Introduction

Metabolic syndrome (MetS) refers to a cluster of five risk factors i.e. hyperglycemia, hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C) and abdominal obesity (1) that increase the risk for cardiovascular disease and type 2 diabetes (2,3,4). The basis of MetS is the insulin resistance associated with abdominal obesity and this adiposity is a criterion for MetS rather than weight (5). The concept of MetS has been criticized (6,7) despite its wide acceptance by the World Health Organization (8), the National Cholesterol Education Program–Adult Treatment Panel III (9) and the International Diabetes Federation (10). In addition to the features of MetS, other indices such as the Framingham and PROCAM scores (11) provide additional evidence for increased cardiovascular risk (5). In Canada, 20% of the adult population has MetS (12), with prevalence increasing with age (13) and those with MetS are reported to have double the annual health care costs and use health services more frequently than those without (14, 15). Lifestyle intervention trials have demonstrated the potential to improve clinically relevant outcomes. The Diabetes Prevention Program in non-diabetics with elevated fasting blood glucose was the first large controlled trial of lifestyle intervention demonstrating a much lower rate of clinical diabetes over 4 years (2%) compared to those treated with metformin (8%) or a placebo (11%) (16). A more recent large controlled trial from Spain showed that the Mediterranean diet alone (no physical activity component) reduced the risk of cardiovascular events by 30% over 4 years in patients who were already receiving pharmacological therapy (17). A recent meta-analysis of smaller clinical trials reported that diet and exercise are effective in resolving MetS and reducing the severity of its related abnormalities (18). Aerobic exercise training resulting in increased aerobic capacity has been shown to reduce insulin resistance, which is the basis of the metabolic syndrome (19).

Despite these promising results, uptake of lifestyle-focused preventive care for cardiovascular risk into Canadian primary care settings remains limited (20). Demonstration of

the feasibility of efficacious interventions is needed. In asymptomatic patients, the presence of MetS would be first detected by the Family Physician (FP) and in a recent primary care consensus statement, lifestyle modification has been emphasized as a key therapy (21). We hypothesized that a team based program led by the FP (called the Canadian Health Advanced by Nutrition and Graded Exercise [CHANGE] program) that educates the patient about the risks of MetS and empowers them to undertake an individualized supervised program of diet modification and exercise, would be feasible, sustainable over a year of observation, improve aerobic capacity and diet quality, reverse MetS and improve its components at 12 months.

Methods

Setting and design

This was a prospective, longitudinal before-after feasibility study conducted in 3 diverse primary care clinics across Canada, with recruitment from October 2012 - December 2014. Eligibility criteria were designed to enroll adult patients that met the criteria for MetS (1). We excluded patients who, for medical/safety/logistic reasons, would be unable to participate in the longitudinal design of the study (refer to supplementary file for eligibility criteria). Approvals were obtained from local ethics boards and eligible patients were approached for consent and placed in the CHANGE Program by their FP. Each patient was seen by the registered dietitian (RD) for individualized counselling, based on a care map that incorporated evidence from clinical trials and principles of health behaviour change from the integrated behavioural model (22), with an emphasis on the Mediterranean diet (23). Each patient was also seen by the clinic kinesiologist for assessment of their fitness and physical activity habits and for an individualized fitness plan that included supervised and unsupervised aerobic activity, resistance training and flexibility exercises. Fitness, muscular endurance, vigor and flexibility were assessed using established assessment tests (24). The program prescribed follow up visits with the FP at 3, 6, 9 and 12 months for a review of blood pressure, glucose, lipids (triglycerides, high density lipoprotein

cholesterol [HDL-C]), medications and changes in waist circumference and body weight. Weekly visits with the dietitian and kinesiologist for first 3 months were followed by monthly visits for 9 months. Ongoing encouragement was provided by all staff to support the patient in making lifestyle changes based on progress achieved in MetS components.

Outcomes

The co-primary outcomes of the study were feasibility (defined by % diet and exercise visits attended over 12 months) and the reversal of MetS, defined as less than 3 out of the 5 criteria where the 5 criteria are defined in the legend to table 1. Secondary outcomes included: a) improvement in the individual components of MetS, b) diet quality as determined by two 24-hour recalls one week apart that were used to calculate the Canadian Health Eating Index (HEI-C) (25) and Mediterranean Diet Score (MDS) (26), c) aerobic capacity assessed by maximal oxygen consumption (VO_2 max) (27), d) PROCAM score for assessing risk of myocardial infarction (11) (The PROCAM score was chosen due to its simplicity and accuracy at predicting global risk of myocardial infarction in clinical practice and its relevance to MetS), and e) continuous metabolic syndrome score (cMetS Score) (28), which is believed to be more sensitive than the common binary score.

Sample Size

We aimed to enroll a total of 300 patients from 3 sites. This sample size would provide a 95% chance of estimating the true MetS reversal rate to within 5%, assuming the reversal rate was ≤25%, as was observed. Conservatively assuming that the number of dietitian contacts and fitness visits were uniformly distributed between 0 and 21, this sample size would have a 99% chance of estimating the true proportion of prescribed visits and contacts attended at the participating sites to within 5%. For continuous outcomes, this sample size would provide 93%

power at two-sided alpha=0.05 to detect a within patient change that is 1/5th of the standard deviation of the change values, which is considered a small effect size by Cohen's convention (29).

Statistical analyses

Analysis included all patients with any follow-up data regardless of compliance with the program. Enrolled patients who did not meet the criteria for MetS at baseline or who had a baseline fasting blood glucose >11 mmol were excluded. Baseline characteristics were compared between patients who did and did not have the 12-month lab assessment using independent t-test for continuous variables and the Chi-Squared test for categorical variables. For all continuous outcomes, data at each time point is presented as raw mean ± standard deviation. To reduce potential biases due to missing data, we estimated the expected mean values and the expected change from baseline using the linear mixed effect model including all available assessments and allowing for an unstructured within patient correlation. This model, estimated by restricted maximum likelihood, treated time as a categorical variable, and included age and sex as covariates. When some, but not all, lab variables were available at an assessment, we used the expectation-maximization (EM) algorithm to impute the most likely missing values based on the available values. A non-parametric loess smoother (30) was used to display the association between the baseline PROCAM risk and the change in this risk by 12 months. All p-values are two sided without adjustment for multiplicity of tests. To address the multiplicity of outcome testing, a False Discovery Rate was calculated for all outcome p-values and is discussed in the interpretation (31). We considered statistical significance confirmed when the False Discovery rate remained below 0.05. All analyses were performed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Patient recruitment and feasibility

Recruitment into the CHANGE program over the 2-year period at the 3 participating sites met the target rate of an average of 4 patients per site per month for a total recruitment of 305 patients. Twelve patients were excluded. Figure 1 (appendix) details the follow-up of the enrolled patients (n = 305). Baseline patient characteristics are presented in Table 1. Of the 293 included patients, 40 (14%) did not have 12-month lab data. Patients without a 12-month lab assessment tended to be younger, with fewer co-morbidities, and with a lower baseline PROCAM risk of major cardiovascular events, yet heavier and have a worse HEI-C. The median [1st quartile to 3rd quartile] diet contacts and fitness visits were 19 [14 to 21] and 16 [10 to 20], indicating that the median patient had 90% of the 21 prescribed dietitian contacts and attended 76% of the 21 prescribed fitness visits.

Aerobic Capacity and Diet Quality

The average of the age-sex standard population based percentiles of aerobic capacity as measured by VO_2 max increased significantly over 12 months (mean percentile increase 16% [95% CI, 13% to 18%, p<0.0001]). Both diet quality scores, HEI-C and MDS improved significantly over time, [95% CI 7.6% to 11.6% and 1.1% to 1.6% respectively, p<0.0001] (Table 2).

Metabolic Reversal

At 12 months, 19% of patients (95% CI, 14% to 24%) showed reversal of MetS, the rate plateaued at 6 months but remained stable for 12 months showing no regression with time (Table 3). Compared to baseline, the percentage of patients who had a decrease in the number of MetS criteria was 33% at month 3 (n=263); 41% at month 6 (n=244); 43% at month 9 (n=227) and 42% at month 12 (n=253) (data not shown). Systolic and diastolic blood pressures,

triglycerides and waist circumference all improved significantly at 3, 6, 9 and 12 months (all p<0.0001), whereas improvements were seen in HDL-C levels only after 6 months (Table 4, appendix). Reductions in fasting blood glucose were significant at 3 and 6 months but not at 9 or 12 months.

PROCAM Risk Score and Continuous Metabolic Syndrome Score

At 12 months, the average PROCAM 10-year risk of myocardial infarction or acute coronary event decreased by 1.4% (95% CI, 0.9% to 2.0%, p<0.0001) from a baseline risk of 8.4%. Patients with the highest baseline risk experienced the most substantial improvement in the PROCAM risk score on average (Figure 2). The cMetS score decreased by 0.4 (95% CI, 0.3 to 0.5, p<0.0001) at 12 months.

Interpretation

In this multicenter feasibility project, we successfully enrolled 305 patients over 2 years across 3 diverse Canadian primary care settings. The majority of patients were able to continue for 12 months of observation (n = 253/293) and many of those that did not have a 12-month lab assessment were unable to do so due to work related issues (e.g. long distance truck driving). Attendance at the intended diet and fitness visits was generally good. We demonstrated a significant reversal rate of MetS and significant improvements in aerobic and diet indices at 3 months that were sustained at 12 months**.** This was associated with a significant improvement in blood pressure, triglycerides and waist circumference at 3, 6, 9 and 12 months (all p<0.0001). When the False Discover Rate was calculated to account for the multiplicity of outcome testing, all outcomes with a nominal p<0.05 had a False Discover Rate below 5% and thus all conclusions remained intact. This robustness to adjustment for multiple comparisons is a consequence of most of the p-values being so highly statistically significant.

The “lost to follow-up” rate of 14% in this study is within the ranges seen in other lifestyle intervention studies in primary care patients with MetS [11% (24) to 30% (32)]. The baseline HEI-C seen in this study was similar to that reported in another Canadian cohort (24), while no comparable Canadian data exist regarding MDS. The change in the individual components of MetS in our study are also comparable to other studies (32, 33). The improvements in fitness and cardiovascular risk factors are similar to those reported in the first year of follow up in a recent multi-center randomized trial that promoted weight loss and physical activity in overweight patients with type 2 diabetes (34). Contrary to the Look AHEAD trial, our intervention focused on reversing MetS (and not only weight loss) and emphasized changes in the dietary composition (e.g. the Mediterranean diet pattern) (35). The relevance of purely reversing MetS has been criticized by some (6,7) and therefore it is noteworthy that our intervention was associated with a 17% relative risk reduction in the 10-year risk of acute myocardial infarction from baseline (11). In addition, the reduction in the cMetS score by 0.4 at 12 months translates into a relative reduction of 19% and 17% in the incidence of cardiovascular disease and coronary heart disease over 9-years, respectively (28). Of greater importance is that our results show that the program seemed to have had the greatest effect on those with the highest risk of an acute myocardial infarction at baseline. In high risk patients with insulin resistance, the use of a clinically approved drug aimed to target this resistance, pioglitazone, was associated with a significantly lower incidence of stroke or myocardial infarction compared to placebo (9% vs.11.8%, $p<0.007$) over 4.8 years, but was associated with serious side effects that included fractures, weight gain, and edema (36).

In the present study, at baseline, 74% of the patients were being treated with pharmacotherapy for hypertension and 44% for hyperglycemia, yet these patients continued to have uncontrolled hypertension and hyperglycemia, consistent with MetS. Hypertriglyceridemia was rarely treated with pharmacotherapy (4%) in our study population, while no effective

pharmacotherapy exists for low HDL-C and abdominal obesity. Hence despite the use of pharmacotherapy, there is a clear need for better control of MetS and we have demonstrated that this can be achieved through a feasible diet and exercise program in a primary care setting.

One strength of this study is the demonstration of the value of a primary care team to deliver an individualized approach for the management of MetS. In addition to a reversal of MetS, we have demonstrated that a lifestyle intervention like the CHANGE program may have a positive impact on cardiovascular outcomes with the greatest effect seen in those with the highest risk. A recent Canadian study reported the infrequent assessment of cardiovascular risk and counselling on healthy behavioural changes, and concluded that a paradigm change in assessing and managing cardiovascular risk via aggressive lifestyle interventions is warranted (20). The CHANGE program addresses these concerns within a primary care setting. Limitations of this study include the lack of a control group however the intent of this study was to demonstrate the feasibility of this approach in real life primary care settings. Furthermore, the before and after nature our longitudinal cohort does allow us to make some inferences, albeit weak inferences, about the effectiveness of the program. As the study was conducted at 3 centres, we acknowledge that the results may not be generalizable to all primary care teams across Canada and that program modifications may need to be made to meet the needs of diverse primary care teams. Like any lifestyle intervention trial requiring patient consent, selection bias when enrolling patients likely occurred. Social desirability bias might affect reported food intake, but this would be comparable at all three points of diet assessment for each patient. Recall bias, generally under-reporting, was minimized by shortening the diet recall period to the past 24 hours and using the multi-pass method developed by the National Cancer Institute (37). Two recalls were taken, about one week apart at each assessment point, and the mean values recorded due to the high intra-individual variation in food intake day to day. Recall bias would not affect clinical indicators which were used to calculate reversion of MetS and the

PROCAM score, so while diet recall issues are relevant in diet counselling they would have little to no impact on study results.

