Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

Change in Weight, BMI, and Body Composition in a Population-Based Intervention Versus Genetic-Based Intervention: The NOW Trial

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Objective: The aim of this study was to compare changes in body fat percentage (BFP), weight, and BMI between a standard intervention and a nutrigenomics intervention.

Methods: The Nutrigenomics, Overweight/Obesity and Weight Management (NOW) trial is a parallel-group, pragmatic, randomized controlled clinical trial incorporated into the Group Lifestyle Balance™ (GLB) Program. Statistical analyses included two-way ANOVA and split-plot ANOVA. Inclusion criteria consisted of: BMI ≥ 25.0 kg/m^2, ≥18 years of age, English speaking, willing to undergo genetic testing, having internet access, and not seeing another health care provider for weight-loss advice outside of the study. Pregnancy and lactation were exclusion criteria. GLB groups were randomly assigned 1 to 1 ($N = 140$) so that participants received either the standard 12-month GLB program or a modified 12-month program (GLB plus nutrigenomics), which included the provision of nutrigenomics information and advice for weight management. The primary outcome was percent change in BFP. Secondary outcomes were change in weight and BMI.

Results: The GLB plus nutrigenomics group experienced significantly ($P < 0.05$) greater reductions in percent and absolute BFP at the 3-month follow-up and percent BFP at the 6-month follow-up compared with the standard GLB group.

Conclusions: The nutrigenomics intervention used in the NOW trial can optimize changes in body composition up to 6 months.

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Study Importance

What is already known?

- Individual weight-loss outcomes differ, even when participants follow the same nutrition plans, in part because of genetic variation (e.g., genetic variation in the FTO, APOA2, TCF7L2, and PPARg2 genes).
- Several companies and health care professionals are offering consumers genetically guided weight-loss advice, yet research has not yet assessed the effectiveness of such interventions in a pragmatic setting.

What does this study add?

- Nutrigenomics can help reduce body fat after 3- and 6-month follow-ups, beyond a gold-standard weight-loss intervention, but after 12 months, reductions in body fat are similar to the gold-standard weight-loss intervention.
- It is feasible to incorporate nutrigenomics into the publicly funded, group-based Group Lifestyle Balance Program (formerly the Diabetes Prevention Program).

Introduction

Weight management is an ongoing challenge for a substantial proportion of the population. It is estimated that two-fifths of the adult population worldwide are attempting to lose weight, with another quarter of the population attempting to maintain weight (1). Patients' motivations for weight control are broad and they include desires to improve health, well-being, physical appearance, fitness, and self-esteem (1).

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Clinical practice guidelines for overweight and obesity management state that there is "strong evidence" (National Heart, Lung, and Blood Institute Grade A) for the effectiveness of several interventions in achieving sustained weight loss (2). Despite this knowledge, successful long-term weight loss still proves to be challenging. Although there are numerous weight-management programs available to the public, the Group Lifestyle Balance™ (GLB) program (formerly referred to as the Diabetes Prevention Program) can be considered the gold-standard weight-management intervention for long-term, sustainable weight loss and diabetes prevention (3,4). This program meets all of the clinical practice guideline criteria while addressing various modifiable health and lifestyle behaviors (2).

With increasing knowledge of how individual genetic variation affects nutrient metabolism, absorption, and other physiological processes, genetics are an important factor to consider in weight-management interventions. The science of nutrigenomics explores interactions between nutrition, genetics, and health outcomes (5).

Consumers have demonstrated positive attitudes toward nutrigenetic testing (6). As such, many consumer nutrigenomics and lifestyle genomics tests are available to the general public and they often include personalized weight-management lifestyle advice. Primary research has demonstrated several relationships between genetic variation, weight and/or body composition, and specific dietary and physical activity (PA) strategies. Study designs are variable, including studies that are observational and interventional in nature (7-12). For example, results from a 2-year randomized controlled trial (RCT) demonstrated the enhanced utility (for weight management) of following a higher protein nutrition plan for individuals with the AA variant of the *FTO* gene (rs9939609; in strong linkage disequilibrium with rs1558902) (7). Although there have been substantial advancements in research demonstrating interactions among genes, nutrients, and weight-related outcomes, the efficacy of the practical application of this science in a clinical setting has yet to be thoroughly explored. Given the potential for genetically tailored lifestyle advice to motivate behavior change (13), coupled with scientific evidence demonstrating that genetically tailored nutrition plans can optimize weight-related outcomes (7-12), it was hypothesized that genetically based lifestyle advice would result in enhanced weight-related outcomes for patients. To date, only three studies have assessed the efficacy of using actionable nutrigenomics and lifestyle genomics interventions to optimize weight management (14-16). These studies provided a solid starting point for enhancing our knowledge on this topic but exhibited notable limitations related to statistical power, study methods, and the quality of the interventions delivered to study participants. These specific limitations have been further detailed elsewhere (17). Researchers have yet to conduct an adequately powered RCT of actionable nutrigenomics advice for weight management with a predetermined weight-related primary outcome. An RCT with long-term (12-month) follow-up has also not yet been conducted. Overall, findings in the current body of knowledge have been variable (14-16), with some promise for the use of genetically based advice to optimize weight management (14). The present RCT aimed to address the limitations of the current body of knowledge by conducting an adequately powered RCT with a predetermined weight-related primary outcome, assessing participants over a 12-month follow-up period, and employing an actionable genetic intervention with health care professional involvement. Ultimately, the present RCT aimed to answer the following important research question: Does the provision of personalized, genetic-based lifestyle information and advice enhance weight loss and improve body composition to a greater extent than the gold-standard, population-based weight-management program?

