**Lifestyle Genomics**

## Research Article

# Can a Lifestyle Genomics Intervention Motivate Patients to Engage in Greater Physical Activity than a Population-Based Intervention? Results from the NOW Randomized Controlled Trial

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**Abstract**

***Background:*** Lifestyle genomics (LGx) is a science that explores interactions between genetic variation, lifestyle components such as physical activity (PA), and subsequent health- and performance-related outcomes. The objective of this study was to determine whether an LGx intervention could motivate enhanced engagement in PA to a greater extent than a population-based intervention. ***Methods:*** In this pragmatic randomized controlled trial, participants received either the standard, population-based Group Lifestyle Balance™ (GLB) program intervention or the GLB program in addition to the provision of LGx information and advice (GLB + LGx). Participants (*n* = 140) completed a 7-day PA recall at baseline, 3, 6, and 12 months. Data from the PA recalls were used to calculate metabolic equivalents (METs), a measure of energy expenditure. Statistical analyses included split plot analyses of covariance and binary logistic regression (generalized linear models). Differences in leisure time PA weekly METs, weekly minutes of moderate + high-intensity PA, and adherence to PA guidelines were compared between groups (GLB and GLB + LGx) across the 4 time points. ***Results:*** Weekly METs were significantly higher in the GLB + LGx group (1,114.7 ± 141.9; 95% CI 831.5–1,397.8) compared to the standard GLB group (621.6 ± 141.9 MET/week; 95% CI 338.4–904.8) at the 6-month follow-up (*p* = 0.01). All other results were non-significant. ***Conclusions:*** The provision of an LGx intervention resulted in a greater weekly leisure time PA energy expenditure after the 6-month follow-up. Future research should determine how this could be sustained over the long-term. ***Clinical Trial Registration:*** NCT03015012.

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## Introduction

Regular physical activity (PA) is associated with numerous health benefits, including reduced stress and increased energy levels, as well as a reduced risk of cardiovascular disease, arthritis, and obesity [1]. Physical inac-

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tivity is a major modifiable risk factor for several chronic diseases such as obesity, hypertension, cardiovascular disease, and type 2 diabetes [1]. Although the health benefits of PA and increased energy expenditure are well established, nearly 30% of the population globally is not achieving the recommended PA guidelines [2]. Concerns related to physical inactivity are greatest in high-income Western countries, with over 40% of the population failing to achieve the recommended PA guidelines, and substantial reductions in PA energy expenditure observed over recent decades [2]. As such, novel, innovative strategies are needed to motivate the general public to participate in PA in order to improve the health and well-being of the population.

There have been considerable scientific advancements exploring how genetics and PA interact to impact health and performance outcomes. It is well established that genetic variation within the fat mass and obesity-associated (*FTO*) gene is associated with a significantly increased risk of obesity [3]. Furthermore, single-nucleotide polymorphisms located within certain genes can impact individual responses to different PA approaches for weight management [4–7]. For example, research has consistently demonstrated that increased PA can attenuate the obesity-associated effects in high-risk *FTO* genotypes and that PA can enhance weight loss in individuals with specific single-nucleotide polymorphisms within the FTO gene [4–11]. Genetic variation can also help us to understand individual variations in athletic predisposition. Single-nucleotide polymorphisms located within the genes adrenergic receptor beta 3 (*ADRB; rs4994*), nuclear factor erythroid 2-related factor 2 (*NRF2; rs12594956*), glutathione S-transferase pi 1 (*GSTP1; rs1695*), and nuclear factor I A antisense RNA 2 (*NFIA-AS2; rs1572312*) have been associated with genetic predisposition to excel at aerobic/endurance-based activities [12–15]. When it comes to speed and power phenotypes, the CC and TC genotypes in the α-actinin-3 (*ACTN3; rs1815739*) gene express an association with genetic predisposition to excel at activities requiring strength and speed [15–19]. This science, referred to as lifestyle genomics (LGx), is the study of interactions between genetic variations, lifestyle factors, and health and performance outcomes [20]. The abovementioned LGx information and advice are available to the public through consumer genetic testing.