In conclusion, we demonstrate that it is feasible to recruit patients with MetS to a lifestyle program of diet and exercise in a primary care setting that includes the FP, dietitian and kinesiologist. Such a program may be associated with a reversal of MetS and has the potential to improve clinical outcomes such as the risk of acute myocardial events. Although not all primary care settings have access to dietitians and exercise specialists, several jurisdictions have recognized the importance of the patient's medical home incorporating an interdisciplinary team (38). Our work raises the need for FPs to recognize lifestyle as highly relevant (39) and for dietitian and exercise specialists to be on primary care teams.

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Appendix Figure 1. Participant Flow

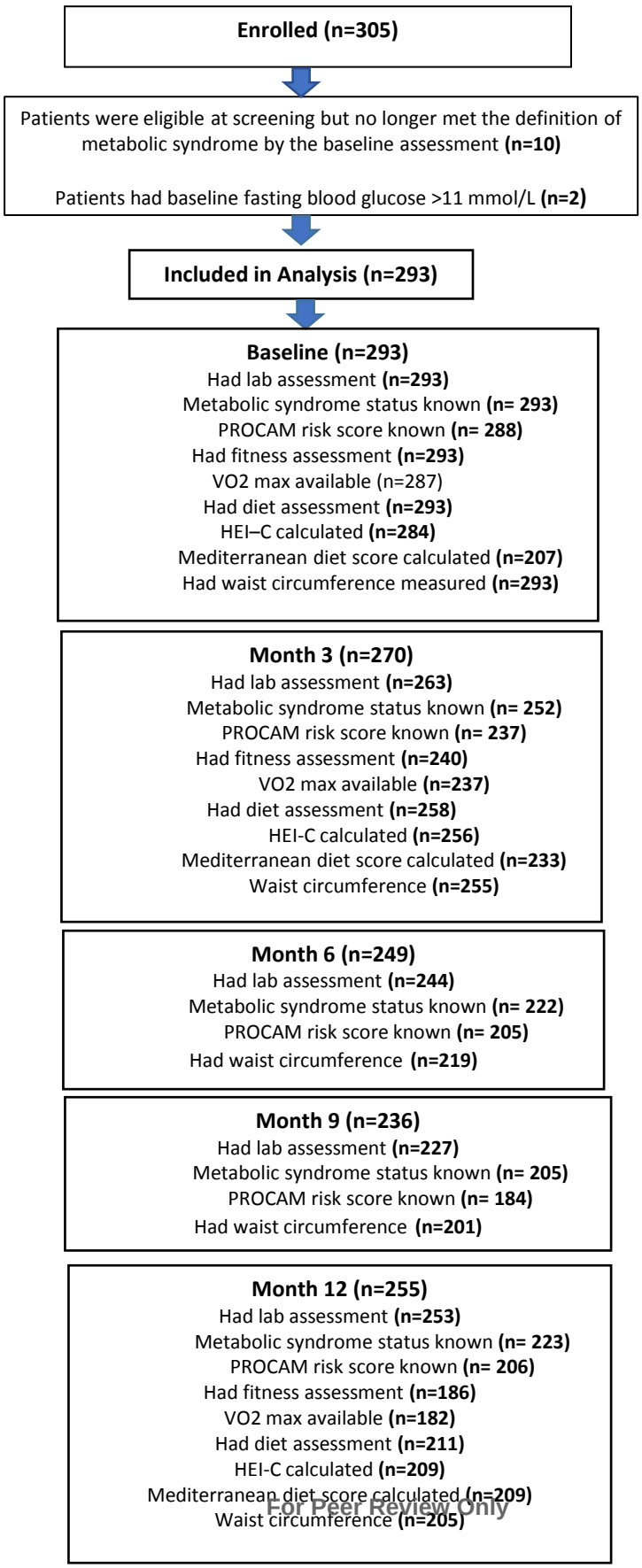


Table 1. Baseline patient characteristics

	All eligible patients (n=293)	Patient with 12 months Lab Assessment (n=253)	Patient without 12 month Lab Assessment (n=40)	p-values
Age (years)	59.1±9.7	60.3±9.0	51.4±11.1	<0.001
Female (%)	152 (52)	131 (52)	21 (53)	0.93
Charlson co-morbidity index	0.8±0.9	0.9±0.9	0.6±0.9	0.02
Height (meters)	1.7±0.1	1.7±0.1	1.7±0.1	0.02*
Weight (kg)	90.8±14.7	89.4±13.4	99.5±18.8	<0.001
BMI (kg/m^2)	31.9±3.3	31.7±3.4	33.4±2.8	0.002
Current smoker (%)	29 (10)	27 (11)	2 (5)	0.55
PROCAM risk (%)	8.2±6.4	8.6±6.3	5.6±6.8	0.006
VO_2max (percentile)	46.8±24.0	46.2±24.0	50.4±24.6	0.31
HEI-C	57.9±14.2	58.6±14.3	52.8±12.8	0.03
Mediterranean diet score	4.7±1.6	4.8±1.6	4.3±1.7	0.12
LDL-C (mmol/L)	2.6±1.1	2.6±1.1	2.9±1.0	0.06
Metabolic Syndrome Criteria				
1. Blood pressure or pharmacotherapy – number (%) meeting criteria	256 (87)	227 (90)	29 (73)	0.002
Systolic blood pressure (mmHg)	133.5±14.5	133.5±14.8	133.8±12.9	0.88
Diastolic blood pressure (mmHg)	80.6±9.1	79.9±9.0	84.9±9.0	0.001
Received Pharmacotherapy for elevated blood pressure (%)	218 (74)	196 (77)	22 (55)	0.002
2. Fasting blood glucose or pharmacotherapy – number (%) meeting criteria	240 (82)	212 (84)	28 (70)	0.04
Blood glucose (mmol/L)	6.6±1.4	6.6±1.4	6.1±1.1	0.04
Received pharmacotherapy for elevated blood glucose levels (%)	129 (44)	120 (47)	9 (22)	0.003
3. Triglyceride or pharmacotherapy – number (%) meeting criteria	187 (64%)	162 (64)	25 (62)	0.85
Triglyceride level (mmol/L)	2.2±1.7	2.2±1.8	2.2±1.1	0.98
Pharmacotherapy for cholesterol (%)	11 (4)	10 (4)	1 (2)	0.65
4. HDL-C – number (%) meeting criteria	138 (47)	119 (47)	19 (47)	0.99
HDL-C (mmol/L)	1.2±0.3	1.2±0.3	1.2±0.3	0.33
5. Waist circumference – number (%) meeting criteria	277 (95)	237 (94)	40 (100)	0.1
Waist circumference (cm)	108.1±9.4	107.3±8.9	113.4±10.7	<0.001

Values are reported as mean±standard deviation or n (%).

BMI-Body mass index, PROCAM risk-PROCAM estimated risk of major cardiac event in next 10 years.

HEI-C Canadian Healthy Eating Index, LDL-C - low density lipoprotein cholesterol, HDL-C – high density lipoprotein cholesterol

Definition of metabolic syndrome criteria:

1. Blood pressure ≥130/85 mmHg or receiving pharmacotherapy
2. Fasting blood glucose ≥5.6 mmol/L or receiving pharmacotherapy
3. Triglyceride level ≥1.7 mmol/L or receiving pharmacotherapy
4. Male patients with an HDL-C level < 1.0 mmol/L or female patients with an HDL-C level < 1.3 mmol/L.
5. Waist circumference as determined by a pre-specified technique:
   - Europids, Whites, sub-Saharan Africans, Mediterranean, middle east (Arab) ≥ 94 cm Males, 80 cm Female.
   - Asian and South Central Americans ≥ 90 cm males and 80 cm females
   - US and Canadian Whites ≥ 102 cm males, 88 cm females.

* Although the height rounds to 1.7 meters in both groups, the actual values are 1.72 and 1.68 which is a statistically significant difference (p=0.02), but not a clinically important difference.

Table 2: Change in aerobic capacity and diet quality

Month	Raw values (n*) mean±std	Maximum likelihood mean±SE	Maximum likelihood change from baseline mean (95% CI)	p-value
Age-sex standardized VO_2 max percentile				
0	(287) 46.8±24.0	46.9±1.2		
3	(238) 59.7±22.4	60.5±1.1	13.6 (11.7 to 15.6)	<0.0001
12	(182) 63.0±20.6	62.5±1.2	15.6 (13.3 to 17.9)	<0.0001
(HEI-C) Canadian Healthy Eating Index (range 0 to 100)				
0	(284) 57.9±14.2	57.9±0.8		
3	(256) 68.6±12.4	68.5±0.8	10.6 (8.8 to 12.4)	<0.0001
12	(209) 68.0±14.1	67.5±0.9	9.6 (7.6 to 11.6)	<0.0001
(MDS) Mediterranean diet score range (0-14)				
0	(207) 4.7±1.6	4.8±0.1		
3	(233) 6.1±2.0	6.2±0.1	1.4 (1.1 to 1.6)	<0.0001
12	(209) 6.2±1.9	6.2±0.1	1.4 (1.1 to 1.6)	<0.0001

STD=Standard deviation; SE=standard error; CI=Confidence interval

* number of patients where the variable was captured.

The maximum likelihood mean and change use all available data to estimate the expected values utilizing within patient correlations between outcomes and time points. The maximum likelihood mean is estimated for a 60-year-old assuming even numbers of males and females.

Table 3. Reversal of metabolic syndrome

Month	Observed metabolic reversal rates	
	Number reversed/total number assessed (% reversal)	95% CI of % reversal
0	0/293 (0)	0 to 0
3	35/263 (13)	9 to 17
6	53/244 (22)	17 to 27
9	49/227 (22)	16 to 27
12	48/253 (19)	14 to 24

CI- Confidence interval

Appendix Table 4. Changes in PROCAM Score and continuous metabolic syndrome score and criteria and weight

Month	Raw values (n*) mean±std	Maximum likelihood estimate (n†) mean±SE	Maximum likelihood change from baseline mean (95% CI)	p-value
PROCAM 10-year risk myocardial infarction or acute coronary death				
0	(288) 8.2±6.4	(293) 8.4±0.3		
3	(237) 6.9±5.4	(263) 7.2±0.3	-1.3 (-1.8 to -0.8)	<0.0001
6	(205) 6.8±5.2	(244) 6.9±0.3	-1.6 (-2.2 to -1.0)	<0.0001
9	(184) 7.0±5.1	(227) 6.9±0.3	-1.6 (-2.2 to -1.0)	<0.0001
12	(206) 7.3±5.1	(253) 7.0±0.3	-1.4 (-2.0 to -0.9)	<0.0001
Continuous metabolic syndrome score				
0	(293) 2.6±1.1	(293) 2.6±0.1		
3	(236) 2.0±1.1	(263) 2.0±0.1	-0.6 (-0.7 to -0.5)	<0.0001
6	(193) 1.9±1.1	(244) 2.1±0.1	-0.5 (-0.6 to -0.4)	<0.0001
9	(175) 2.0±1.1	(227) 2.1±0.1	-0.4 (-0.6 to -0.3)	<0.0001
12	(189) 2.0±1.1	(253) 2.2±0.1	-0.4 (-0.5 to -0.3)	<0.0001
Systolic blood pressure (mmHg))				
0	(293) 133.5±14.5	(293) 133.5±0.9		
3	(256) 127.1±12.7	(263) 127.0±0.8	-6.5 (-8.1 to -4.9)	<0.0001
6	(229) 129.7±13.5	(244) 129.5±0.8	-4.0 (-5.8 to -2.2)	<0.0001
9	(210) 130.3±13.6	(227) 129.9±0.8	-3.6 (-5.5 to -1.8)	0.0002
12	(230) 130.1±12.5	(253) 130.3±0.7	-3.3 (-5.1 to -1.4)	0.0005
Diastolic blood pressure (mmHg)				
0	(293) 80.6±9.1	(293) 80.3±0.5		
3	(256) 76.9±8.8	(263) 76.8±0.5	-3.5 (-4.5 to -2.5)	<0.0001
6	(229) 77.6±8.3	(244) 77.8±0.5	-2.5 (-3.5 to -1.5)	<0.0001
9	(210) 78.0±7.7	(227) 78.2±0.5	-2.1 (-3.1 to -1.1)	<0.0001
12	(230) 77.2±8.3	(253) 77.6±0.5	-2.7 (-3.8 to -1.6)	<0.0001
Fasting glucose (mmol/L)				
0	(293) 6.6±1.4	(293) 6.6±0.1		
3	(247) 6.4±1.3	(263) 6.4±0.1	-0.2 (-0.3 to -0.1)	0.006
6	(227) 6.4±1.3	(244) 6.4±0.1	-0.2 (-0.3 to -0.0)	0.0055
9	(202) 6.5±1.6	(227) 6.5±0.1	-0.0 (-0.2 to 0.1)	0.5627
12	(225) 6.6±1.5	(253) 6.6±0.1	-0.0 (-0.2 to 0.1)	0.5776
LDL-C (mmol/L)				
0	(288) 2.6±1.1	(293) 2.6±0.1		
3	(250) 2.6±1.1	(263) 2.5±0.1	-0.1 (-0.2 to -0.0)	0.0167
6	(223) 2.5±1.1	(244) 2.5±0.1	-0.1 (-0.2 to 0.0)	0.0566
9	(206) 2.6±1.1	(227) 2.5±0.1	-0.1 (-0.2 to 0.0)	0.1259
12	(236) 2.6±1.0	(253) 2.6±0.1	-0.1 (-0.1 to 0.0)	0.2194