How might these results change the direction of research or the focus of clinical practice?

- Future research should focus on other health-related outcomes that could improve from genetically guided lifestyle advice offered in a pragmatic setting (e.g., blood pressure, blood glucose, cholesterol, etc.).
- Clinicians and researchers should consider the use of nutrigenomics weight-loss interventions for clinical cases in which short- to moderate-term weight (body fat) loss could be beneficial for major patient outcomes (e.g., pretransplant to increase chances of survival; prior to total joint arthroplasty to increase chances of implant survivorship and postoperative functional scores; in kidney, heart, liver and lung disease patients for transplant listing, etc.).

Methods

The Nutrigenomics, Overweight/Obesity and Weight Management (NOW) trial is a pragmatic, parallel-group, superiority RCT, which was approved by The Western University Research Ethics Board. Complete details of the study methods for this clinical trial, including a Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) flow diagram, have been published elsewhere (18). Briefly, the addition of personalized, genetic-based lifestyle advice to the GLB program was compared (1:1) with the gold-standard, population-based GLB intervention program for weight management. Inclusion criteria consisted of having BMI ≥ 25.0 kg/m^2, being ≥18 years of age, being English speaking, being willing to undergo genetic testing, having internet access, and not seeing another health care provider for weight-loss advice outside of the study. Pregnancy and lactation were considered exclusion criteria. This study took place at the East Elgin Family Health Team (EEFHT) in Aylmer, Ontario, Canada, and it was registered with ClinicalTrials.gov (NCT03015012). It was hypothesized that the provision of genetically based lifestyle information and advice would result in significantly greater improvements (reductions) in weight, BMI, and body fat percentage (BFP) compared with the provision of population-based information and advice after 3-, 6-, and 12-month follow-ups.

Recruitment

Adults from Elgin and Middlesex counties in Ontario, Canada, were either referred to the GLB program by health care professionals in the area or signed up for the program through word-of-mouth referrals from members of the community. Participants expressing interest in joining the GLB program were invited to the EEFHT for an in-person NOW trial information meeting and provided written, informed consent if they decided to take part in the study.

Primary and secondary outcomes

The primary outcome of this RCT was percent change in BFP. Changes in weight and BMI were secondary outcomes.

Sample size

As indicated in the study protocol (18), to detect a 4% change in BFP, using an SD of 6.1%, the sample size calculation indicated that a total of 74 participants (37 participants per group) were needed to test the primary outcome of this trial with 80% power and an α value of 5%.

Randomization and blinding

For the cohort randomization, randomly permuted blocks were generated by one author (JRH) using the original generator on an internet-based randomization program (www.randomization.com). This allowed for prerandomization of GLB groups to determine whether the group intervention sessions would be population based or genetically based (see "Interventions and data collection"). Participants selected a GLB group that best suited their schedule and they were blinded to the group assignment at this time. Four authors were blinded throughout the duration of the study, with one author unblinded (JRH) for logistical reasons, as this investigator was responsible for generating the randomization sequence, scheduling participants, arranging the genetic testing, facilitating all group and one-on-one sessions, and completing data collection.

Run-in

Baseline data collection occurred within approximately 14 days (mean ± SD = 9.3 ± 5.7) prior to the intervention start date. No lifestyle advice was provided to participants during this run-in period.

Interventions and data collection

Participant recruitment took place between April 2017 and September 2018. Recruitment ended in September 2018, given the allocated timeline for this project and given that the target recruitment sample number had been achieved. One author (JRH) was responsible for enrolling participants and assigning them to interventions (on the basis of their availability and the GLB group times and dates selected by the blinded participants). Data collection and lifestyle interventions occurred between May 2017 and September 2019, with staggered cohorts throughout this period. Group allocation was concealed for the participants until the first group intervention session (after baseline data collection). Those randomly assigned to the population-based lifestyle intervention (GLB) group participated in the standard 22-session, 12-month GLB program, which focuses on guiding participants to consume a tailored, calorie-controlled nutrition plan with approximately 25% of calories from total fat (19). They also received an additional information session at the beginning of the intervention (beyond the standard 22 sessions) detailing population-based guidelines for 11 nutrition and PA-related items: calories, protein, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, sodium, snacking, overall PA, endurance, and strength or power as previously published (18). Individuals randomly assigned to the standard GLB program received their nutrigenomics/lifestyle genomics report after the 12-month study was complete.