Genetic testing holds promise as a lifestyle intervention with the continual advancement of genomic science research. A recent systematic review found that providing personalized lifestyle recommendations based on genetics can help to encourage lifestyle behavior changes, especially when the genetic information includes actionable lifestyle recommendations [21]. Genetic research assessing behavioral changes should also remain cognizant of established behavior change theory in order to provide participants with interventions that are likely to facilitate health behavior changes [21, 22]. With this in mind, the purpose of the present study, a secondary outcome analysis of the Nutrigenomics, Overweight/Obesity and Weight Management (NOW) trial, was to determine whether providing actionable, genetic-based PA information and advice motivates primary care patients to engage in greater PA compared to the provision of population-based information and advice. The interventions included in this trial were designed to optimize health behavior changes based on the Theory of Planned Behavior (TPB).

## Methods

### Study Design

The NOW trial was a pragmatic randomized controlled trial involving 140 participants with follow-up after 3, 6, and 12 months. Participants were primarily middle-aged, middle-income, Caucasian women with obesity (class II). The full study details, including a CONSORT flow diagram, sample size calculation based on the primary outcome of the trial (body composition, $n = 74$), and a summary of participant characteristics, have been published elsewhere [23–25]. In brief, the sample consisted of participants who were recruited from the Group Lifestyle Balance™ (GLB) program at the East Elgin Family Health Team in Aylmer, ON, Canada. The GLB program was 12 months in duration and aimed to provide lifestyle information and advice for weight management through 23 group-based sessions. Through computer-generated block randomization (using randomly permuted blocks) conducted by the first author, half of the GLB program groups were randomized (1:1) to receiving population-based lifestyle information and advice (GLB group) and the other half were randomized to receiving genetic-based lifestyle information and advice (GLB + LGx group). Four of the authors (J.G., J.A.S., C.O., and J.M.) were blinded to the group assignments. Patients expressing interest in the GLB program were invited to participate in this study by the first author if they met the following inclusion criteria: BMI ≥25.0, age ≥18 years, English-speaking, willing to undergo genetic testing, having access to the internet, and not seeing another healthcare provider for weight loss advice outside of this study. Pregnancy and lactation were exclusion criteria. Recruitment ended after enough participants had been recruited for 10 randomized GLB groups, at which point the sample size had been exceeded. PA recommendations were communicated during GLB group sessions and reinforced during 3 follow-up one-on-one sessions at 3, 6, and 12 months. The interventions for the standard GLB and GLB + LGx groups were identical in duration (1 × 90-min and 22 × 60-min group-based sessions and 4 × 30-min one-on-one sessions). Staggered cohorts were implemented between May 2017 and September 2019, while balancing seasonality between the 2 intervention groups. This study is registered with clinicaltrials.gov. (NCT03015012).

*Population-Based Intervention (Standard GLB Group)*

Standard, population-based lifestyle advice was provided to participants in the standard GLB group intervention by the first author, who was a certified GLB program facilitator. The population-based reports were reviewed at the 3 follow-up one-on-one appointments occurring after 3, 6, and 12 months. With respect to PA, participants were advised to aim to complete at least 150 min/week of moderate-intensity PA with resistance activities at least 2 days a week. They were further advised to find endurance and strength-based activities that they enjoy in order to meet this guideline. The following 3 components of the TPB were incorporated into the intervention strategy: subjective norms, perceived behavioral control, and attitudes [26]. To affect change in subjective norms, the intervention was primarily group-based and allowed for a supportive group environment. Participants shared and discussed their progress with their peers as they worked toward similar goals and behaviors. To affect change in perceived behavioral control, the group sessions focused on gradually increasing PA levels that were safe and realistic. Lastly, to affect change in attitudes towards PA, participants were informed of the positive health impacts of PA and its importance for weight management. The complete population-based guidelines that participants received have been published elsewhere [23].