HDL-C (mmol/L)				
0	(291) 1.2±0.3	(293) 1.2±0.0		
3	(251) 1.2±0.3	(263) 1.2±0.0	-0.0 (-0.0 to 0.0)	0.6208
6	(226) 1.2±0.3	(244) 1.2±0.0	0.0 (0.0 to 0.0)	0.0137‡
9	(208) 1.2±0.3	(227) 1.2±0.0	0.0 (0.0 to 0.1)	0.0019‡
12	(241) 1.3±0.3	(253) 1.2±0.0	0.1 (0.0 to 0.1)	<0.0001
Triglycerides (mmol/L)				
0	(293) 2.2±1.7	(293) 2.2±0.1		
3	(252) 1.8±1.1	(263) 1.8±0.1	-0.4 (-0.5 to -0.2)	<0.0001
6	(226) 1.9±1.0	(244) 1.8±0.1	-0.3 (-0.5 to -0.2)	<0.0001
9	(208) 1.9±0.9	(227) 1.8±0.1	-0.4 (-0.5 to -0.2)	<0.0001
12	(240) 1.9±0.9	(253) 1.9±0.1	-0.3 (-0.4 to -0.1)	0.0003
Waist circumference (cm)				
0	(293) 108.1±9.4	(293) 108.1±0.5		
3	(249) 105.2±9.0	(263) 105.4±0.5	-2.7 (-3.1 to -2.3)	<0.0001
6	(215) 103.3±9.5	(244) 104.5±0.6	-3.6 (-4.2 to -3.0)	<0.0001
9	(193) 103.2±9.6	(227) 104.5±0.6	-3.5 (-4.1 to -2.9)	<0.0001
12	(204) 103.0±10.2	(253) 104.4±0.6	-3.7 (-4.3 to -3.0)	<0.0001
Weight (kg)				
0	(293) 91.0±15.2	(293) 90.7±0.8		
3	(251) 88.5±14.2	(263) 88.9±0.8	-1.8 (-2.2 to -1.5)	<0.0001
6	(220) 86.9±14.1	(244) 88.5±0.8	-2.3 (-2.7 to -1.9)	<0.0001
9	(199) 87.1±14.6	(227) 88.4±0.8	-2.3 (-2.8 to -1.8)	<0.0001
12	(206) 86.5±14.8	(253) 88.3±0.8	-2.5 (-3.0 to -2.0)	<0.0001

STD=Standard deviation; SE=standard error; CI=Confidence interval; LDL-C= Low-density lipoprotein cholesterol, HDL-C=High density lipoprotein-cholesterol , kg-kilogram

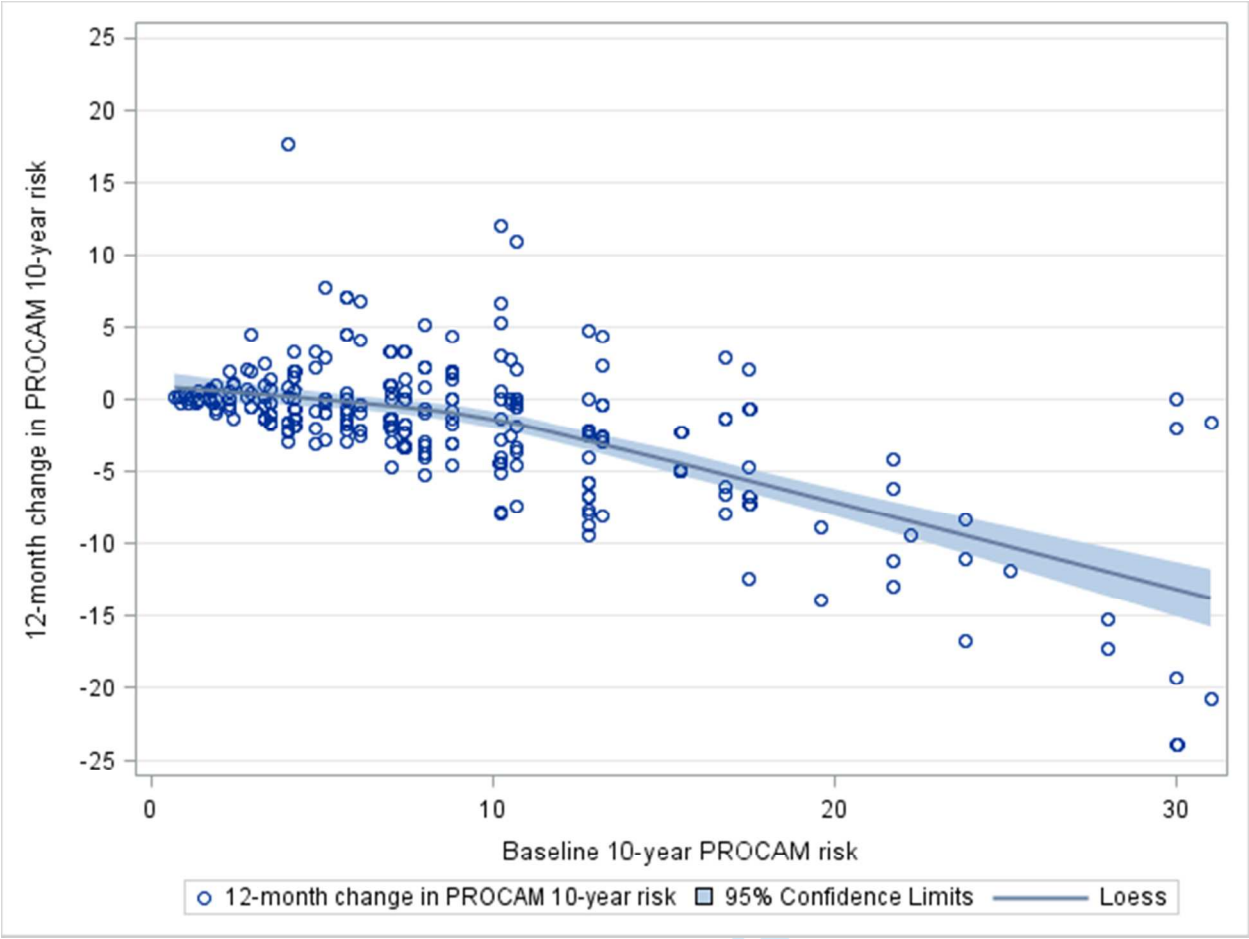
* Number of patients where the variable was known.

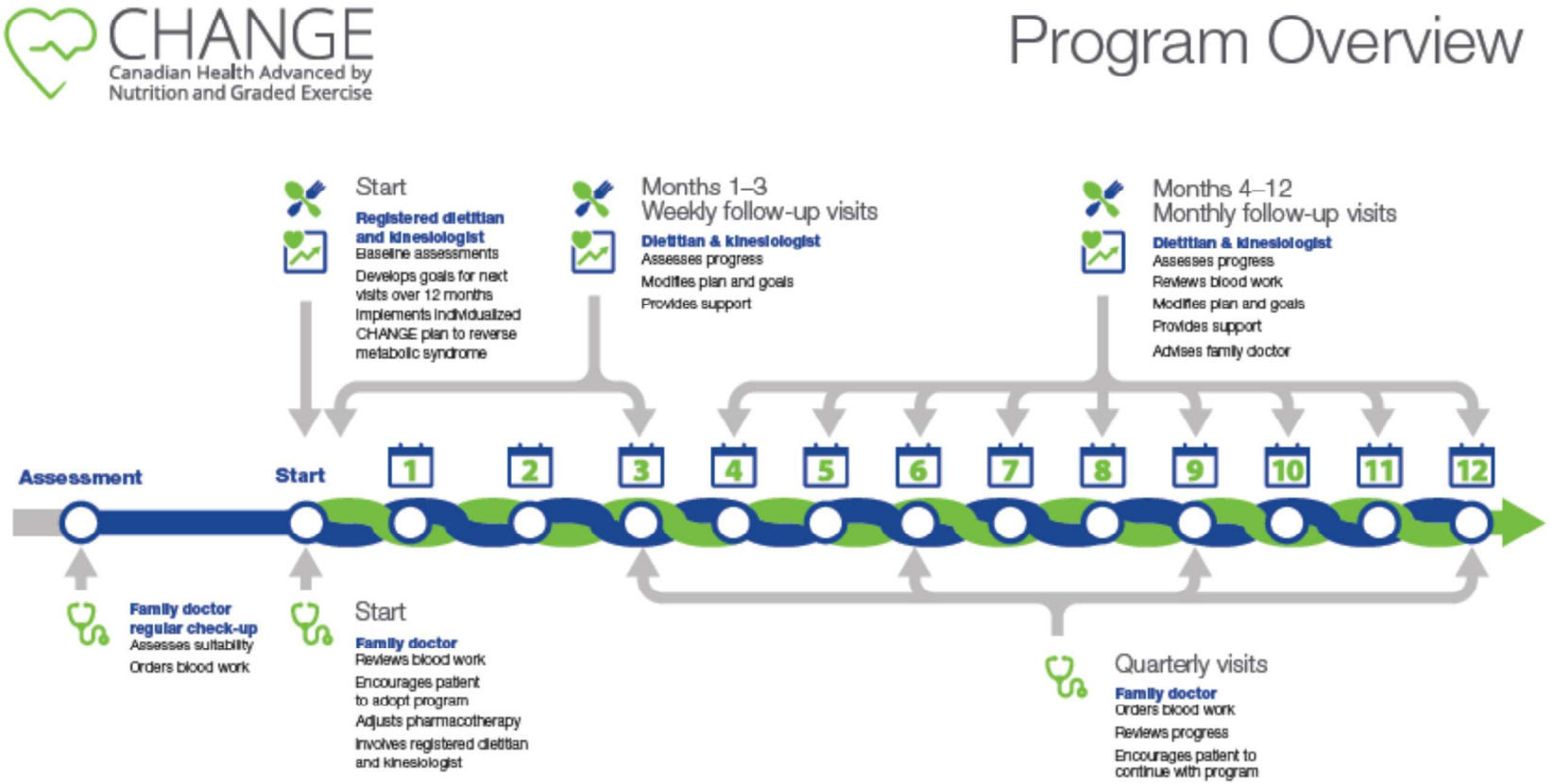
† Number of patients with any lab assessment so missing values could be imputed based on the correlation with the available lab values.

‡ Although the change rounds to 0.0, the actual differences are non-zero and statistically but not clinically significant.

The maximum likelihood mean and estimated change use all available data to estimate the expected values utilizing within patient correlations between lab values and time points. The maximum likelihood mean is estimated for a 60-year-old assuming even numbers of males and females.

Figure 2. Change in PROCAM risk compared to baseline risk




CHANGE
Canadian Health Advanced by Nutrition and Graded Exercise
Program Overview
Start
Registered dietitian and kinesiologist
Baseline assessments
Develops goals for next visits over 12 months
Implements individualized CHANGE plan to reverse metabolic syndrome
Months 1–3
Weekly follow-up visits
Dietitian & kinesiologist
Assesses progress
Modifies plan and goals
Provides support
Months 4–12
Monthly follow-up visits
Dietitian & kinesiologist
Assesses progress
Reviews blood work
Modifies plan and goals
Provides support
Advises family doctor
Assessment
Start
1
2
3
4
5
6
7
8
9
10
11
12
Family doctor regular check-up
Assesses suitability
Orders blood work
Start
Family doctor
Reviews blood work
Encourages patient to adopt program
Adjusts pharmacotherapy
Involves registered dietitian and kinesiologist
Quarterly visits
Family doctor
Orders blood work
Reviews progress
Encourages patient to continue with program

Canadian **H**ealth **A**dvanced By **N**utrition and **G**raded **E**xercise CHANGE Health Paradigm

Demonstration Project

Protocol

Version June 29th 2012

Overall Objective

The overall objective of the CHANGE initiatve is to *change* the delivery of care in primary care clinics to treat disease by reducing reliance on drugs and hospitals through the promotion of scientifically validated nutritional concepts and exercise. Specifically, the objective of the CHANGE demonstration project is to identify patients from primary care clinics with metabolic syndrome who are not morbidly obese and use diet and exercise interventions to reverse the changes, reduce reliance on pharmacotherapy and prevent progression to diabetes and cardiovascular disease. If the results of this demonstration project are positive, we will widely disseminate the knowledge and tools to other sites to support their adoption.

Background

Hypertension**,** cardiovascular disease, strokes, diabetes and their complications including renal failure and neuropathy are major contributors to healthcare costs[1]. Metabolic Syndrome, a widespread genetic trait refers to a group of factors that increase risk for these diseases. Progression of the components of the metabolic syndrome can be significantly reduced by dietary manipulation and exercise[2,3].

