidelines for the *Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* (13).

One point of debate in the literature is whether or not MNOB individuals are at an increased risk for future negative health outcomes, such as cardiovascular disease and mortality. Some report that cardiovascular mortality risk in MNOB is similar to that observed in normal weight individuals (27). Conversely, others studies report similar elevated cardiovascular disease (28) and mortality risk (1,28) among MNOB and MAOB individuals. This, along with our data is in support of the current US obesity treatment guidelines that recommend WL for all obese patients regardless of their metabolic profile. Nevertheless, the potential benefits of WL need to be weighed against the potential negative effects of repeated failed WL maintenance (29-31), as less than 10% of individuals who lose weight are able to maintain their losses for more than a year (32).

The strengths and limitations of this study warrant mention. This study was conducted in a sample from the communities of Hamilton, Halton and Burlington, Ontario, Canada. Further, there was a lack of data on ethnicity and socioeconomic status, thus it is unknown if the results of the study are generalizable to other populations. This study is the largest to date to compare the effects of WL in MNO and MAO men and women. The WMC operates under the Ontario Health Insurance Plan therefore the services are free of charge to the patient, thus making it accessible to a wider range of socioeconomic status. However, our participant pool may have been subject to self-selection or volunteer bias. Further, it should be mentioned that participants included in the analyses had devoted a considerable amount of time to the WMC clinic (at least 3 months or at least three visits). Although purely speculative, our patient population may have been more concerned about their health and losing weight, in comparison to patients who discontinued treatment, as we do not know the reasons that led them to discontinue treatment at the clinic.

In summary, we suggest that a clinically significant WL of 5% using a lifestyle-based approach is beneficial to the cardiometabolic profile of MAO and MNO individuals. However, the positive lifestyle modifications associated with attempting to lose weight may be associated with improvements in metabolic health in MAO even in the absence of WL. O

Acknowledgments

The authors would like to gratefully acknowledge the patients who volunteered their medical data for the research study. The study could not have been completed without the work of the staff at each of the Wharton Medical Clinic-Weight Management Centres and the help of the York volunteers from the Body Composition Analysis Lab. Mitacs-Accelerate had no role in this study. The authors 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 analysis.