*LGx Intervention (GLB + LGx Group)*

Participants randomized to the GLB + LGx group intervention received personalized genetic-based PA information and advice, with the report reviewed at the 3 follow-up one-on-one appointments occurring after 3, 6, and 12 months. Participants were counselled on actionable genetic-based recommendations, which were based on a genetic testing report that is commercially available to the general public through healthcare professionals. Participants with the AA genotype in the *FTO* gene *(rs9939609)* were instructed to achieve a PA target of 30–60 min/day, 6 days a week (180–360 min/week) of moderate-intensity activity, with strengthening activities at least 2 days a week. Participants were informed that achieving this higher PA target (compared to population-based recommendations) could lead to an "enhanced weight loss response." Participants with the TA or TT genotype of *FTO* *(rs9939609)* were instructed to work toward the abovementioned population-based PA guidelines (150 min weekly with muscle-strengthening activities 2 days a week). The genetic intervention also aimed to positively impact key components of the TPB including: subjective norms, perceived behavioral control, and attitudes toward PA [26]. In addition to the effects on subjective norms, the perceived behavioral control and attitudes mentioned in Population-Based Intervention (Standard GLB Group), the genetic intervention further aimed to affect these components through the provision of individualized DNA-based information and recommendations for PA. To optimize changes in perceived behavioral control and attitudes, individuals in the genetic group were also informed about whether or not they had a genetic predisposition to excel at endurance and/or strength-based activities. The genetic variants that were included in the genetic report and used to assess genetic predisposition to excel in endurance/aerobic-based activities were: *ADRB (rs4994), NRF2 (rs12594956), GSTP1 (rs1695)*, and *NFIA-AS2 (rs1572312)*. Furthermore, participants were provided with information on their genetic predisposition to excel at strength and power-based PA based on *ACTN3 (rs1815739)* genetic variation. For example, individuals with the TC or CC variant of *ACTN3*

*(rs1815739)* were informed: "You have an enhanced genetic predisposition to excel in strength and power-based PA." Those who did not have such genetic variants were informed that they had a typical genetic predisposition to excel in strength/power or endurance activities. A sample genetic report that participants received has been published elsewhere [23]. The standard GLB program was modified to replace standard population-based advice.

*Genotyping*

Oragene ON-500 saliva collection kits (DNA Genotek, Ottawa, ON, Canada) were used to collect DNA samples of the participants at the East Elgin Family Health Team. 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 single-nucleotide polymorphisms listed above.

*Data Collection and Outcomes*

Participants were followed up for 12 months, with data collection occurring at baseline (during a 2-week run-in period in which group allocation was concealed for the participants) and 3, 6, and 12 months. Staggered cohorts were implemented between May 2017 and September 2019. Data were collected through self-reported past-week PA recalls of leisure-time activity only. This included the type of activity, duration, and intensity (light, moderate, or vigorous). Leisure time PA was defined as any planned activity completed outside of work. In cases where participants did not follow the instructions to include only leisure time PA and also listed job-related activity, the job-related activity was excluded from the analyses, as further detailed below, given that evidence suggests that recreational (leisure time) PA has greater health benefits than non-recreational PA [27]. Change in metabolic equivalents (METs) between groups was a predetermined secondary outcome of the NOW trial; changes in minutes of leisure time PA and PA adherence were exploratory analyses.

*Data Analysis*

All analyses were by originally assigned groups. The Compendium of Physical Activities [28] was used to calculate METs (a measure of energy expenditure) of participants' leisure time PA. One MET is defined as the amount of oxygen used by the body while sitting at rest and it is equal on average to 3.5 mL oxygen/kg/min [28]. Activities on the compendium were matched to the participant's type and intensity of activity to find an appropriate MET value. Following this, the duration in minutes of the participants' activity was multiplied by the MET value to calculate the total METs. A database was created to record the PA codes (obtained from the compendium) used for each activity to ensure consistency among the participants' activities. For example, all moderate-intensity walking was coded as: *17,220, walking, 4.0 m/h level, firm surface, very brisk pace*, with an MET value of 5.0. For activities that could be classified as several different MET items or if a MET code did not exist for an activity, consensus through discussion was reached by 2 authors (T.L. and J.R.H.) to determine the best fit for the particular activity. For example, an MET code did not exist for the activity pickleball. This was a recurring activity among participants, and therefore consensus was reached to use code 15,500, with an MET value of 6.0 (paddleball, casual, general). In addition, the proportion of participants meeting the genetic (personalized) and population-based PA targets was assessed in