Individuals randomized to the personalized, genetically based nutrition and PA intervention (GLB plus nutrigenomics [GLB + NGx]) received the same calorie targets as those in the standard GLB program and information and/or advice on the 11 nutrition and PA-related items, with their actionable advice being based on individual genetic variation in 12 unique genetic variants: fat mass and obesity-associated (*FTO*) gene (rs9939609); uncoupling protein 1 (*UCP1*) gene (rs1800592); transcription factor 7–like 2 (*TCF7L2*) gene (rs7903146); apolipoprotein A2 (*APOA2*) gene (rs5082); peroxisome proliferator–activated receptor gamma 2 (PPARg2) gene (rs1801282); angiotensin I–converting enzyme (*ACE*) gene (rs4343); melanocortin 4 receptor (*MC4R*) gene (rs17782313); adrenoceptor beta 3 (*ADRB3*) gene (rs4994); nuclear factor, erythroid 2–like 2 (*NRF2*) gene (rs12594956); glutathione S-transferase P1 (GSTP1) gene (rs1695); nuclear factor I A–antisense RNA 2 (*NFIA-AS2*) gene (rs1572312); and actinin alpha 3 (*ACNT3*) gene (rs1815739). A sample genetic report has been previously published elsewhere (18). These genetic variants were chosen as they are reflective of current consumer weight–related nutrigenetic testing available through health care providers globally, such as physicians, dietitians, and nurses. Some examples of actionable genetic information provided to participants include, "You can enhance your weight loss if you consume 25% to 35% of calories from protein" or, "You can enhance your weight loss if you consume less than 10% of calories from saturated fat." Participants were then provided with extensive nutrition education to provide direction on how to practically achieve these targets and how to track their intake to determine whether they were achieving these targets. Participants in the standard GLB program were given similar guidance, but it was specific to achieving the total fat intake target. Participants were also involved in the 12-month GLB program, which was modified by the program facilitator (JRH) throughout its duration to highlight nutrition and PA guidelines that may differ according to genetic variation (18). In addition to the 22 GLB program group sessions, a supplementary group session occurred at the beginning of the program, which consisted of an overview of the nutrition and PA advice, based on genetics. Furthermore, all participants' nutrition and PA guidelines (for both the GLB and GLB + NGx groups) were reviewed during their three follow-up data-collection appointments (occurring at months 3, 6, and 12) with a registered dietitian.

No additional human resources were required beyond standard care to run the interventions. All group and one-on-one sessions were facilitated by the same researcher (JRH) to optimize reliability and to standardize the interventions.

Baseline and follow-up anthropometric data included weight and height (used to calculate BMI), as well as body composition, measured using the Bodystat 1500MDD (Bodystat, Douglas, Isle of Man, UK) bioelectrical impedance analysis device.

Genotyping

Oragene ON-500 saliva collection kits (DNA Genotek, Ottawa, Ontario, Canada) were used to collect DNA samples of participants at the EEFHT. The saliva samples were shipped to the University of Toronto and stored at −80 °C. The iPLEX Gold assay with mass spectrometry–based detection on the Sequenom MassARRAY platform was used for genotyping of the 12 single-nucleotide polymorphisms (CD Genomics, Shirley, New York).

Statistical analysis

All statistical analyses were completed using SPSS Statistics version 26.0 (IBM Corp., Armonk, New York). A systematic review of determinants of weight-loss maintenance was used to help determine factors to include in the attrition-bias analysis (20). Two-way ANOVA facilitated the analysis of potential attrition bias for the following participant

