nature human behaviour

SUPPLEMENTARY INFORMATION

https://doi.org/10.1038/s41562-018-0483-4

In the format provided by the authors and unedited.

Learning one's genetic risk changes physiology independent of actual genetic risk

Bradley P. Turnwald[1]*, J. Parker Goyer[1], Danielle Z. Boles[1], Amy Silder[2], Scott L. Delp[2] and Alia J. Crum[1]

[1]Department of Psychology, Stanford University, Stanford, CA, USA. [2]Department of Bioengineering, Stanford University, Stanford, CA, USA.
*e-mail: turnwald@stanford.edu

Supplementary Information for

Learning one's genetic risk changes physiology independent of actual genetic risk

B.P. Turnwald, J.P. Goyer, D.Z. Boles, A. Silder, S.L. Delp, & A.J. Crum

correspondence to: turnwald@stanford.edu

Table of Contents

Supplementary Methods

Experimental Design: Participants were recruited via flyer and indicated interest via email. The flyer advertised a study that was recruiting participants to "help scientists create personalized nutrition and exercise programs," and that "by participating in this Experiment, [participants] will help develop nutrition and exercise regimens to optimize personal health and fitness." Participants were under the impression that they would be genotyped to learn exactly which diets and exercises are best suited for them. The consent and genotyping appointment involved a 1-hour visit to either the Stanford Clinical Translational Research Unit or the Stanford Sports Medicine Center to consent, give a saliva sample, and take baseline surveys. After the consent and genotyping appointment, participants were allocated (see below) to the exercise experiment (Experiment 1) or to the satiety experiment (Experiment 2). Participants in the exercise experiment returned to the Stanford Sports Medicine Center 1-3 weeks after their consent and genotyping session for their baseline session, which involved completing a maximal effort treadmill test. They returned 1 week later for their second session (genetic risk session) in which they received their randomly assigned genetic risk and re-ran the maximal effort treadmill test. Participants in the satiety experiment (Experiment 2) returned to the Stanford Clinical Translational Research Unit 1-3 weeks after their consent and genotyping session for their baseline session, which involved an overnight fast, consuming a 480-calorie meal, and submitting blood samples. They returned 1 week later for their second session (genetic risk session) in which they received their randomly assigned genetic risk, consumed the same meal, and gave blood samples at the same time points. All participants were debriefed and paid $85 for their participation at the end of their genetic risk session. Details for each session of the experiments are described below.

Participants: Participants were individuals age 18-50, in good health, and not pregnant or diabetic. For the 116 participants in Experiment 1 [(42.2% male (*N*=49), 57.8% female (*N*=67)], the mean age was 24.7 (*SD*=5.2; range 18-41) and mean BMI was 23.3 (*SD*=3.6; range 17.2–37.0). The population was 26.7% Asian, 3.4% Black, 6.9% Latino, 51.7% White, and 11.2% multiracial or other, and 63.8% had completed at least a bachelor's degree.

For the 107 participants in Experiment 2 [(31.8% male (*N*=34), 68.2% female (*N*=73)], the mean age was 26.1 (*SD*=6.8; range 18-49) and mean BMI was 23.8 (*SD*=4.0; range 17.8–43.4). The population was 17.8% Asian, 1.9% Black, 7.5% Latino, 58.9% White, and 10.3% multiracial or other, and 65.4% had completed at least a bachelor's degree. Age and education data were incomplete or missing from four participants. There were no significant differences in age, gender, race, or BMI between individuals informed that they had the high-risk genotype and individuals informed that they had the protective genotype in Experiment 1 (*P*'s≥0.13) or Experiment 2 (*P*'s≥0.33).

Experiment Allocation and Attrition: Across both experiments, 271 participants were genotyped. The allocation to the exercise experiment or satiety experiment went as follows: (1) Because participants homozygous for the high-risk allele (AA genotype for *CREB1* rs2253206 and AA genotype for *FTO* rs9939609) were rarest, these individuals were allocated to the exercise experiment (if AA *CREB1* genotype) or satiety Experiment (if AA *FTO* genotype), respectively. (2) Next, if participants did not have the high-risk genotype for either gene, participants homozygous for the protective allele (GG for C*REB1* and TT for *FTO*) were allocated to the exercise experiment (if GG *CREB1* genotype) or satiety experiment (if TT *FTO* genotype), respectively. (3) Participants that were heterozygous for both genes of interest were randomly assigned to the exercise experiment or satiety experiment. As described later, all participants in both experiments were randomly assigned to receive either high-risk or protective genetic test results in the genetic risk session using a 1:1 ratio, so that approximately equal numbers of each actual genotype received high-risk and protective genetic test results.