**Table 1.** Genetic variation among the participants in the GLB + LGx group

| PA component, gene (SNP) | Genotype distribution (*n*, %) | Participants with an enhanced response/athletic advantage genotype (*n*, %) | Associated genetic-based information |
|---|---|---|---|
| Total PA, FTO (rs9939609) | AA (21, 30.0) TA (27, 38.6) TT (22, 31.4) | Enhanced weight loss response (21, 30.0) | Enhanced weight loss response with greater PA (30–60 min/day, 6 days a week, with strength-based activities at least 2 days a week) |
| Endurance, ADRB (rs4994) | TT (64, 91.4) TC (6, 8.6) CC (0, 0.0) | | |
| Endurance, NRF2 (rs12594956) | AA (22, 31.4) AC (34, 48.6) CC (14, 20.0) | Enhanced athletic advantage (14, 20.0); ultra-athletic advantage (2, 2.9) | Genetic predisposition to excel in endurance-based PA (based on an algorithm of 4 genotypes) |
| Endurance, GSTP1 (rs1695) | AA (21, 30.0) AG (41, 58.6) GG (8, 11.4) | | |
| Endurance, NFIA-AS2 (rs1572312) | AA (1, 1.4) CA (8, 11.4) CC (61, 87.1) | | |
| Strength/Power, ACTN3 (rs1815739) | TT (21, 30.0) TC (30, 42.9) CC (19, 27.1) | Enhanced athletic advantage (30, 42.9); ultra-athletic advantage (19, 27.1) | Genetic predisposition to excel in strength-based PA |

order to measure PA adherence. Furthermore, differences between groups in total minutes of moderate- and high-intensity activity over time were assessed. Adherence to PA targets was dependent on group and genotype (for the GLB + LGx group). For the standard GLB group and the GLB + LGx "typical weight loss response" group (*FTO* rs9939609 TA or TT genotype), participants were considered to be adhering to the PA guidelines if they completed at least 150 min/week of moderate- and/or high-intensity activity. For the GLB + LGx "enhanced weight loss response" group (*FTO* rs9939609 AA genotype), adherence was considered to be at least 30–60 min/day, 6 days a week (≥180–360 min/week) of moderate- and/or high-intensity activity.

SPSS version 26.0 was used to conduct all statistical analyses. Extreme (far out) outliers, defined as ±3 IQR, were identified using SPSS Descriptive Statistics and removed (e.g., 12,150 weekly leisure time METs were calculated for one participant who reported 7.5 consecutive hours per day of leisure time activity, 6 days a week), as these were likely a reflection of over-reporting (online suppl. material, for all online suppl. material see www.karger.com/doi/10.1159/000510216). Split plot analysis of covariance was used to analyze between-group differences in the amount (min) of moderate- and high-intensity weekly leisure time PA, as well as the total weekly leisure time METs from baseline to 3, 6, and 12 months of follow-up. Binary logistic regression (generalized linear models) was used to assess differences between groups for the proportion of participants adhering to the PA guidelines at each time point. Baseline PA levels (min, METs, and adherence) were controlled for in all of the analyses, with $p < 0.05$ considered statistically significant.

## Results

Table 1 indicates the genetic results of the participants randomized to the GLB + LGx group. Weekly MET were significantly higher in the GLB + LGx group compared to the standard GLB group at 6 months (Table 2). For weekly minutes of PA, while not statistically significant ($p = 0.18$; Table 2), only the GLB + LGx group achieved >150 min/week of moderate- and high-intensity PA, on average. There were no significant differences in adherence to the PA targets in the GLB + LGx group compared to the standard GLB group ($p = 0.25$ at 3 months, $p = 0.18$ at 6 months, and $p = 0.99$ at 12 months). Overall, the GLB + LGx intervention led to an enhanced leisure time PA energy expenditure after the 6-month follow-up, compared to the standard, population-based GLB intervention.

## Discussion

Our findings demonstrated that the provision of genetic-based PA information and advice enhanced leisure time PA energy expenditure after the moderate-term, 6-month

**Table 2.** Weekly duration of moderate + high-intensity PA and weekly MET

|  | Baseline | 3 months | 6 months | 12 months |
|---|---|---|---|---|
| *PA, min/week* | | | | |
| GLB | 90.1±0.0 (90.1–90.1) | 122.8±23.7  75.4–170.2) | 114.8±26.3 (62.2–167.3) | 144.6±24.6 (95.4–193.7) |
| GLB + LGx | 90.1±0.0 (90.1–90.1) | 136.2.0±23.4  89.5–182.8) | 169.2±25.9 (117.4–221.0) | 112.8±24.3  64.4–161.2) |
| *MET, n/week* | | | | |
| GLB | 727.9±0.0 (727.9–727.9) | 1,071.0±142.0  787.6–1,354.3) | **0.621.6±141.9 (338.4–904.8)** | 951.5±126.9 (698.3–1,204.7) |
| GLB + LGx | 727.9±0.0 (727.9–727.9) | 884.3±142.0  600.9–1,167.6) | **1,114.7±141.9 (8,31.5–1,397.8)** | 818.5±126.9 (565.2–1,071.7) |