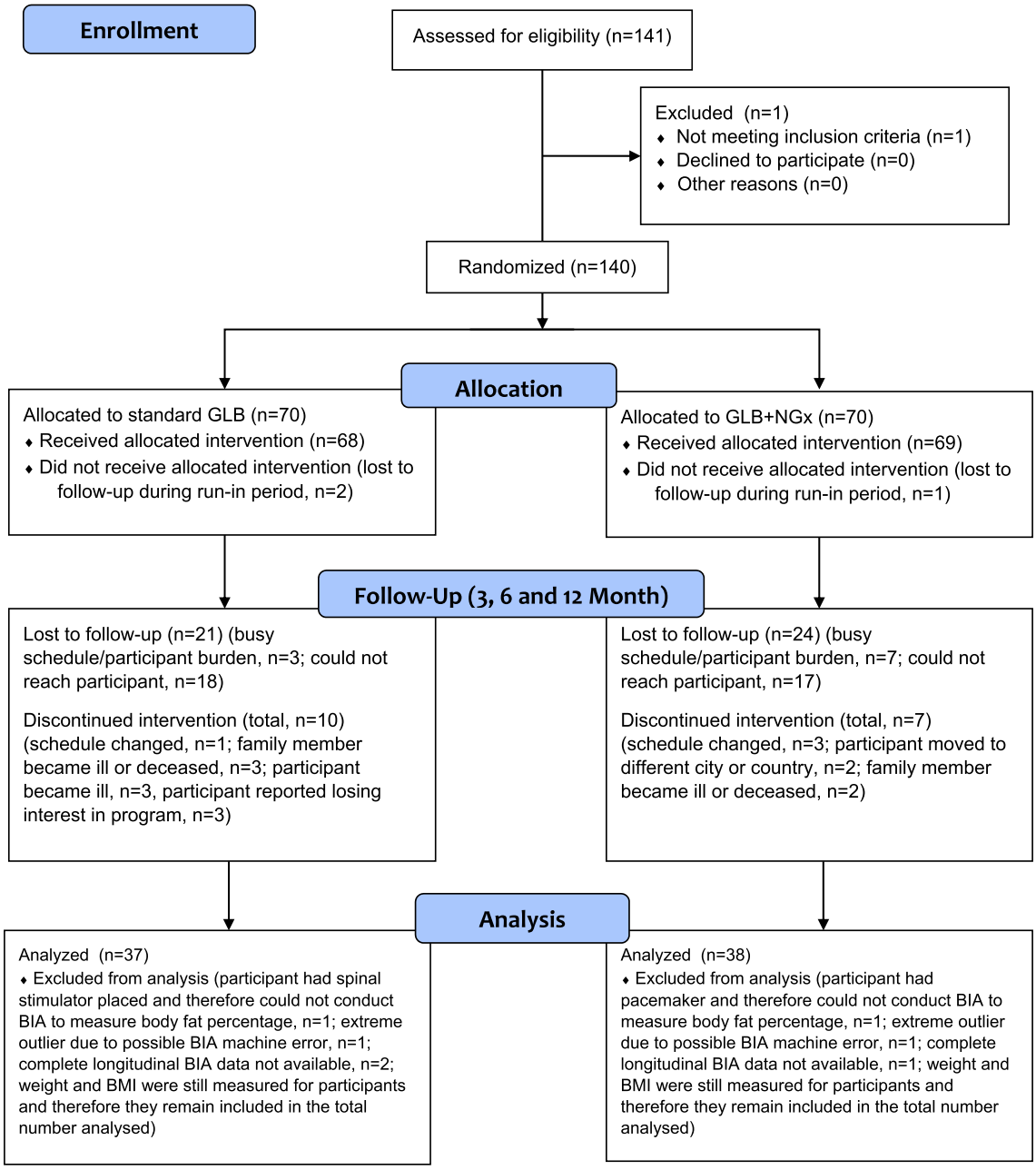

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram. BIA, bioelectrical impedance analysis; GLB, Group Lifestyle Balance; GLB + NGx, GLB plus nutrigenomics.

characteristics: level of education, annual household income (Canadian dollars), age (years), baseline stage of change (transtheoretical model), and perceived difficulty managing weight. To account for potential bioelectrical impedance analysis equipment error, descriptive statistics were used to identify far-out outliers, which were then removed from the final analyses (Figure 1). Split-plot ANOVA was used to assess between-group changes in anthropometric data from baseline to 3-, 6-, and 12-month follow-ups. Changes in weight, BMI, and BFP were all prespecified outcome measures. Hypothesis tests were two-sided and $P<0.05$ was considered statistically significant.

Results

Baseline participant demographic and clinical characteristics are presented in Table 1, with the characteristics of individuals who remained in the study outlined in Supporting Information Table S1. Longitudinal data were available for 75 participants who completed anthropometric data collection for all four time points (Figure 1). No statistically significant sources of attrition bias were revealed for level of education, annual household income (Canadian dollars), age (years), baseline stage of change (transtheoretical model), and perceived difficulty managing

weight. There were no reported harms or unintended consequences reported in either group.

Far-out (extreme) outliers ($n=2$) were removed from the body composition data (one in the standard GLB group and one in the personalized GLB + NGx group). Results from the analyses of changes in anthropometric characteristics are outlined in Tables 2 and 3 as well as in Figure 2. After 3- and 6-month follow-ups, the GLB + NGx group had significantly ($P<0.05$) greater reductions in percent BFP change (3 months: −5.0% ± 5.5% BFP change; 6 months: −7.7% ± 6.3% BFP change) compared with the standard GLB group (3 months: −2.2% ± 4.1% BFP change; 6 months: −4.8% ± 4.9% BFP change). The GLB + NGx group additionally had significantly ($P<0.05$) greater reductions in absolute BFP change after 3 months (GLB + NGx: −2.1% ± 2.0% absolute BFP change; standard GLB: −1.0% ± 1.9% absolute BFP change). There were no significant interactions between groups and BFP (percent and absolute) after the 12-month follow-up ($P>0.05$). Furthermore, although the GLB + NGx group had clinically meaningful, greater reductions in weight and BMI after 3 and 6 months (percent and absolute) compared with the standard GLB group, there were no significant interactions between groups in weight or BMI at 3-, 6-, and 12-month follow-ups ($P>0.05$).

TABLE 1 Baseline demographics and clinical characteristics of study participants ($N=140$)

	GLB group (mean ± SD)	GLB + NGx group (mean ± SD)
Age (y)	56.4 ± 12.1	53.5 ± 13.6
Gender	84.3% female	89.9% female
Ethnicity	98.6% white	97.1% white
Annual household income (Can $)	73,943 ± 41,403	71,389 ± 44,301
Weight (lb)	217.3 ± 49.0	215.4 ± 51.8
BMI (kg/m^2)	36.7 ± 7.3	37.3 ± 9.7
Body fat (%)	46.7 ± 7.0	45.7 ± 7.9

Can $, Canadian dollars; GLB, Group Lifestyle Balance; GLB + NGx, GLB plus nutrigenomics.