Of the 271 participants genotyped, 40 participants never completed a baseline session, due to either not responding to emails, moving away, ineligibility, or being screened out for having a genotype for which the quota had already been reached. In Experiment 1 (exercise), three participants were lost to attrition after completing their baseline session, due to moving away (2) or not responding to follow-up appointment emails (1). Data from two other participants were excluded due to errors in the protocol during the treadmill test. In Experiment 2 (satiety), one participant was lost to attrition during the baseline session due to feeling faint during blood draws, one participant stopped responding to follow-up appointment emails after completing their baseline session, and one participant's data was excluded because no determination of actual *FTO* genotype could be made.

Experiment 1 Procedures, **Baseline Session:** Participants were instructed to refrain from exercising at minimum 24 hours prior to their appointment time and knew that they would be running a treadmill test at their appointment.

Upon arrival, participants responded to questions about their typical exercise behaviour and their diet in the preceding 24 hours. The maximum effort treadmill test used was a modified Astrand test[63]. There was a 4-minute walking warmup, followed by a 2-minute period in which the speed of the treadmill was gradually increased to their final running speed (a speed that was customized for each participant to feel like a speed at which they could run for 15 minutes). This exact same speed was used in their final session that was completed after receiving genetic information (genetic risk session). At minute 6, the final speed was set (range: 4.0 – 8.0 mph; *M*=5.9mph; *SD*=0.9), and every 2 minutes thereafter the incline increased by 2.5%. Participants ran to exhaustion, which they indicated by giving two "cut" motions with their hand. At the first "cut" motion, the experimenter urged them to continue running as long as they possibly could, and at the second "cut" motion, the experimenter immediately stopped the treadmill and the test ended. Additionally, every two minutes, participants indicated their rating of perceived exertion (RPE)[64] by pointing to a scale of *6 (no exertion at all)* to *20 (maximum exertion)*. Participants were given no feedback on their performance and were told that they would receive all feedback at their final session.

Experiment 1 Procedures, Genetic Risk Disclosure Session: Participants who completed the baseline session returned approximately 1 week later for their genetic risk disclosure session. Upon arrival participants were told that they would be running the same exercise test as in the previous week. Participants were told that they would then receive all of their physiological and genetic data at the end of the session that day, except for "their most important genetic test result" that the experimenter would share with them first. Participants then were told that the *CREB1* gene was a predictive gene for aerobic exercise performance and was one of the major genes that was being examined in the present experiment. Participants received an envelope containing their randomized genetic test result (either high-risk or protective) and a short pamphlet detailing the impact that the *CREB1* gene has on physiology, sensory experience, and behaviour during aerobic exercise. Participants had 10 minutes to read through their genetic test report and pamphlet, and then answered a short survey. The survey served as a manipulation check, as it asked participants to fill in their test result, to confirm that they understood their test result, and to indicate the level of risk, worry, and control that they felt. The experimenter responded to any questions that participants had at this point by asking them to hold all questions until the end of the session when they could look at all of the physiological and genetic data. Participants were then briefly reminded of the protocol for the treadmill test, and then the exact same protocol (same speed within participants, and same time increments and increases in incline for all participants) was followed as at their baseline session. After participants finished running and had time to stretch, catch their breath, and hydrate, they answered a 20-minute survey. Participants were then carefully debriefed on the true goal of the experiment.

Experiment 2 Procedures, Baseline Session: Participants were instructed to fast overnight for 12 hours prior to their morning appointment time. They were informed that they would consume a meal and that their blood samples would be collected before and after consumption. Upon arrival, participants responded to questions about their diet in the preceding 12 hours. Participants were led to a private space in the hospital unit and sat in a comfortable patient examination chair. Nursing staff inserted an intravenous catheter into participants' non-dominant forearm. After 20 minutes to allow for equilibration, the nurse returned to take the pre-consumption, fasting state blood sample. Participants were then instructed to consume the experiment meal, which consisted of an 8 fl. oz., 480 cal nutrition shake (Resource 2.0, NestleHealthSciences) from a glass in its entirety at a relatively constant rate over the course of 5 minutes. Fifteen minutes after consuming the meal in its entirety, nursing staff returned to collect the 15 minutes post-consumption blood sample. A final blood sample was collected 25 minutes later (40 minutes post-consumption), and nursing staff removed the intravenous catheter. Participants scheduled their next session for approximately 1 week later. They were told that they would receive their genetic test results at that session, as well as consume the same meal and give blood samples again, ostensibly to improve the accuracy of their results.