References

1. Kuk JL, Ardern CI. Are metabolically normal but obese individuals at lower risk for all-cause mortality? *Diabetes Care* 2009;32:2297-2299.
2. Wildman RP, Muntner P, Reynolds K, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). *Arch Intern Med* 2008;168:1617-1624.
3. Brochu M, Tchernof A, Dionne IJ, et al. What are the physical characteristics associated with a normal metabolic profile despite a high level of obesity in postmenopausal women? *J Clin Endocrinol Metab* 2001;86:1020-1020.
4. Karelis AD, St-Pierre DH, Conus F, et al. Metabolic and body composition factors in subgroups of obesity: what do we know? *J Clin Endocrinol Metab* 2004;89: 2569-2569.
5. St-Pierre AC, Cantin B, Mauriege P, et al. Insulin resistance syndrome, body mass index and the risk of ischemic heart disease. *CMAJ* 2005;172:1301-1301.
6. Lau DC, Obesity Canada Clinical Practice Guidelines Steering Committee and Expert Panel. Synopsis of the 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children. *CMAJ* 2007;176: 1103-1103.
7. Stern JS, Hirsch J, Blair SN, et al. Weighing the options: criteria for evaluating weight-management programs. The Committee to Develop Criteria for Evaluating the Outcomes of Approaches to Prevent and Treat Obesity. *Obes Res* 1995;3: 591-591.
8. Goldstein DJ. Beneficial health effects of modest weight loss. *Int J Obes Relat Metab Disord* 1992;16:397-415.
9. Shin MJ, Hyun YJ, Kim OY, et al. Weight loss effect on inflammation and LDL oxidation in metabolically healthy but obese (MHO) individuals: low inflammation and LDL oxidation in MHO women. *Int J Obes (Lond)* 2006;30: 1529-1529.
10. Arsenault BJ, Cote M, Cartier A, et al. Effect of exercise training on cardiometabolic risk markers among sedentary, but metabolically healthy overweight or obese post-menopausal women with elevated blood pressure. *Atherosclerosis* 2009;207: 530-530.
11. Janiszewski PM, Ross R. Effects of weight loss among metabolically healthy obese men and women. *Diabetes Care* 2010;33:1957-1957.
12. Karelis AD, Messier V, Brochu M, et al. Metabolically healthy but obese women: effect of an energy-restricted diet. *Diabetologia* 2008;51:1752-1752.
13. National Heart, Lung, and Blood Institute (NHLBI) Obesity Education Initiative.*The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*.2000:1-94.
14. Mifflin MD, St Jeor ST, Hill LA, et al. A new predictive equation for resting energy expenditure in healthy individuals. *Am J Clin Nutr* 1990;51:241-241.
15. Frankenfield D, Roth-Yousey L, Compher C. Comparison of predictive equations for resting metabolic rate in healthy nonobese and obese adults: a systematic review. *J Am Diet Assoc* 2005;105:775-775.
16. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2012;35 (suppl 1):S64-S71.
17. National Cholesterol Education Program. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report.2002;106:3143-3421.
18. Rosendorff C, Black HR, Cannon CP, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. *Circulation* 2007;115:2761-2761.
19. Hansen TW, Jeppesen J, Rasmussen S, et al. Ambulatory blood pressure and mortality: a population-based study. *Hypertension* 2005;45:499-504.
20. Cooney MT, Dudina A, De Bacquer D, et al. HDL cholesterol protects against cardiovascular disease in both genders, at all ages and at all levels of risk. *Atherosclerosis* 2009;206:611-616.
21. Stefan N, Kantartzis K, Machann J, et al. Identification and characterization of metabolically benign obesity in humans. *Arch Intern Med* 2008;168:1609-1609.
22. Genelhu VA, Celoria BM, Duarte SF, et al. Not all obese subjects of multiethnic origin are at similar risk for developing hypertension and type 2 diabetes. *Eur J Intern Med* 2009;20:289-289.
23. Aguilar-Salinas CA, Garcia EG, Robles L, et al. High adiponectin concentrations are associated with the metabolically healthy obese phenotype. *J Clin Endocrinol Metab* 2008;93:4075-4075.
24. Jennings CL, Lambert EV, Collins M, et al. Determinants of insulin-resistant phenotypes in normal-weight and obese Black African women. *Obesity (Silver Spring)* 2008;16:1602-1609.
25. Weiss R, Taksali SE, Dufour S, et al. The ‘‘obese insulin-sensitive" adolescent: importance of adiponectin and lipid partitioning. *J Clin Endocrinol Metab* 2005;90: 3731-3737.
26. Pekkanen J, Linn S, Heiss G, et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *N Engl J Med* 1990;322:1700-1707.

27. Katzmarzyk PT, Church TS, Janssen I, et al. Metabolic syndrome, obesity, and mortality: impact of cardiorespiratory fitness. *Diabetes Care* 2005;28:391-397.
28. Arnlov J, Sundstrom J, Ingelsson E, et al. Impact of BMI and the metabolic syndrome on the risk of diabetes in middle-aged men. *Diabetes Care* 2011;34:61-65.
29. Blair SN, Shaten J, Brownell K, et al. Body weight change, all-cause mortality, and cause-specific mortality in the Multiple Risk Factor Intervention Trial. *Ann Intern Med* 1993;119:749-757.
30. Lissner L, Odell PM, D'Agostino RB, et al. Variability of body weight and health outcomes in the Framingham population. *N Engl J Med* 1991;324:1839-1839.
31. Holbrook TL, Barrett-Connor E, Wingard DL. The association of lifetime weight and weight control patterns with diabetes among men and women in an adult community. *Int J Obes* 1989;13:723-723.
32. Wadden TA. Treatment of obesity by moderate and severe caloric restriction. Results of clinical research trials. *Ann Intern Med* 1993;119:688-688.