Discussion

This study provides several notable, novel contributions to the literature. From a public health perspective, it is the first study to explore short-, moderate-, and long-term anthropometric changes resulting from the standard GLB program in a population of adults with baseline BMI ≥ 25.0 kg/m^2, regardless of having a prediabetes diagnosis. Although originally piloted and intended for diabetes prevention in individuals with a prediabetes diagnosis (3), public health officials have since encouraged the GLB program expansion to more broad patient populations such as those with BMI ≥ 25.0 kg/m^2 (21). This study demonstrates that a clinically meaningful 3% to 5% sustained weight loss (2) can be achieved with program expansion to this broader population, thus supporting public health authority recommendations. Additionally, to our knowledge, this is the first study to explore body composition changes within the GLB program. Measures of body composition are superior to weight and BMI, given that body composition accounts for changes in fat, water, and muscle mass as opposed to overall weight changes (22).

Gold-standard clinical practice guidelines for weight-management interventions indicate that such interventions should include calorie restriction; participation in a comprehensive lifestyle program for ≥6 months with at least 14 sessions in 6 months; counseling on the cardiovascular benefits associated with ≥3% to 5% weight loss; participation in long-term (≥12-month) weight-loss maintenance programs; and regular contact with an "interventionist" who assists with engagement in PA and monitoring body weight regularly (2). Both the standard GLB and GLB + NGx interventions adhered to these guidelines. A minimum of 3% to 5% sustained weight loss is clinically meaningful to produce several health benefits, including reduced triglycerides, reduced blood glucose and hemoglobin A_{1C}, and a reduced risk of developing type 2 diabetes; higher weight loss is associated with greater benefits (2). Both the standard GLB and GLB + NGx groups achieved such sustained weight loss over a 12-month period, demonstrating the success of both the standard and modified (personalized) versions of the GLB program. Because there were no significant differences in percent weight loss and change in BFP between groups after the 12-month follow-up, we cannot conclude that the addition of genetic information was beneficial for long-term weight-related outcomes. However, reduced statistical power due to participant dropout may have contributed to the lack of significant differences for weight and BMI, particularly at the 3- and 6-month

TABLE 2 Anthropometric measurements at baseline, 3, 6, and 12 months

	Baseline (mean ± SD, 95% CI)	3 months (mean ± SD, 95% CI)	6 months (mean ± SD, 95% CI)	12 months (mean ± SD, 95% CI)
GLB group				
Body fat (%)	48.18 ± 6.60, 45.6 to 50.7	47.16 ± 7.18,[a] 44.5 to 49.9	45.91 ± 6.97,[b] 43.3 to 48.9	44.70 ± 7.02, 42.1 to 47.4
Weight (lb)	219.83 ± 49.71, 206.1 to 233.5	212.97 ± 49.36, 199.4 to 226.6	211.72 ± 51.41, 197.7 to 225.8	213.51 ± 51.64, 199.2 to 227.8
BMI (kg/m^2)	37.82 ± 7.70, 35.6 to 40.1	36.65 ± 7.91, 34.3 to 39.0	36.38 ± 8.12, 34.0 to 38.7	36.68 ± 8.07, 34.2 to 39.1
GLB + NGx group				
Body fat (%)	44.93 ± 7.95, 42.5 to 47.4	42.77 ± 8.29,[a] 40.2 to 45.4	41.55 ± 8.24,[b] 39.0 to 44.1	42.32 ± 8.15, 39.7 to 44.9
Weight (lb)	203.34 ± 32.29, 189.8 to 216.9	194.56 ± 32.10, 181.1 to 208.0	192.48 ± 32.60, 178.6 to 206.4	196.85 ± 34.16, 182.7 to 211.0
BMI (kg/m^2)	35.22 ± 6.06, 33.0 to 37.5	33.72 ± 6.13, 31.4 to 36.0	33.36 ± 6.20, 31.0 to 35.7	34.11 ± 6.46, 31.8 to 36.5

Standard GLB group: weight and BMI, $n=37$; body fat, $n=33$. GLB + NGx group: weight and BMI, $n=38$; body fat, $n=35$. Analyses were all by originally assigned groups. GLB, Group Lifestyle Balance; GLB + NGx, GLB plus nutrigenomics.
[a] $P=0.023$. P interaction for body fat (%) = 0.002, effect size = 0.087.
[b] $P=0.022$. P interaction for body fat (%) = 0.002, effect size = 0.087.