The aging population, with both metabolic syndrome and muscular weakness, is going to result in an enormous social and financial burden not only for medical care but also for families caring for such patients. Existing knowledge would suggest that dietary modification and exercise training would substantially reduce the costs and complications of these medical conditions[4,5,6,7] but the application of these results to prevent disease has been a dismal failure in general and in particular, in our country

The Canadian Guidelines for the diagnosis and management of cardiometabolic risk identify patients with metabolic syndrome who have an increased risk of cardiac and vascular disease and diabetes[8]. Although other factors, such has smoking, hypercoagulability and increased expression of proinflammatory cytokines increase cardiometabolic risk, these changes are closely related to the metabolic syndrome. “Health behavior interventions” are identified as critical to preventing the occurrence of cardiovascular disease and diabetes. These interventions can be associated with appropriate pharmacotherapy where required. The guidelines recommend a multidisciplinary team to manage these interventions. In addition it is also recommended that ethnicity be considered in these interventions.

The current model of advice about preventive care is through family doctors (FD) in the primary care setting. FDs tend not to advise their patients about diet and exercise for a variety of reasons including a lack of education about these modalities, a lack of support from professionals qualified to assess and advise about diet and exercise, the belief that drugs are better, lack of time and a lack of reimbursement in addition to patient barriers to adoption[9] . Accordingly, we propose to implement a ‘program’ of nutrition and exercise interventions imbedded into the primary care setting that are tailored to reduce the risk of metabolic syndrome and overcome these barriers.

The various traits associated with the metabolic syndrome are strongly influenced by genetic factors, i.e. the heritability of abdominal obesity and insulin resistance are estimated to be as high as 70%[10]. Numerous genetic polymorphisms (also referred to as markers) have been linked to the various traits associated with metabolic syndrome. It is hypothesized that these markers can be used as a means to better predict the variable responses observed in individuals following a lifestyle intervention. Several companies have begun to commercialize direct-to-consumer genetic-testing to provide nutritional counseling to individuals based on the analysis of a small subset of polymorphisms[11]; however, there is an absence of scientific research to either support or refute the value of genetic markers for predicting an individual’s response. Considering common genetic markers in a lifestyle intervention study will enable us to assess their value for predicting response.

Evidence that Nutritional Intervention Positively Affect Health Outcomes of Patients with Metabolic Syndrome

The Mediterranean diet, a diet high in fruits, vegetables, fish, less red meat and more alpha linoleic acid (an omega 3 fat obtained from olive oil), has been promoted as a model for healthy eating. The first evidence supporting the benefits of a Mediterranean diet were reported in the Lyon Diet Heart Study[12], in which 605 patients with myocardial infarction were assigned to the diet vs. the American Heart Association Step 1 diet (maximum of 30% of energy from fat, with less than 10% of total energy from saturated fat and dietary cholesterol limited to 300 mg/d). After a follow up of 27 months, the rate of coronary events was reduced by 73% and mortality by 70% with the Mediterranean diet. The beneficial effects of the Mediterranean-style diet supplemented with nuts or virgin olive oil is thought to be via the modulation membrane properties of cells as demonstrated by studies of changes in the composition of erythrocyte membranes in hypertensive patients with a high risk for cardiovascular disease[13]. In other large population based trials adherence to such diets was also found to be associated with a reduction in cardiac deaths[14],[15]and non-fatal myocardial infarctions[14] and deaths due to cancer[15]. Epidemiological data also show that long-chain n-3 polyunsaturated fatty acids (LC n-3 PUFA) improve insulin resistance. In an 8 week dietary intervention, consumption of fish oil daily was a significant predictor of fasting insulin and insulin resistance when compared to a lean fish, fatty fish or a no fish diet[16]. Supplementation of diet with n-3 PUFA (1 g daily X 3.5 yrs) was also associated with a decrease in the risk of death (14%-20%) and cardiovascular death (17%-30%) in a large randomized controlled trial (RCT) of 11,324 patients surviving recent (< or = 3 months) myocardial infarction[17].

Populations eating mainly vegetarian diets have lower blood pressure levels than those eating omnivorous diets. The DASH diet, a diet high in fruits, vegetables with low-fat dairy products reduced saturated and total fat, whole grains, lean meats, fish/poultry and nuts/beans and reduced sweets/sugar-containing beverages, is recommended by several organizations including the American Heart Association and the National Heart, Lung and Blood Institute to help prevent and treat hypertension. In a clinical trial 459 adults with systolic blood pressures <160 mmHg and diastolic blood pressures of 80 to 95 mm Hg, were fed a control diet that was low in fruits, vegetables, and dairy products, with a fat content typical of the average diet in the United States for 3 weeks[18]. They were then randomly assigned to receive either a control diet, a diet rich in fruits and vegetables, or a "combination" diet rich in fruits, vegetables, and low-fat dairy products and with reduced saturated and total fat for 8 weeks. Both the combination diet & the fruits-and-vegetables diet reduced systolic and diastolic blood pressure more than the control diet. Similar reductions in blood pressure were seen in other studies of hypertensive subjects following The DASH diet [19],[20],[21].

In postmenopausal women (average age 54.6 yr, range 44-65 yr) with a body mass index of 27 to 39 kg/m2, a lower glycemic index diet program (incorporating 30 g of soy protein and 4 g of phytosterols per day) X 12 weeks resulted in a significantly greater improvement was observed in CVD risk factors (total cholesterol, low-density lipoprotein cholesterol and triglycerides) than with standard therapy (American Heart Association Step 1 diet; AHAD)[22]. Overweight individuals with metabolic syndrome are at increased risk of type 2 diabetes and coronary vascular disease. Weight gain and features of the syndrome may be ameliorated by dietary intervention. In overweight individuals with > or =3 metabolic syndrome risk factors, a low fat complex CHO diet can result in moderate weight loss and some improvement in serum cholesterol and triglycerides[23].

In patients already on lipid-lowering medications at maximal doses, intensive dietary intervention and addition of plant stanols (in margarine) resulted in clinically relevant reduction of low-density lipoprotein cholesterol (LDL) without a decrease in postprandial triglyceridemia[24]. Low-fat milk products enriched with plant stanol esters lowered both total cholesterol and LDL cholesterol in a statistically significantly manner in subjects with mild or moderate hypercholesterolemia[25]. In a multicenter, randomized, double-blind study conducted in men and women with primary hypercholesterolemia with baseline LDL cholesterol >/=97 mg/dl, the addition of sterol-ester margarine to statin therapy offered LDL cholesterol reduction

equivalent to doubling the dose of statin[26].Observational and clinical studies suggest that high protein intake, particularly protein from plant sources, might reduce blood pressure. In data analyses from PREMIER, an 18 month clinical trial that examined the effects of protein intake, dietary plant protein and fruit and vegetable intake in 810 subjects was inversely associated with both systolic and diastolic BP at 6 months[27]. Many of the key features of the various diets studied share common features; greater reliance on less refined carbohydrates, increased fruits and vegetables, limited saturated fat with increased mono-unsaturated and omega-3 fats, increased low-fat dairy products and moderate protein intake. Adoption of such diets often is associated with modest weight loss and improvement in cardiovascular risk.

Evidence that Exercise Intervention Positively Affect Health Outcomes of Patients with Metabolic Syndrome

For the purposes of this review, the type of exercise can be broken down as moderate intensity i.e. walking, aerobic exercise (at least 60% max capacity) and strength/resistance training. The literature supporting each type is briefly presented below.

In a large pseudo-experimental cohort study in Norway, a community-based 3-year theory-driven, low-cost, population-based tailored exercise intervention program increased physical activity levels, reduced weight gain, and reduced risk factors for type 2 diabetes and cardiovascular disease (triglycerides, cholesterol-to-HDL cholesterol ratio, systolic blood pressure & glucose levels) in patients ages 30-67 yrs[28]. Recent levels of physical activity, after adjusting for baseline age, chronic diseases, functional status, and lifestyle factors are reported to be an important factor for mortality risk among elderly men[29].

The benefits of aerobic exercise programs on reducing insulin resistance and cardiovascular risk are well documented. In hypertensive women (aged 35.5-37.7±5.5-7.2 yrs), a 6 week Physical Aerobic exercise program (45-60 min, X5/week) under the supervision of a physiotherapist, resulted in significantly improvements in cardio-respiratory and BP values, when compared to oral and written instructions about the benefits of aerobic physical exercise for controlling BP[30]. A 12 week moderate exercise training program (at 65% maximal aerobic capacity) i.e. 45 min, X3/week resulted in a significant reduction in plasma levels of triglycerides, fructosamine and glycohemoglobin in non insulin diabetic patients. The improvement in metabolic control persisted significantly in patients who continued to exercise at varying levels at home during 1 year of follow-up[31].

High intensity strength training over 8 weeks has been shown to result in significant gains in strength and functional status, in a population of 100 nursing home residents[32]. In another RCT in 100 frail nursing home subjects, high-intensity resistance exercise training was found to be feasible and an effective means of counteracting muscle weakness and physical frailty in very elderly people. Fiatorne et al showed that resistance exercise training over a 10-week period had a marked effect in overcoming muscular weakness compared to non exercisers in 87 yr olds[33]. In another RCT of 62 community-dwelling Hispanics (>55 y) with type 2 diabetes, 16 weeks of strength training resulted in improved muscle quality and reduced insulin resistance[34].

Current guidelines for the management of hypertension recommend regular, moderate intensity aerobic exercise such as brisk walking as a means of blood pressure reduction. In a recent study , a 24-wk walking program meeting the American College of Sports Medicine and the Centers for Disease Control and Prevention, physical activity recommendation (30 min of daily moderate-intensity physical activity) was found to be effective in lowering systolic blood pressure (BP) in 24 postmenopausal women with borderline to stage 1 hypertension[35]. Other studies have shown similar reductions in lipid levels and/or improvements in glycemic control with moderate intensity walking[36],[37]. Given the poor adherence to structured exercise programs, such as combined resistance and endurance type exercise or medical fitness intervention programmes, walking should be considered as a feasible and effective option in the elderly.

Effects of combined diet and exercise on metabolic syndrome

The combined diet and exercise approach, better known as lifestyle intervention, has been found to to reverse metabolic abnormallities, reduce reliance on pharmacotherapy and prevent progression to diabetes and cardiovascular disease.The following is a brief review of the recent literature citing the beneficial effects of lifestyle intervention on metabolic syndrome.

To determine the effect of intensive lifestyle intervention and metformin therapy on the incidence and resolution of metabolic syndrome, participants from research and community-based centers with impaired glucose tolerance (fasting glucose level ≥5.3 mmol/L) were randomized to an intensive lifestyle intervention consisting of 150 minutes of exercise per week designed to achieve and maintain a 7% weight loss, metformin therapy (850 mg twice daily), or placebo groups. In the lifestyle group, the incidence of the metabolic syndrome was reduced by 41% group vs. 17% in the metformin group compared with placebo at follow up (mean 3.2 yrs), showing that lifestyle intervention can improve metabolic syndrome[38]. Lifestyle intervention improved body weight and insulin sensitivity after 3 years in Dutch participants with impaired glucose tolerance. In the intervention group, diabetes incidence was reduced by 58%[39].

In a longitudinal cohort from the Data from an Epidemiological Study on the Insulin Resistance Syndrome (D.E.S.I.R), the impact of 3-year changes in lifestyle habits on metabolic syndrome parameters and on body mass index (BMI) were investigated in 4000 free-living subjects, aged 30-65 years,. Increases in physical activity over the 3-year period were associated with beneficial effects on syndrome parameters (i.e. lowering of insulin, glucose, systolic blood pressure and waist circumference), particularly in men[40]. In a 6 month intervention involving either aerobic exercise training alone or exercise combined with a structured weight loss program, the combined approach was found to be an effective treatment for hyperinsulinemia and lowering of diastolic BP in obese (BMI >or= 30) older (>or=65 y) patients with metabolic syndrome[41]. A 6-month lifestyle intervention decreased multiple metabolic CHD risk factors simultaneously in obese older adults when compared to no intervention [42].

The addition of exercise to diet therapy is reported to improve physical function and other obesity- and aging-related metabolic abnormalities[43]. A short-term (8 weeks), diet and exercise program, reported decreased weight, body fat, and central adiposity; improved indexes of metabolic syndrome; and increased self-reported wellness in 41 overweight or obese adults in a church congregation[44] . Exercise plus dietary counseling by exercise physiologists and dietitians for 12 wks improved body composition, lipid profiles, and several psychological parameters in obese adults when compared to exercise alone.[45].