Values are presented as means ± SE (95% CI). Values in bold are statistically significant. $p = 0.01$; $n = 71$ (GLB, $n = 35$; GLB + LGx, $n = 36$).

follow-up. This demonstrates that genetically tailored PA information and advice exhibit clinical potential. Future research should explore how this enhanced leisure time PA energy expenditure can be sustained in the long term given that leisure time PA energy expenditure contributes to improved cardiometabolic, brain, and bone health among others [29]. Some prior studies have also shown that disclosure of genetic information can enhance PA habits [30, 31], though research in this area has been inconsistent [32–34]. Furthermore, much of the research in this area has provided participants with genetic interventions that were unlikely to facilitate changes in PA habits based on established theory and knowledge on facilitating health behavior changes [21, 26]. For example, in one study measuring PA outcomes resulting from disclosure of genetic susceptibility to Alzheimer disease, if participants inquired about any prevention strategies for the onset of Alzheimer disease, the presenter would communicate that there "are no effective methods of treatment or prevention to date" [34]. Thus, it is perhaps not surprising that this study found no change in PA habits [34]. Therefore, genetic interventions need to consider current knowledge on how to best facilitate behavior changes if they are aiming to facilitate successful lifestyle change outcomes.

While the present study demonstrated greater leisure time PA METs in the GLB + LGx group after the moderate-term, 6-month follow-up, this greater engagement in PA with the provision of genetic information and advice was not enhanced in the short term (3 months) or the long term (12 months). Given that the GLB and GLB + LGx interventions were highly intensive, with 23 group-based sessions, and focused on several lifestyle changes (predominantly nutrition and PA), it is possible that participants were focused on other lifestyle components of the interventions during the first 3 months and/or the last 6 months. In addition, the final 6 months of the GLB curriculum include a minimal focus on moderate- to high-intensity PA, with only 2 PA-related sessions, primarily focused on sitting less, good posture, and stretching [23]. This was a limitation of the intervention. We hypothesize that a greater focus on moderate-to-high intensity PA during the second half of the interventions (for both intervention groups) would have resulted in the 6-month findings being sustained in the long term; future research should seek to explore this. In addition, the sample size may have limited our abilities to detect significant differences in the exploratory analyses. Moreover, given the study population, the results are primarily generalizable to middle-aged, Caucasian women with obesity who are interested in weight management.

Nonetheless, our results indicate that it is possible to use genetic information and advice to motivate individuals to enhance PA energy expenditure. The NOW trial communicated the PA information and recommendations within the GLB program, which is a gold-standard, group-based, lifestyle change weight management program but is only offered in a select few clinics in Canada and approximately 50 healthcare facilities in the USA [35]. Therefore, future pragmatic research should further seek to assess PA outcomes resulting from a genetic intervention compared to the standard of care, which typically consists of the communication of population-based PA recommendations in a one-on-one setting with a healthcare provider. It should be noted that standard of care typically requires a patient to purchase an LGx test, which is not feasible for all at a public health level. In addition, future research should aim to assess other outcomes resulting from LGx interventions such as measures of cardiometabolic health, stress, the types of PA that participants engaged in, and strength/endurance level. This future work should also use direct measures of PA, such as through the use of accelerometers, rather than self-reported data.

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## Conclusion

This is the first study to assess changes in PA resulting from a population-based versus a genetic-based intervention within a weight management program. Overall, results from the NOW trial provide some promise to the body of research evaluating the impact of genetic-based recommendations on PA behaviors. While the provision of an LGx intervention resulted in a greater leisure time PA energy expenditure after a 6-month follow-up, future research should determine how this could be sustained over the long term.

## Statement of Ethics

This study was approved by the Western University Research Ethics Board (108511) and all of the participants provided written informed consent.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

## Author Contributions

J.R.H., J.G., J.A.S, C.O., and J.M. were involved in designing this study. J.R.H. conducted this study at the East Elgin Family Health Team. T.L. calculated METs, with supervision from J.R.H. T.L., J.R.H. and J.A.S. completed the statistical analyses. T.L. and J.R.H. wrote the first draft of this paper and revised subsequent drafts. All of the authors revised the drafts, approved the final version of this paper, and are accountable for all aspects of this work.

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