TABLE 3 Change in anthropometric measurements at 3, 6, and 12 months

	3 months (absolute Δ ± SD, 95% CI)	3 months (percent Δ ± SD, 95% CI)	6 months (absolute Δ ± SD, 95% CI)	6 months (percent Δ ± SD, 95% CI)	12 months (absolute Δ ± SD, 95% CI)	12 months (percent Δ ± SD, 95% CI)
GLB group						
Body fat (%)	−1.02 ± 1.89,[a] −0.4 to −1.7	−2.24 ± 4.13;[b] −0.5 to −3.9	−2.27 ± 2.26, −1.4 to −3.2	−4.80 ± 4.85;[c] −2.8 to −6.8	−3.48 ± 2.55, −2.6 to −4.4	−7.31 ± 5.35, −5.4 to −9.2
Weight (lb)	−6.86 ± 7.36, −4.5 to −9.2	−3.23 ± 3.57, −2.1 to −4.4	−8.11 ± 9.11, −4.7 to −11.5	−3.96 ± 4.70, −2.3 to −5.7	−6.32 ± 9.25, −2.6 to −10.0	−3.13 ± 4.81, −1.3 to −4.9
BMI (kg/m^2)	−1.12 ± 1.28, −0.8 to −1.6	−3.27 ± 3.60, −2.1 to −4.4	−1.44 ± 1.64, −0.9 to −2.0	−4.06 ± 4.70, −2.4 to −5.8	−1.14 ± 1.67, −0.5 to −1.8	−3.22 ± 4.79, −1.4 to −5.0
GLB + NGx group						
Body fat (%)	−2.12 ± 1.96,[a] −1.5 to −2.8	−4.95 ± 5.52;[b] −3.3 to −6.6	−3.38 ± 2.83, −2.5 to −4.2	−7.74 ± 6.33;[c] −5.8 to −9.6	−2.61 ± 2.66, −1.7 to −3.5	−6.00 ± 5.76, −4.1 to −7.9
Weight (lb)	−8.77 ± 7.04, −6.4 to −11.1	−4.37 ± 3.44, −3.2 to −5.5	−10.86 ± 11.48, −7.5 to −14.2	−5.38 ± 5.57, −3.7 to −7.0	−6.48 ± 12.91, −2.8 to −10.1	−3.26 ± 6.03, −1.5 to −5.0
BMI (kg/m^2)	−1.50 ± 1.19, −1.1 to −1.9	−4.35 ± 3.45, −3.2 to −5.5	−1.86 ± 1.97, −1.3 to −2.4	−5.35 ± 5.62, −3.7 to −7.0	−1.11 ± 2.24, −0.5 to −1.7	−3.24 ± 6.06, −1.5 to −5.0

Standard GLB group: weight and BMI, *n*=37; body fat, *n*=33. GLB + NGx group: weight and BMI, *n*=38; body fat, *n*=35. Differences in percent weight and BMI change are due to rounding. Analyses were all by originally assigned groups.
Δ, change; GLB, Group Lifestyle Balance; GLB + NGx, GLB plus nutrigenomics.
[a]$P = 0.018$. P interaction for absolute body fat percentage $\Delta = 0.002$, effect size = 0.087.
[b]$P = 0.026$. P interaction for percent body fat percentage $\Delta = 0.003$; effect size = 0.076.
[c]$P = 0.036$. P interaction for percent body fat percentage $\Delta = 0.003$; effect size = 0.076.

follow-ups. Concerns with a lack of statistical power have also been noted in previously published RCTs in this area (15,16). Furthermore, in the present study, the GLB program eligibility criteria were broadened to include individuals with overweight or obesity, regardless of having a prediabetes diagnosis. Previously, the GLB program was studied in samples of patients with prediabetes. Notably, this previous research demonstrated slightly greater weight loss than the NOW trial (4). It is possible that individuals with prediabetes are more motivated to engage in lifestyle change and weight management, given the fear of their disease advancing to type 2 diabetes. In patients with overweight or obesity, but not necessarily with a prediabetes diagnosis, this fear would be lesser. Clinically meaningful changes in BFP are not well established, but given that there were clinically meaningful changes observed for weight at all time points, this further demonstrates that the overall change in BFP would also be considered clinically meaningful. With body fat mass specifically having major impacts on health outcomes (22), a 3% to 5% change in BFP is likely of greater clinical benefit than a 3% to 5% change in overall weight, which may also include reductions in muscle.