In the Diabetes Prevention Study, a lifestyle intervention program involving diet-exercise was found to be efficacious in improving plasma glucose levels, blood pressure, serum lipids and anthropometric indices in 523 overweight subjects with impaired glucose tolerance when compared to control group. The intervention included ongoing sessions with a nutritionist aimed at reducing weight, decreasing the intake of saturated fat and increasing the intake of dietary fibre as well as providing guidance to increase their physical activity. The control subjects received general information at the start of the trial about the lifestyle changes necessary to prevent diabetes and at annual follow-up visits. In the first year, weight loss was higher in the intervention while plasma glucose concentrations were significantly lower than the control group, respectively.[46]

Lifestyle modifications have been recommended as the initial treatment strategy for lowering high BP. One hundred thirty-three sedentary, overweight men and women with non-medicated high-normal BP were randomly assigned to aerobic exercise only; a behavioral weight management program, including exercise; or a control group. Participants in the weight management group generally had larger reductions in BP, exhibited significantly lower fasting and postprandial glucose and insulin levels than compared to aerobic exercise alone or control. Based on these results, aerobic exercise combined with weight loss is recommended for the management of elevated BP in sedentary, overweight individuals[47].

Patients that are motivated to trial a lifestyle approach can cease drug therapy and be adequately maintained by the prescription of lifestyle advice via their Family Doctor. This was well demonstrated in a RCT in which patients (n = 45) with a history of hypertension (BP < 160/ 95 mm Hg for 6 months) randomized to continued medication vs. withdrawal of medication. Drug therapy in the withdrawal group was recommenced if BP was found to be >160/95 mmHg on two consecutive visits. Both groups were counseled regarding lifestyle behavior change by their GP and were provided with specifically developed self-help materials. At the 9-month follow-up, there were no cardiovascular events; 71% of subjects remained off drug therapy and were well controlled. Although no significant differences were observed in mean systolic or diastolic BP and cholesterol levels, the group stopping therapy had a 6% reduction in body mass index after 9 months. These data suggest that cessation of drug therapy may be an important motivating factor to achieve weight loss.[48]

In a two-year study on the possibility of replacing antihypertensive drugs by non-pharmacological therapy, 400 patients from eight health centers were followed up monthly with blood pressure measurements at home plus advice about changes of lifestyle including salt restriction, weight reduction, physical activity, and reduction of alcohol and tobacco. A total of 44% had discontinued drugs after two years without any increase in diastolic blood pressure. Twenty-five per cent reduced their weight by 4% or more, while 35% increased their physical activity. In one health centre 69% of patients were not taking drugs after two years. In some health centers the non-pharmacological treatment was quite successful, but in others the attempt failed[49]. It would seem that more tailored approaches to lifestyle intervention are needed.

Integrating the evidence from the previous mentioned studies would suggest that a combined tailored approach of lifestyle intervention with regular follow up is the ideal way to reducing the risks of metabolic syndrome in a non pharmacological manner.

Genetic determinants of metabolic syndrome and their interaction with lifestyle interventions

Considerable efforts have been made in recent years to identify the genetic contribution to obesity and insulin resistance. Increased abdominal obesity, insulin resistance, dyslipidemia, and elevated blood pressure are all hallmarks of the metabolic syndrome. Each of these traits has a genetic basis to it. The heritability of these traits is estimated to be as high as 70%; however, such estimations do not take into account the increasingly recognized influence of gene-environment and gene-gene interactions. As an example, obesity is recognized to be a multi-factorial disorder that stems from the interplay between genetic, behavioral, lifestyle, and environmental factors, as well as the influence of fetal programming[50,51]. This complex interplay underlies the considerable inter-individual variability that occurs in the development and severity of obesity and obesity-related complications within a population[52]. This multi-factorial complexity must also be considered for the other hallmarks of metabolic syndrome, such as insulin resistance, dyslipidemia, and blood pressure. Taken together, this suggests that integrating lifestyle interventions with genetic information may lead to a more personalized method to reduce the risks of metabolic syndrome.

Large genome wide association studies (GWAS) have identified numerous genetic loci associated with BMI and waist-to-hip ratio; however, each of these individual loci has only a small effect on BMI and/or waist-to-hip ratio[53,54]. In fact the combined results of GWAS have been shown to explain <10% of the variability observed with obesity; reinforcing that genetics is not the sole determinant regarding body weight. The greatest effect that has been reproducibly reported is with the fat-mass and obesity associated (FTO) gene, where each risk allele increases BMI between 0.26-0.66 kg/m^2 [55]. This modest effect on body weight reinforces that our current understanding of the molecular and genetic components of obesity remain incomplete, thus highlighting that genetic information alone is insufficient to successfully treat the metabolic syndrome effectively.

Studies have begun to examine (in a retrospective manner) whether single nucleotide polymorphisms (SNP) in candidate genes are associated with responses to lifestyle interventions. For example, a recent study examined whether a FTO variant (rs9939609) was associated with adiposity and cardiorespiratory

fitness before and after a 6-month moderate exercise period in white women[56]. Although the authors did not identify a genotype-by-exercise interaction, they did note that women with the risk allele who exceeded physical activity recommendations experienced greater benefits regarding weight loss and cardiorespiratory fitness. However, an alternate study by Muller et al reported that FTO variants did not alter weight loss or circulating triglyceride levels in German children following a 6-month lifestyle intervention[57]. Such conflicting results are not uncommon when considering genetic-based work because most studies tend to use small cohort sizes. This reinforces that importance of performing replication studies to improve our understanding of the relationship between common genetic variants and weight loss during a lifestyle intervention.

Dyslipidemia is another hallmark of metabolic syndrome, with low levels of high-density lipoprotein (HDL)-cholesterol in particular a major risk factor for the development of cardiovascular complications. Apolipoprotein A1 (ApoA1) is the primary apolipoprotein associated with HDL. A common SNP (-75A/G) in the promoter region of ApoA1 has been demonstrated to be associated with blood pressure and variability in HDL response to statins and fish oil supplementation[58]. Ruano et al examined whether this SNP influenced HDL levels following a 6-month aerobic exercise program. Although no genotype-specific changes were observed with regard to total HDL levels, the authors reported there was a genotype-specific effect on HDL particle size. This SNP has been repeatedly associated with fasting HDL levels; however, little research has examined whether this SNP influences an individual's response to a lifestyle intervention. Therefore further studies focused on this SNP and its effect on weight loss and altered clinical parameters are crucial.

To the best of our knowledge only a single research study has examined the added value of genetic information for weight maintenance in a prospective manner. In 2007, a personalized energy-restricted diet (i.e. genetic testing complemented by specific dietary advice and/or supplement consumption to account for deficiencies) was implemented in a clinical trial and compared to a generic energy-restricted diet[59]. In other words, some subjects consumed a common energy-restricted diet, whereas other subjects consumed an energy-restricted diet in accordance with genetic information. The authors clearly stated the intention was not to design personalized weight loss diets *per se*; rather they sought to optimize a subject's nutrient intake in light of the current understanding of genomic variation and diet-gene interactions to better motivate these individuals for compliance and weight loss. A panel of SNPs related to folic acid metabolism, phase II enzyme detoxification, oxidant balance, bone health, inflammation and lipid metabolism were genotyped; no polymorphisms modulating obesity risk were examined. The results suggested that those in the 'genetic-tested' group were significantly more likely to maintain weight loss in the longer term (300+ days) as compared to the 'non-tested' group. Although encouraging, such a result must be replicated in larger cohorts prior to the wide-spread implementation of nutrigenomics as a means to combat obesity.

Objectives of the Project:

Specifically the objectives of this demonstration project are to:

1. Develop and implement a program through FDs supported by kinesiologists and dietitians to show that a regimen of nutritional modification and graded exercise over a 1 year period will:
    a. Reduce components of the Metabolic syndrome referred to above
    b. Reduce reliance on pharmacological drug use.
    c. Evaluate the feasibility of team-based approach to manage MS
2. Explore the relationship of the response to lifestyle changes on cardiometabolic risk according to genotype.

Study Design & Setting: A Prospective, cohort study of 300 patients enrolled from 3 primary care clinics, where assigned primary care physicians from large practices will enroll patients with the metabolic syndrome. The principal investigators from the centers are:

Polyclinic, Toronto (Dr. Lew Pliamm)
Laval (Dr. Gilles Lortie)
Edmonton (Dr. Douglas Klein)

Study Population
Inclusion Criteria: Adult Patients identified by their family doctor as having the metabolic syndrome.

- Age ≥ 18

Metabolic syndrome is defined as having 3 out of 5 of the following criteria:

- Fasting Blood Glucose ≥ 5.6 mmol/L or receiving pharmacotherapy
- Blood Pressure of ≥ 130/85 mm Hg or receiving pharmacotherapy.
- Triglyceride of ≥ 1.7 mmol/L or receiving pharmacotherapy
- HDL-C < 1.0 mmol/L Males and <1.3 mmol/L females
- Abdominal circumference as determined by a pre-specified technique:
    - Europids, Whites, sub-Saharan Africans, Mediterranean, middle east (Arab) ≥ 94 cm Males, 80 cm Female.
    - Asian and South Central Americans ≥ 90 cm males and 80 cm females
    - US and Canadian Whites ≥ 102 cm males, 88 cm females.

Exclusion Criteria: We propose to exclude patients who, for medical reasons, would be unable to exercise or have a life-limiting illness that such a longitudinal study would not be appropriate. Subjects meeting any one of the following exclusion criteria will not be enrolled into the study.

1. Inability to speak, read or understand English and/or French for the Laval University participants.
2. Having a medical or physical condition that makes moderate intensity physical activity (like a brisk walk) difficult or unsafe.
3. Diagnosis of Type 1 diabetes mellitus
4. Type 2 diabetes mellitus if any one of the following are present
    a. Proliferative diabetic retinopathy
    b. Nephropathy (serum creatinine > 160 µmol/L)
    c. Clinically manifest neuropathy defined as absent ankle jerks
    d. Severe hyperglycemia (FBS > 11 mmol/L)
    e. Peripheral vascular disease
5. Significant medical co-morbidities, including uncontrolled metabolic disorders (e.g., thyroid, renal , liver), heart disease, stroke and ongoing substance abuse
6. Clinically significant renal failure
7. Diagnosis of psychiatric disorders (cognitive impairment) that would limit adequate informed consent or ability to comply with study protocol
8. Diagnosis of cancer (other than non-melanoma skin cancer) that was active or treated with radiation or chemotherapy within the past 2 years
9. Diagnosis of a terminal illness and/or in hospice care
10. Pregnant, lactating or planning to become pregnant during the study period
11. Investigator discretion for clinical safety or protocol adherence reasons
12. Chronic inflammatory diseases.
13. Body Mass Index > 35

Recruitment Procedures

Patients coming to the physician's office who are noted to have one of the components of this syndrome will be evaluated by the physician for the other components which will allow the diagnosis of the metabolic syndrome.

Study Intervention

The proposed interventions will include a combined diet and exercise program delivered by the Family Doctor (FD) in collaboration with the dietitian and kinesiologist, led by the FD and will be guided by 3 key principles: 1) The nutrition and exercise intervention will be individualized and graded (build up slowly over time); 2) behavior modification will be provided by constant support and evaluation by the FD as well as the dietitian and kinesiologist; and 3) the program will be supervised and implemented in conjunction with the FD.

A brief outline of the intervention with the person most responsible is as follows:
1. Enroll patient, complete baseline measurements and stabilize medication (FD).
2. Create a diet plan tailored to the individual patient based on the literature review (Study Dietitian).
3. Create exercise plan tailored to the individual patient based on literature review (Study Kinesiologist).

Details for each of these interventions is outlined below.

Role of the Physician

Identify the presence of the syndrome: The FD will determine if the patient has metabolic syndrome during routine physical examination or annual checkup according to the inclusion criteria. The FD will order fasting blood glucose, triglyceride and HDL-C as initial bloodwork as part of routine assessment. Since these tests are well recognized as being part of routine screening done by FDs, they should not be viewed upon as tests done for research purposes only. In addition the FD will measure blood pressure and waist circumference to complete the assessment for diagnosing the metabolic syndrome.

Determine the ability of the patient to follow a Diet-Exercise program: At the time of the physical examination/annual checkup, the FD is to carry out a complete history, physical examination and mental evaluation to determine the presence of physical or neurological and cognitive disorders which may prevent an exercise program or require modifications. In this context it is important to recognize that frailty, age or even neurological conditions like paraplegia are not absolute impediments to exercise. Refer to the exclusion criteria. Furthermore, gastrointestinal disease, intolerance, allergies and bowel habits need to be assessed to advise the study dietitian so that an appropriate diet plan can be followed. The FD is also to assess general eating and exercise patterns which may alert the physician to risks of enhancing metabolic syndrome[60].

Additional Blood Work at baseline: If the patient has metabolic syndrome according to the parameters described in the inclusion criteria, the FD is to order the following blood work, considered to be standard testing when evaluating the risk of hypertension, cardiovascular disease or diabetes:
- serum creatinine, urinary albumin/creatinine ratio to assess renal function and
- C- reactive protein (CRP) to assess inflammation

Assess stage of readiness to CHANGE: The FD is to gather baseline information related to the patient's readiness to change according to this simple validated set of questions:
1. I have not really thought about the role of diet-exercise (Pre-contemplative stage)
2. I have thought about diet-exercise but have not got to doing it (Contemplative).
3. I go on a program of diet-exercise from time to time but stop (Action).
4. I have been regularly exercising and trying to eat a good diet (Maintenance).