Notably, the GLB + NGx group experienced significantly greater reductions in BFP after 3 and 6 months compared with the standard GLB group; adiposity is a more meaningful weight-related outcome compared with weight or BMI, given the more accurate associations between adiposity (as opposed to weight or BMI) and health, including associations with cardiometabolic disease (23). Thus, the 3- and 6-month findings speak to the scientific validity and/or clinical utility of the nutrigenetic and lifestyle genomics information and advice provided to participants. The precise details of the genetic information provided, including a sample genetic report, have been previously detailed elsewhere (18). There are many clinical cases in which short- and moderate-term weight or fat loss and/or achieving a specific BMI cutoff has demonstrated positive impacts on major and critical patient outcomes. Examples include pretransplant weight loss to reduce the risk of organ rejection, reduce the risk of wound complications, reduce hospital length of stay, and increase chances of survival (24,25); presurgery weight loss to reduce the risk of complications after hernia repair (26); weight loss to be eligible as a living organ donor at most transplant centers (27); weight loss to improve pregnancy rates in patients with infertility (28); and weight loss prior to total joint arthroplasty to increase chances of implant survivorship and postoperative functional scores (29). With this in mind, studying the effectiveness of nutrigenomics and lifestyle genomics interventions for these specific clinical cases, and others in which short- to moderate-term reductions in weight-related outcomes are beneficial, is an important recommended next step for the field of precision nutrition. Interestingly, a 2014 study found that only 6% of clinical dietitians working in a publicly funded health setting participated in nutrigenomics training, as opposed to 33% of industry dietitians and 14% of private practice dietitians (30). This suggests that there is likely minimal uptake of nutrigenomics in acute care settings such as hospitals (perhaps in part because of the lack of pragmatic research demonstrating the efficacy of nutrigenomics in these settings), where the cases mentioned earlier are more prevalent; perhaps these are the clinical settings in which patients could benefit most from nutrigenomics and lifestyle genomics weight-management interventions?

Our finding of significant differences in BFP between groups diminishing at the 12-month follow-up is intriguing, especially given that the GLB + NGx group made significantly greater dietary changes and adhered more closely to specific dietary advice compared with the standard GLB group at 12 months (31). There are multiple possible

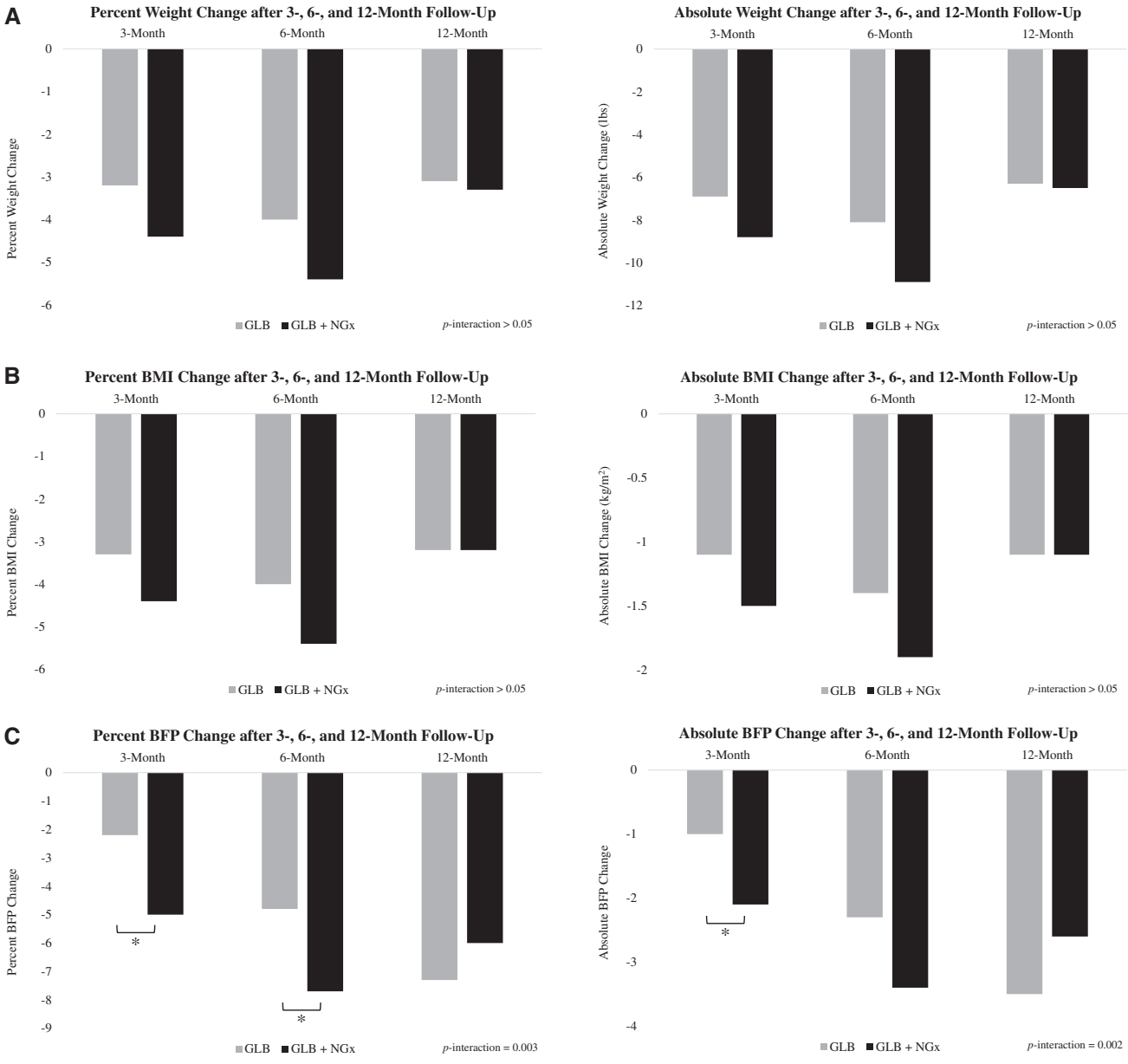

Figure 2 Change in anthropometric measures after 3-, 6-, and 12-month follow-ups. *Significant difference between groups ($P < 0.05$). GLB, Group Lifestyle Balance; GLB + NGx, GLB plus nutrigenomics.

explanations for these findings. First, biological mechanisms promote weight regain after periods of weight loss. Over time, physiological mechanisms, including adipose cellularity, endocrine function, energy metabolism, neural responsivity, and addiction-like neural mechanisms, promote weight regain after a period of weight loss (32). This includes metabolic adaptation, which refers to the concept that following weight loss, individuals experience a greater reduction in metabolic rate than would be expected based on an individual's body composition (32). Ultimately, there are several biological mechanisms leading the body to resist weight loss and drive weight regain. This could explain why results from the NOW trial demonstrate weight regain occurring from the 6-month to the 12-month follow-up in both the GLB and GLB + NGx groups. It is possible that the faster rate of BFP loss experienced in the GLB + NGx group led to an earlier onset of the biological responses promoting weight regain, which could help explain why there were no significant differences in BFP at 12 months. Indeed, research supports this idea (33). Second, although the biological mechanisms promoting weight regain provide a plausible explanation for our findings, it is also possible that participants noticed some weight regain occurring between 6 and 12 months, thus becoming increasingly motivated at 12 months to follow the genetically guided advice (31).

There are some limitations of the present work that should be noted. Difficulty with participant retention is common in weight-loss

intervention research (34-37), but this reduced statistical power and it may have limited the ability to detect statistical significance for the secondary outcomes, weight and BMI. Thus, the dropout rate for the NOW trial was not remarkable. Previous research was conducted within the GLB program at the EEFHT and five other Ontario primary care locations. In this previous study, the GLB program was offered during a 9-month period, and dropout rates throughout the study were 26.8% at 3 months, 46.8% at 6 months, and 63.0% at 12 months (34). This is the most comparable study to the NOW trial, given the direct similarities in the intervention (GLB program) and setting (EEFHT in Aylmer, Ontario). With a longer intervention and study duration of 12 months, the NOW trial still had an overall retention rate approximately 17% higher than that of previous research in the GLB program, which ran for only 9 months (34). We suspect that the provision of genetic information (at baseline for the GLB + NGx group and after 12 months for the standard GLB group) enhanced overall interest in the intervention and study, therefore helping to improve retention. This participant interest is further highlighted in Figure 1, whereby 140 participants enrolled in the NOW trial out of the 141 patients who were invited to join the study. Reasons for reduced participant retention can include scheduling conflicts, dissatisfaction with treatment, and lack of time to meet the study requirements (36). Having a lower education level (less than university level) and having a higher level of obesity are also risk factors for dropping out of weight-loss programs or studies (38,39). These factors contributed to participant dropout in the NOW trial, as further indicated in Figure 1, Table 1, and Table 2. In addition, based on the analyses conducted in the present study, it cannot be determined whether the enhanced BFP reduction resulted from enhanced motivation to improve nutrition and PA habits or more effective nutrition and PA advice in the GLB + NGx group (or both). Future research should seek to determine this.

The results of this study are primarily generalizable to populations of middle-aged, middle socioeconomic status, white women with obesity (class II) enrolled in a lifestyle-change weight-management program. Given that participants who were enrolled in the GLB program were invited to participate in the study, this appears to be a representative sample of individuals interested in this weight-management program. Furthermore, the NOW trial study population is similar to other reported GLB study populations (40-43).

This study further demonstrated the feasibility of communicating genetically based nutrition and PA information and advice in a group setting. The literature supports that group-based nutrition education can be more effective in motivating nutrition behavior change and can be more meaningful for patients (44,45). However, because this type of personalized nutrition advice is typically communicated in one-on-one patient settings, future research should seek to compare a nutrigenetic and/or lifestyle genomics intervention with standard of care, rather than gold-standard care, as we have done here. Although the GLB program is the gold standard, it is currently offered in only nine primary care facilities in Canada (46). In the United States, this program is currently offered to the general public in more than 50 facilities (46). As such, the standard of care for weight management in dietetics typically consists of individual lifestyle counseling.

Conclusion

Nutrigenomics interventions can produce clinically meaningful health-related outcomes for patients over the short term, moderate term, and long term, with additional benefits observed above those achieved with gold-standard care over the short term and moderate term. Clinicians should consider implementing the GLB + NGx intervention for patients. As research continues to advance with the hopes of nutrigenetic tests becoming increasingly accurate, genetic-based lifestyle interventions hold considerable promise for improving health and well-being in a manner that is innovative and exciting for patients and health care professionals alike. It is certainly a science worth exploring further.O

Acknowledgments

Although data will not be available in a public database, deidentified study data will be shared upon reasonable request up until September 2026 (at which time the study data will be destroyed in accordance with the Western University research ethics policy) by contacting the corresponding author. The full study protocol is published and available to the public (18).

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