Enrollment into CHANGE: If the inclusion and exclusion criteria permit the patient to be enrolled, the FD will obtain informed consent and enroll the patient and proceed with taking blood for DNA isolation and ApoA1 analysis. Isolation of DNA is to examine whether improvements in cardiometabolic risk in response to lifestyle changes vary according to genotype and ApoA1 analysis is to examine the response of diet to metabolic syndrome. A blood sample of approximately 17 ml will be needed at the start and also at the end of the study acoording to procedures outlined in the supplementary laboratory procedures. The FD will also keep a log of the following patients:

1. Patients who do not meet criteria despite having the metabolic syndrome
2. Patients refusing consent and reasons for refusal.

Determine if initial pharmacotherapy is essential: The FD is to determine if initial pharmacotherapy is needed or whether changes need to be made. As a general guideline, this is usually indicated under the following circumstances[8] .

- Triglycerides >5 mmol/L
- LDL-C >5 mmol/l
- BP >160 mm systolic or 100 mm diastolic
- Renal insufficiency GFR <50 mL/min/1.73m2

Counsel the persons and "Nudge" them to adopt a Diet-Exercise program (behavior modification exercise): The data obtained above will allow the FD to motivate the patient and create a plan for correcting the metabolic syndrome based on clinical examination, laboratory tests and response to the questions about readiness to change. The term "Nudge" is the process of showing that the patient has freedom of choice at the same time facilitating change. This process is implemented by discussing the alternatives available while showing the unique benefits of change, facilitating is implementation physically and providing support for that direction. The discussion with the patient depends upon the stage of readiness mentioned above.

- Pre-contemplative stage: The patient needs to be given a personalized commentary about the physician's findings and health risks. Then information provided about the benefits of diet and exercise in reducing the risks followed by access to written material or websites (Appendix I). If the patient is eager to follow the diet-exercise plan then he/she should be introduced to the Dietitian and Exercise therapist. If there is concern, reluctance or confusion about the findings, then another appointment is to be scheduled as he/she is in the contemplative phase.
- Contemplative Phase: Patients in this phase of thinking it is necessary for the FD to:
    - Increase their motivation to change lifestyle
    - Imbue them with the belief that diet-exercise will benefit them.
    - Discuss and allay fears about this process
    - Clarify misconceptions
    - Indicate the degree of support available from Dietitians and exercise therapist
- Action and Maintenance Phase: very important to praise their effort, demonstrate improvements achieved in the parameters of the metabolic syndrome.

Although the FD is primarily responsible for convincing the patient to adopt the diet-exercise intervention, the dieititian and kinesiologist must re-enforce the FDs message.

Interact with Dietitian and Exercise therapist about the regimen: It is critical that the patient be introduced to the dietitian and exercise therapist in a manner which indicates that the treatment is a direct continuation of his/her physician's management and not a transfer of care. This can be done by sending the dietitian and exercise therapist a Physician Referral Form detailing the following:

- Severity of metabolic syndrome
- Stage of readiness to undertake program
- Complications and limitations of the patient.
- Drug history and its effect of the proposed therapy

- Relevant indications to be considered in the diet-exercise program. This refers to relevant notes that are presented by dietitians and kinesiologists and that are worth of consideration.
- Follow up plans with physician and need for report of the success and problems encountered by the dietitian-kinesiologist.

Follow progress and modify pharmacotherapy, encourage compliance and remove barriers to compliance: Regular follow up modification of drug requirements and encouragement to the patient is required at 3 monthly intervals for a year or more as deemed necessary by the FD.
Blood for CBC, fasting glucose, serum creatinine, Hb A1C, total cholesterol, LDL and HDL as well as triglycerides will be drawn 1 week prior to seeing FD and results will be available at the visit. .

At each visit with the FD the patient will be assessed for:

1. Development of clinical cardiovascular disease
2. Change in blood pressure
3. Change in weight
4. Change in waist circumference
5. Change in fasting blood glucose and Hb A1C
6. Total, LDL and HDL cholesterol and triglyceride

In addition the FD will discuss any difficulties with following program and will reinforce the benefits of the program as well as congratulate the patient on following it. The FD will then check the criteria for continuing on pharmacotherapy and make changes to medications based on the criteria described earlier for instituting pharmacotherapy.

Initially, patients will meet weekly with the study dietitian and kinesiologist to monitor success of the intervention, ascertain barriers and facilitators, and ensure compliance. The duration of these weekly visits will vary for different patients and will be left up to the discretion of study personnel.

Dietary Intervention

Although the literature previously presented shows that diet is an integral part of lowering the abnormalities associated with metabolic syndrome, the most "effective" diet changes remain somewhat controversial, for several reasons. The food "behavior" changes patients achieve are seldom directly assessed in the community setting and most often only daily mean nutrition intakes are reported. The most common diets, the Mediterranean, DASH and weight loss diets, as described earlier substantially overlap on several key features, but differ on some specifics, depending on the patients' specific metabolic profile. Thirdly, some diet changes are easier to change than others, especially substantial changes over the longer term, given people's preferences, habits and lifestyle. Therefore, diet interventions for this project have been designed so the counselling dietitian can choose from a range of options for specific food behaviour changes, and no one approach or diet is solely promoted.

Role of Dietitian

Upon referral of patients by the physician (and receipt of the Physician referral form), the diet intervention will be conducted by a Registered Dietitian (RD) at each clinic, using the Dietary Management Care Map as a guide (See Appendix 1). Local dietitians will be responsible for providing individualized care within the care map framework and will participate in a national mentoring support program from Guelph. They will be provided with a substantive dietary guidance package for each component of the intervention that provides the principles, key advice, strategies, and client resources that can be used to help clients achieve dietary behaviour change.

In the first session, the RD will complete an initial nutrition assessment on each client, followed by a review of the basic principles of dietary intervention for metabolic syndrome with an emphasis on the clinical risk factors identified for the client. A joint goal setting exercise will then be conducted with the

client to determine what dietary changes are feasible, considering intention and barriers to dietary behaviour change.

While calorie reduction can be achieved with a direct focus on limiting total caloric intake, it is also possible to achieve reduction by focusing on changes in the types of foods consumed, through caloric dilution, by increasing fruits, vegetables and fibre intake, without a direct focus on caloric intake. When weight loss is not a direct focus, a number of other specific food behaviour changes will be considered as detailed below, tailored to the individual, their presentation of metabolic syndrome and exercise program.

Diet Management of Dyslipidemia or Hypertension (excluding weight loss)

	Diet Therapy Goals
Carbohydrate control	• *Balance meals* • *decrease* ***added sugars*** • ***glycemic index*** • ***carbohydrate counting***
LDL-C	• ***Fat Quality***: decrease trans and saturated fat (<7-10% of calories); increase monounsaturated fat (***increase nuts***) • increase ***soluble fibre*** (10-25g/day) • increase ***plant sterols*** (2 g/day) • increase ***vegetables and fruit*** (7-10 servings/day according to age and sex) • increase ***plant protein*** (e.g. 50 g/day soy protein or legumes)
Elevated triglycerides	• *Balanced meals,* • *Fat Quality: decrease trans and saturated fat* • increase *omega-3 fat* (1g/day EPA and DHA from fish, fortified foods and/or supplements). (A dose of 2 to 4 g/day EPA and DHA could be considered as a component of medical management for adults with extreme hypertriglyceridemia under the supervision of a physician). • decrease ***sugars and refined carbohydrate*** • alcohol abstinence
Low HDL-cholesterol	• *Fat Quality*: decrease trans fat; increase monounsaturated and omega-3 fat (*increase nuts*) • moderate alcohol intake (if triglycerides are not substantially elevated) • increase ***vegetables and fruit*** • increase ***plant protein***

Elevated Blood Pressure	• ***Reduce sodium***:
	  ○ ≤1500 mg (65 mmol)/day if ≤ 50 years of age
	  ○ ≤1300 mg (57 mmol)/day if 51 to 70 years of age
	  ○ ≤1200 mmol (52 mmol)/day if over 70 years of age
	• DASH Eating Plan (***increase vegetables & fruit, increase fibre, increase nuts, increase low fat dairy)***
	• moderate alcohol intake

Counselling and Education Interactions Using Behavioral Therapy

Initial counselling will consist of individual sessions using motivational interviewing skills and active listening. The target for planned follow-up will be weekly for 3 months, and monthly for 9 months and can consist of either a) individual support (one-on-one) which could consist of face-to-face or phone, e-mail or b) Group support which could consist of group education classes, group seminars (in-person or by phone), conversation maps or grocery store tours, cooking classes etc. Behavioural strategies will be incorporated into all client interactions, consisting of: cognitive behavioural therapy, goal setting, self-monitoring, reinforcement, rewards, problem-solving, relapse prevention and self-help / self-management.

Evaluations

In addition to clinical parameters (blood and body composition measurements, pharmacotherapy) used to document risk factors for metabolic syndrome, the dietary assessment will evaluate the following:

- assessment of calories, macro- and micronutrients, food groups and healthy eating index (HEI)
- the % of subjects who adopt specific changes in target diet behaviours among those who were counselled to do so
- ways to improve uptake of the diet intervention for those who started but did not complete the diet and exercise program.
- the most "effective" modes of follow-up (F/U) in the first 3 months - evaluation of what F/U methods are preferred and what is the completion rate among the different F/U groups; differences in preference by age, gender, working status, general health and household size

Baseline - Complete nutrition assessment including dietary analysis (based on two 24 hour food recalls using ESHA computerized nutrient analysis plus food frequency information), calculation of calories, macro and micronutrients, food groups and healthy eating index (HEI)

Weekly for the first 3 months and then monthly for the next 9 months - follow-up method used (e.g. individual, group, face-to-face, phone, e-mail), dietary changes made (e.g. decrease added sugars, balanced meals, increase plant sterols), dietary goals for next visit, RD recommendations and resources used.

3, 6, 9, 12 months - follow-up nutrition assessment including dietary analysis as at baseline, behaviour changes achieved and barriers to behaviour change. Repeat dietary analysis as at baseline and barriers to behaviour change assessment.

Exercise Prescription and Fitness Program

The basal exercise prescription to every participant will be supervised by a kinesiologist in a fitness center being adjacent or close to each research team being in charge of interventions in the CHANGE Project. In Toronto, exercise will be performed in the fitness center that is adjacent to the clinics where Dr. Jeejeebhoy has a clinical practice in gastroenterology. In Quebec City, the fitness room will be located in the *Laboratoire des sciences de l'activité physique* where Dr. Tremblay maintains the major part of his research activities. In Edmonton, the fitness center will be located at Edmonton Oliver PCN. The clinic kinesiologists will be trained by the Kinesiologist Coordinator at the Laval clinic and will be responsible for providing an individualized exercise plan to each subject enrolled. The exercise plan will also include a fitness assessment to be done by the kinesiologist.

Role of the Kinesiologist

Once participants (patients) will have been recruited by physicians, they will be referred to the kinesiologist at the clinic for the assessment of fitness and physical activity habits and the dietitian for nutritional assessment. The exercise tests that will be administered in each center have been selected on the basis of their applicability in the large majority of fitness centers in Canada as well as for their good

potential compatibility with the physical condition of low to moderately fit individuals. These tests are recommended by the Canadian Society of Exercise Physiology (CSEP) [61] and their administration has to be done according to standard laboratory procedures. Beyond the documentation of the fitness profile of participants, the aerobic fitness test will also be used to determine the eligibility of a participant in the project: it will be based on the absence of detectable signs of misadaptation to exercise following the physician's selection and reference.

Fitness Assessment

Aerobic fitness

The methodology described by Ebbeling et al[62] will be followed to estimate maximal oxygen consumption. The technical details of this test were described by CSEP and are presented in Appendix 2. Beyond the preoccupation to have a marker of maximal aerobic power, the investigators also wish to obtain a standardized measure of the change in heart rate at a given work load before and after the program. For that purpose, the kinesiologist will be requested to slightly push upward the treadmill speed (e.g. 3.6 km per hour instead of 3.4) and this speed will be the same for the first step of the test at the end of the program. The variables that will be computerized from this test will be heart rate, blood pressure and perception of effort (Borg Scale) at a reference treadmill speed as well as maximal oxygen consumption.

Muscular and flexibility tests

Kinesiologists will also assess muscular endurance and vigor with the measurement of partial curl-ups and the adapted push-up test described in Appendix 3A and 3B respectively[61]. A test of flexibility will also be performed since this fitness characteristic is an important determinant of autonomy and daily functionality in aging adults. The flexibility test that will be administered both before and after the program is described in Appendix 4[61]. The variables being computerized from this series of tests will be the maximal number of partial curl-ups (up to 25) and push-ups performed in one minute as well as the distance (cm) being covered by a standardized trunk flexion.

Exercise Program

The modalities of exercise prescription have been fixed to target the largest part of the population aged between 40 and 65 years and to be compatible with the facilities available in the large majority of fitness centers in Canada. In addition, the program will be based on exercise modalities that have been previously experienced in obese subjects being at greater risk to display the metabolic syndrome and that has been shown to be effective to normalize metabolic fitness in these individuals[63,64]. It will also be concordant with the position of the American College of Sports Medicine regarding the prescription and practice of physical activity for older adults[65]. Specifically, the basal exercise prescription will include treadmill work bouts of 20-30 minutes performed at 50% of maximal heart rate 3 times a week. This will be accompanied by muscular and flexibility exercise.

The program is designed in a way to reconcile standardization and flexibility of prescription. Indeed, while the kinesiologists will wish the accomplishment of a standard exercise session, different alternatives of exercise will be available. With respect to the type of aerobic exercise, it will also be acceptable to use an ergocycle, an elliptic machine, a stair machine or a rowing machine, if these equipments are available. Regardless of the type of exercise, its intensity in terms of percent maximal heart rate will be monitored..

Physical activity participation

The kinesiologist supervising exercise in each center will be responsible for the record of what will be performed by every participant within each session of exercise. The information to be computerized will be the type of aerobic exercise (cycling, jogging, swimming, etc.), its duration (min per session) and intensity (heart rate in bpm when available), and its weekly frequency. A record will also be completed about muscular and flexibility exercises in terms of type of exercise and number of repetitions. Beyond the records completed by the kinesiologists, each participant will complete a record book in which the

relevant details (date, type of exercise and duration) about exercise performed outside training centers will be noted. This information will be periodically coded and recorded by the kinesiologists.

Fitness variables will be measured before and after the one-year protocol whereas physical activity participation will be systematically monitored to ensure the adequate compliance of subjects as well as to document their progressive change in physical activity participation.

It is expected that within several weeks, there will be a progression in exercise modalities, in accordance with the exercise tolerance of every participant. Specifically, within the first 3 months of the program, the following progress could be achieved:

- Duration of aerobic exercise progressing from 20-30 to 45-50 minutes per session.
- Intensity of aerobic exercise progressing from 50 to 75% maximal heart rate, with the goal to target an intensity of 65-75% maximal heart rate in most sessions after the first three months.
- Diversity of exercise type increasing according to the preference of participants, if relevant.
- Frequency of exercise increasing from 3 to 5 sessions per week.
- Number of repetitions of muscular and flexibility exercises increasing according to the capacity of participants. The intensity of muscular exercises should be at a level promoting perceived fatigue after 15 to 20 repetitions.

Throughout the program, kinesiologists will pay a particular attention to security in order to prevent injuries and discomfort of any nature. In this regard, the certification of Exercise Physiologist by CSEP will be an asset for every kinesiologist being involved in the CHANGE Project. A non complete adherence or the inability to perform the globality of the exercise prescription is *not* a matter of withdrawal. The kinesiologist will then have to pay a particular attention to the assistance to participants who might experience some difficulty

With respect to exercise being performed outside the fitness center, each participant will be encouraged to take advantage of relevant opportunities in the daily schedule to be physically active. This may include walking the dog, playing with kids or active domestic work. As indicated above, this physical activity participation will be computerized as time of unsupervised physical activity.

The Context of Supervision

The atmosphere of exercise sessions in each fitness center will not be a matter of objective documentation but is perceived as a critical issue for the motivation and compliance of participants. In this regard, kinesiologists will be instructed to promote socialization and a context of pleasantness during exercise sessions with every participant. Accordingly, we also wish to emphasize the relevance of promoting the organization of some group activities favoring socialization and a sentiment of partnership within the CHANGE Project.

Outcomes

The successful outcome is normalization of metabolic risk without pharmacotherapy. The primary outcome of this study will be the proportion of patients that have a reversal of the features of the metabolic syndrome present in individual patients (return to the normal range) or elimination of drug therapy based on normalization of the features of the metabolic syndrome. At 3 months, we will compare glucose, lipid, and cholesterol levels and medication profiles to baseline measures. We will also assess the durability of the treatment effect over time by continuing to measure study outcomes every 3 months during the duration of the study. At each time point, we will also assess compliance with study diet and exercise program. To assess barriers and facilitators to implementation, we will develop a questionnaire for patient barriers and facilitators. Finally, we will obtain permission to link patients' records with administrative databases to compare health care resource utilization pre and post intervention.

Data Collection

The following will be recorded upon enrollment into the study: inclusion criteria met, age, sex ethnicity, reason for visit, medical history, comorbidities, presence of inflammatory conditions, height, weight and BMI. In addition, the recording of serum creatinine, urinary albumin/creatinine ratio, C- reactive protein (CRP) at baseline will be suggested. Nutritional assessment including macronutrient intake, 24-hour food recalls and the health eating index will be recorded at baseline and repeated at 3 and 12 months along with weight changes, waist circumference, hip circumference and barriers to change. Fitness assessment will be done at baseline, 3 and 12 month whereas the type of exercise, duration, frequency # repetitions, heart rate and unsupervised exercise will be documented at baseline and at least every 3 month intervals or more frequently as per discretion of the kinesiologist. Fasting blood glucose, triglyceride and HDL-C will be collected quarterly at follow up appointments as per discretion of the FD. Results of genotyping will be collected at baseline and 12 months. Pharmacotherapy and changes for abnormal lipid levels, blood pressure, renal insufficiency or diabetes, & concomitant medications taken including vitamin/mineral supplements throughout the entire 1 yr period will be recorded. In addition, readiness to change, barriers and facilitators, and compliance to diet and exercise interventions will be recorded.

Data Management

The coordinating centre for this study is located at the Clinical Evaluation Research Unit (CERU) at the Kingston General Hospital and consists of a staff with experience in all phases of the design, conduct, monitoring and interpretation of clinical trials and quality improvement initiatives. The trial project leader will take overall responsibility for the development of the study protocol, informed consent form template, study procedures manuals, day-to-day conduct of the project, visiting all centers, and working with the study investigators to establish the project. CERU will also be responsible for all aspects of data collection and processing, including processing of trial entry data, data entry, questionnaire monitoring, following up on missing information and non-responses. A web-based data entry/query/monitoring system for efficient conduct of the project will be developed that will allow the formal analysis and reporting of the data. The web-based electronic data capture system will have build-in security systems to guard against harmful attacks and unauthorized access.

Sample Size Considerations

We propose to enroll a consecutive sample of 300 eligible patients. We have not performed a sample size calculation; but rather aim to demonstrate the feasibility of the study procedures in a representative sample from each of the three sites (100 patients per site; 3 sites).

Statistical Analyses

The proportion of patients meeting the primary outcome will be reported with corresponding 95% confidence intervals. All standard errors, p-values and confidence limits will account for the patients being nested within physician[66]. *A priori* we deem the 12 month assessment as primary, but we will also report the estimates at 3, 6 and 9 months. We will attempt to collect follow-up on all patients regardless of compliance, and all collected data will be included in the analysis. However, the primary analysis will use multiple imputation based on all available relevant information to minimize the impact of missing data due to loss to follow-up[67]. Furthermore, missing data patterns will be described in detail, and sensitivity analyses will be conducted where patients lost to follow-up are counted as treatment failures and where the last available response is assumed to carry forward (i.e. last-value carried forward).

The responses to the patient and physician barrier questionnaires as well as the distribution of the glucose, lipids, medication profiles and compliance at each time point will be summarized. Changes from baseline in glucose, lipids and medication will be assessed at each follow-up assessment using a linear mixed effects model for longitudinal data[68]. This model will account for the dependence of multiple assessments (i.e. baseline, 3, 6, 9 and 12 month) for a patient and multiple patients per family physician. The model will not assume a linear time trend and will allow for differing variances at each time point and

different covariance between time points[69]. If necessary, a log or other power transformation will be applied to the dependent variable[70]. A secondary exploratory analysis will add covariates including sex and age to the aforementioned model to identify potential barriers and enablers of compliance and improvement.

Trial recruitment and Duration

The purpose of this demonstration project is to use diet and exercise interventions to reverse the changes, reduce reliance on pharmacotherapy and prevent progression to diabetes and cardiovascular disease. The follow up period for the project is 12 months from the time of ernrolment into the project.

It is anticipated that the necessary approvals will be obtained and hiring of staff and training of sites be completed to start recruitment of patients across the 3 centers by Q2 2012. The data analysis and results of the project are anticipated to be ready by the end Q4 2013. If the demonstration project is successful, we plan to disseminate our findings across the health care system and 'change' the way nutrition and exercise information is provided to patients with the metabolic syndrome.

Ethics

Given that our study intervention is not consistent with usual care and that we are drawing extra blood work for genomic analysis, we will need to obtain individual consent to participate in this study. The RC will explain the study procedures and the risk and benefits associated with the project and obtain consent from participating patients. This protocol will be approved by a Research Ethics Boards of the participating clinics or affiliated Universities prior to implementation.

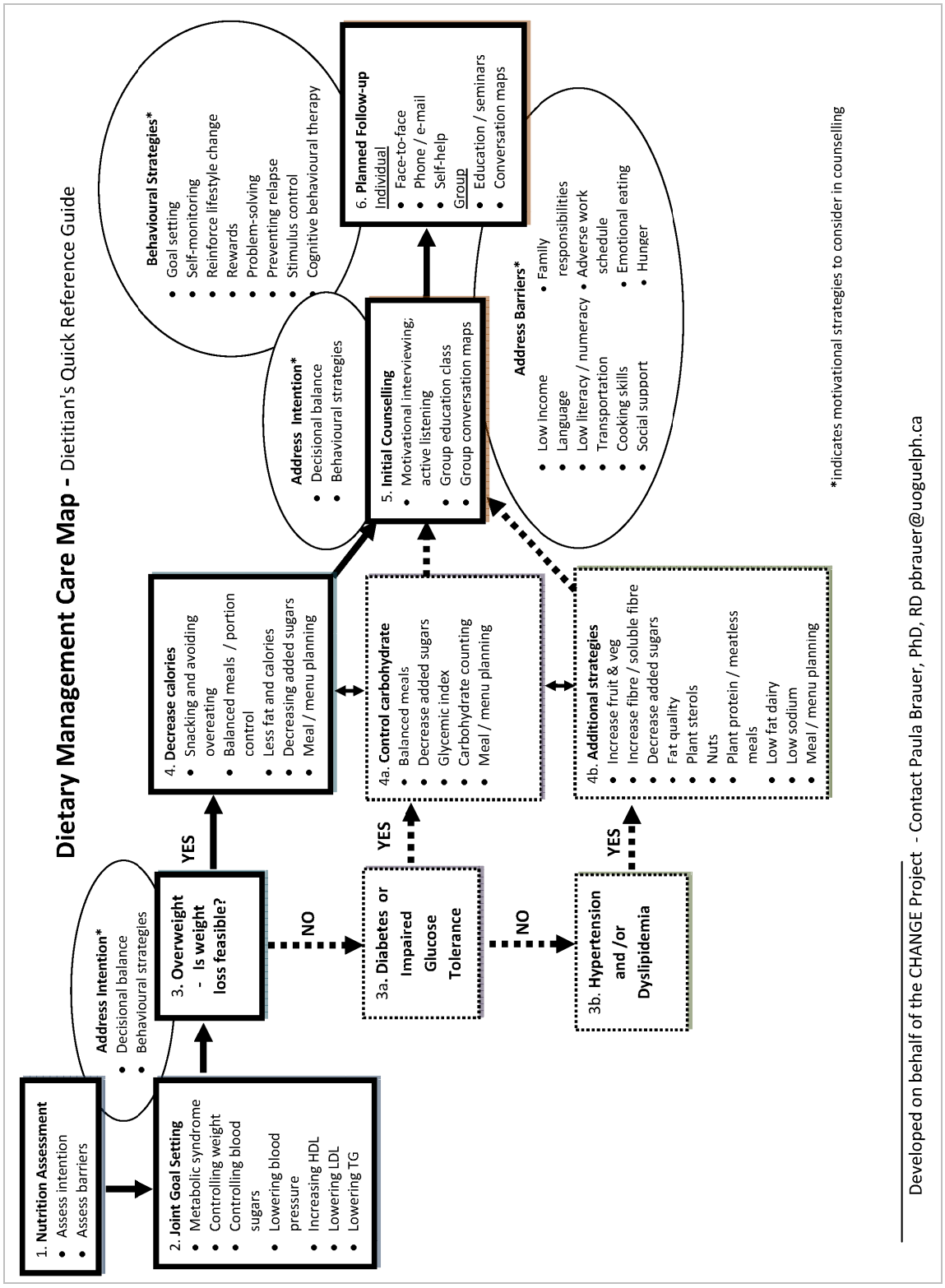
Study Team and Responsibilities

Dr. Khush Jeejeebhoy, Paula Brauer, Angelo Tremblay, Dr. Leah Gramlich, will comprise the study team and be responsible for the content of the interventions of the project. Dr. Daren Heyland and Rupinder Dhaliwal will provide methodological and operational support for the project. Dr. David Mutch will be responsible for the genomic analysis of blood samples.

Summary

Metabolic Syndrome, a group of factors that increase the risk of hypertension**,** cardiovascular disease, strokes & diabetes is a major contributor to healthcare costs. There is strong evidence from recent literature that demonstrates a reduction in these risk factors with the adoption of a combined diet and exercise intervention. The current model of preventive care by FDs does not include a tailored approach towards such a combined diet and exercise regime. The CHANGE demonstration project will identify patients from primary care clinics with metabolic syndrome and it is anticpated that the adoption of a tailored diet and exercise intervention provided by the FD in conjunction with a dietitian and kinesiologist, will result in improvement in metabolic abnormalities, reduce reliance on pharmacotherapy and prevent progression to diabetes and cardiovascular disease in these patients. If the results of this demonstration project are positive, the knowledge and tools developed will be used to widely disseminate to other sites to support their adoption.

Appendix 1



Appendix 2

■ THE SINGLE STAGE TREADMILL WALKING TEST (EBBELING ET AL. 1991)

The single stage treadmill walking test is a submaximal aerobic fitness test that estimates VO_2max. It is suitable for low risk, apparently healthy, non-athletic adults 20-59 years of age. The walking pace required throughout the test also makes it appropriate for participants who experience problems such as knee pain when exercising at a jogging pace. The test can be administered to moderate sized groups of participants with low to moderate fitness levels and requires only a treadmill and a HR monitor.

Protocol

The walking speed for the test is individually determined based on the participant's gender, age, and fitness level.

1. Briefly explain the purpose of the test and how it is conducted.

2. Estimate the participant's age-predicted HRmax (220-age) in bpm then calculate 50% bpm and 70% bpm of his/her HRmax.

3. Have the participant warm up for 4 minutes at a 0% grade and a walking speed that brings the HR to between 50% and 70% of his/her HRmax. (The recommended walking speed is from 3.4 to 4 mph). If the HR is not in this range after the first minute, adjust the speed accordingly.

4. Following the warm-up, keep the participant at the same speed for an additional 4 minutes at a grade of 5%, then record the steady-state HR (SS HR) from the average of the final 30 sec of the last two minutes at the 5% grade. (Note: to achieve steady-state, the HR from the last two minutes must not differ by more than 5 bpm. If the HR differs by more than 5 bpm, extend the test by an additional minute and record the SS HR from the new final two minutes.)

5. Enter this SS HR into the equation below to estimate VO_2max (mL • kg^{-1} • min^{-1}).

6. Allow the participant to cool down at a slow walk and 0% grade for 2-5 min. Monitor and record the HR in bpm every minute.

Interpretation

VO_2max is estimated using the following equation:

Estimated VO_2max (in mL • kg^{-1} • min^{-1}) = 15.1 + (21.8 x speed in mph) - (0.327 x SS HR in bpm) - (0.263 x speed x age in years) + (0.00504 x SS HR in bpm x age in years) + (5.98 x gender: female = 0, male = 1)

To obtain the Health Benefit Zone Rating from Figure 7-12, multiply the estimated VO_2max by 10.

Use Tool # 16a, Ebbeling Single-Stage Treadmill Walking Test Data Collection Form, to track and calculate results

■ EXAMPLE

Client is a 30-year-old male who walked at 3.6 mph at a grade of 5% with a SS HR of 159 bpm.

HRmax = 190 bpm;
50% HRmax = 95 bpm;
70 % HRmax = 133 bpm:

Estimated VO_2max

= 15.1 + (21.8 x 3.6) - (0.327 x 159) - (0.263 x 3.6 x 30) + (0.00504 x 159 x 30) + 5.98 (1)
= 43.2 (mL • kg^{-1} • min^{-1})

Aerobic Fitness Score

= 10 x VO_2max
= 432

Health Benefit Zone: *Good*

1

Appendix 3a

On the return, the shoulder blades and head must contact the mat and the finger tips of both hands must touch the 0 mark.

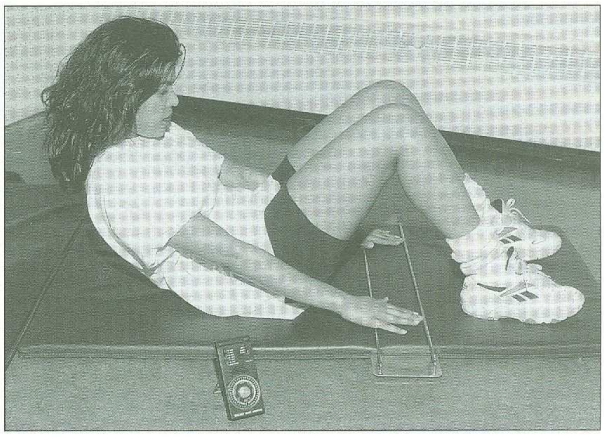
The movement is performed in a slow, controlled manner so that the time to perform the lifting and lowering stages of the curl-up is the same at a rate of 25 curl-ups per minute. Clients should be encouraged to breathe normally throughout, exhaling during the lifting stage.

The subject performs as many consecutive curl-ups as possible, without pausing, to a maximum of 25 in the one-minute time period.

The test is terminated before one minute if clients are:

- experiencing undue discomfort
- unable to maintain required cadence
- unable to maintain the proper curl-up technique (e.g., heels come off the floor) over two consecutive repetitions despite cautions by the appraiser.

Record the number of partial curl-ups completed on the Client Information Sheet. If clients are unable to reach the 10 cm distance for one curl-up, record the actual distance reached and use this as a bench-mark for counselling purposes.



Partial Curl-Up

Partial Curl-Up: *Number completed in one minute to a maximum of 25.*

Vertical Jump

A person who suffers from any back ailment should not perform this test.

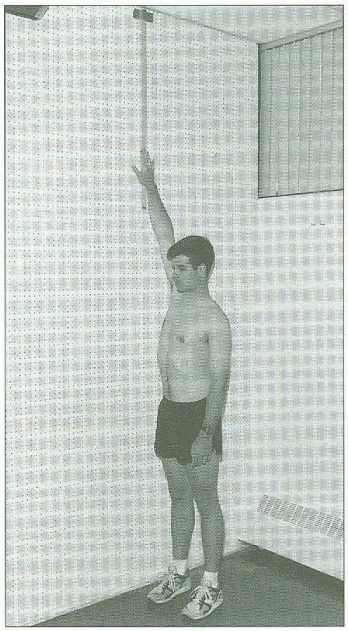
Vertical jump is the fifth musculoskeletal measure. It is scored in two ways: as a straight height jumped, and in terms of leg power. The latter measurement helps to 'fine-tune' the result. The rationale for this is explained in the example on page 7-49.

Equipment

Measuring tape, chair, and chalk.

Procedure

Clients take a standing position facing sideways to a wall on which a measuring tape has been attached. Standing erect with the feet flat on the floor, they reach as high as possible on the tape with the arm and fingers fully extended and the palm toward the wall. This is recorded as the *beginning height*. Next the client should move a safe distance away from the wall (with the hand on the hip, the elbow should *barely* reach the wall). No run up, step up, or pre-jump is permitted.



Beginning Height

Appendix 3b

Push-Ups

A person who suffers from any lower back ailment should not perform this test.

Equipment

Gym mat.

Procedure

It is imperative that clients are well instructed in the correct performance of the push-up.

Males

The client lies on his stomach, legs together. His hands, pointing forward, are positioned *under* the shoulders. He then pushes up from the mat by fully straightening the elbows and using the toes as the pivot point.

The upper body must be kept in a straight line. The client returns to the starting position, chin to the mat. Neither the stomach nor thighs should touch the mat.

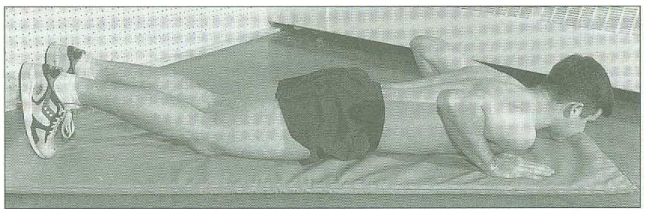
Females

The client lies on her stomach, legs together. Her hands, pointing forward, are positioned *under* the shoulders. She then pushes up from the mat by fully straightening the elbows and using the knees as the pivot point.

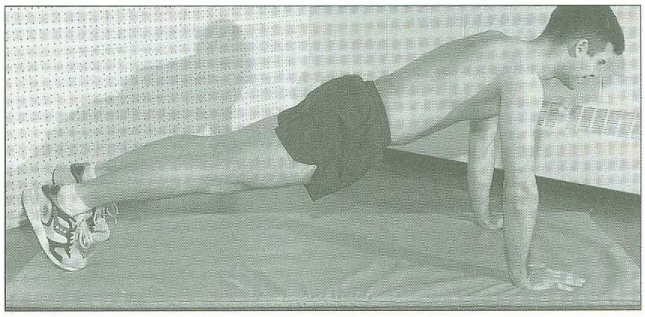
The upper body must be kept in a straight line. Clients return to the starting position, chin to the mat. The stomach should not touch the mat. The lower legs remain in contact with the mat, ankles plantar-flexed (extended), and feet in contact with the mat.

Advise clients that incorrect repetitions, those not meeting the above criteria, will not be counted. The test is stopped when clients are seen to strain forcibly or are unable to maintain the proper push-up technique over two consecutive repetitions. Clients should also be advised to avoid breathholding by breathing rhythmically, exhaling on effort (i.e., exhale during upward phase of the push-up).

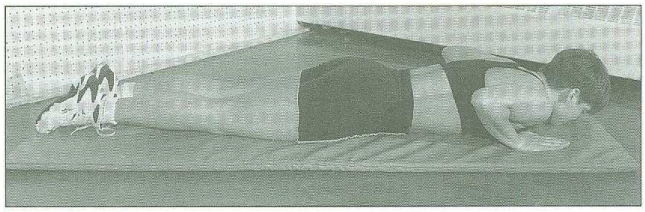
Have clients practice one or two repetitions to check for proper technique before doing the test.



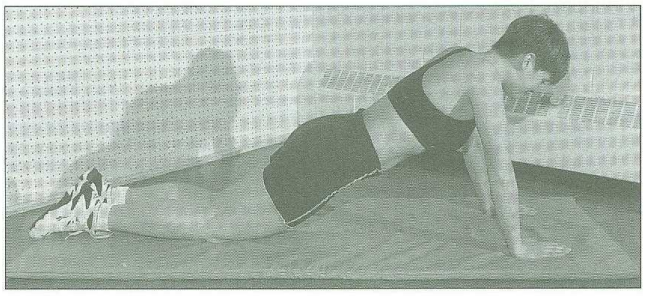
Male Push-Up



Male Push-Up



Female Push-Up



Female Push-Up

*The **Push-Ups** are performed consecutively and without a time limit.*

Appendix 4

Trunk Forward Flexion

Equipment

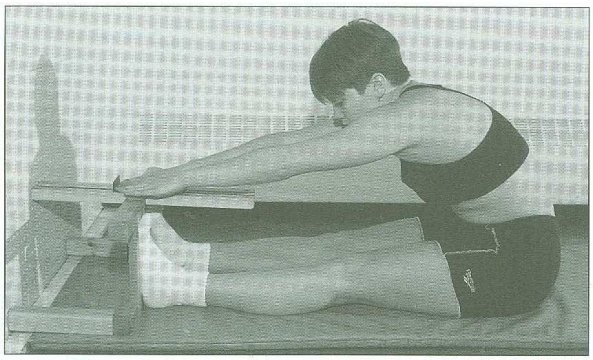
Flexometer (Modified Wells and Dillon).

Procedure

Have clients warm up for this test by performing slow stretching movements (modified hurdle stretch held for 20 seconds repeated twice on each leg) before taking the actual measurements.

Trunk forward flexion: Two trials to determine maximum stretch.

Clients, without shoes, sit with legs fully extended and the soles of the feet placed flat against the flexometer. The flexometer should be adjusted to a height at which the balls of the feet rest against the upper crossboards. The inner edge of the soles are placed two cm from the edge of the scale. Keeping the knees fully extended, arms evenly stretched, and palms down, clients bend and reach forward (without jerking), pushing the sliding marker along the scale with the fingertips as far forward as possible.



Trunk Forward Flexion

The position of maximum flexion must be held for approximately two seconds. Advise clients that lowering the head will maximize the distance reached. If the knees flex, the trial is not counted. Do not attempt to hold the knees down. In addition, do not allow a bouncing or jerking motion.

The test is repeated twice. Record both readings and record the maximum reading to the nearest 0.5 cm.

Partial Curl-Up

Equipment

Gym mat, masking tape, metric ruler, pen, set square, metronome, and string, wire, or velcro strip.

Procedure

Details are provided for the initial set-up, starting position, and action.

■ **Initial Set-up**

Apply masking tape to gym mat as shown in the illustration. Mark distances on tape as shown. Fasten strip of string, wire, or velcro across the mat at the 0 and 10 cm marks.

Set-up for Partial Curl-Up

■ **Starting Position**

Clients lie in a supine position with the head resting on the mat, arms straight at sides and parallel to the trunk, palms of hands in contact with the mat, and the middle finger tip of both hands at the 0 mark. The arms should be fully extended when the finger tips are at the 0 mark. Have them bend their knees at an angle of 90° (using the set square to establish this). Keep the heels in contact with the mat. The test is performed with shoes on.

*The initial phase of the curl-up must involve a **flattening out** of the lower back (i.e., posterior pelvic-tilting) by active contraction of the abdominal muscles.*

■ **Action**

Use the cadence provided on a metronome (set to 50 beats per minute).

This is followed by a slow *curling up* of the upper spine far enough so that the middle finger tips of both hands reach the 10 cm mark. During the curl-up the palms and heels must remain in contact with the mat. Anchoring of the feet is not permitted.

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