Experiment 2 Procedures, Genetic Risk Disclosure Session: Upon arrival at their genetic risk disclosure session, participants were told that they would consume the same meal and have blood samples drawn just as in their baseline session. Participants were told that they would then receive all of their physiological and genetic data at the end of the session that day, except for "their most important genetic test result" that the experimenter would share with them first. Participants were told that the *FTO* gene was a very predictive gene for obesity, related to "not feeling full after a meal," and was one of the major genes that was being examined in the present experiment. Participants then received an envelope containing their randomized genetic test result (either high-risk or protective) and a short pamphlet detailing the impact that the *FTO* gene has on obesity and feelings of hunger and fullness. Participants had 10 minutes to read through their genetic test report and pamphlet, and then answered a short survey, which served as a manipulation check. Participants were prompted to fill in their test result, indicate that they

understood their test result, and indicate the level of risk, worry, and control that they felt (see Supplementary Figure 3). The experimenter responded to any questions that participants had at this point by asking them to hold all questions until the end of the session when they could look at all of the physiological and genetic data. Participants were then briefly reminded of the protocol for the day, and then the exact same protocol was followed as at their baseline session. The pre-consumption blood sample was drawn just after participants viewed their genetic test results and pamphlet and answered the short survey. Once the nurse completed the final blood draw and participants completed a final survey, they were carefully debriefed on the true nature of the Experiment.

Blinding of Experimenters: In Experiment 1 (exercise), the experimenter was a white male and administered the protocol to all 116 subjects. In Experiment 2 (satiety), the experimenter was an Asian female and administered the protocol to all 107 subjects. In both experiments, the experimenter was blind to participants' outcomes from the baseline session and participants' actual genotype. Experimenters were also blind to the randomly assigned genotype at the baseline session until participants received their genetic test report and pamphlets at the genetic risk session. Thereafter, blinding of randomly assigned genotype was not possible given that participants' results were open on the table and many participants asked a question or made a comment to the experimenter which revealed their randomly assigned genotype. Individuals who did not have access to participants' actual or assigned genetic risk level and did not participate in the analyses processed the physiological data from both experiments. An individual who was not present at the experimental sessions analyzed physiological data from both experiments.

Genotyping: Saliva was collected by the passive drool method, and genomic DNA was extracted according to manufacturer instructions using a QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA). All participants were genotyped for *FTO* rs9939609 and *CREB1* rs2253206 at the Stanford Protein and Nucleic Acid Facility (Stanford, CA, USA). Primer sequences are available from the first author upon request. Both *CREB1* rs2253206 and *FTO* rs9939609 were in Hardy-Weinberg Equilibrium (*P*'s$\geq$0.69) in the recruited population.

Measurement of physiological data in Experiment 1: In Experiment 1, the maximal exercise treadmill test was run on a Woodway Pro XL treadmill (Waukesha, WI, USA). Breath-by-breath measures of pulmonary ventilation and gas exchange were measured by a metabolic cart (Quark b^2, Cosmed, Rome, Italy). Before each test, the gas analyzers and the turbine flow meter were calibrated according to the manufacturer's instructions using a gas mixture of known concentration and a 3.0 L calibrated syringe. Breath-by-breath measures were averaged over 30-second intervals using MATLAB vR2015b (The Mathworks, Inc., Natick, MA, USA).

Physiological measures during the maximum exercise treadmill test focused on two summary measures of cardiorespiratory exercise physiology: (1) the respiratory exchange ratio (CO_2:O_2 exchange rate) as the summary measure of metabolic gas exchange, and (2) ventilatory flow rate (breaths/min × L/breath) as the summary measure of physical respiratory physiology. CO_2:O_2 exchange rate is the oxidative capacity to supply the muscles with energy and strongly correlates with increased exercise intensity[65,66] and increased blood lactate[65,67]. Thus, maximum CO_2:O_2 exchange rate is a physiological signature of tolerating lactic acid buildup during strenuous exercise. Ventilatory flow rate is the total volume of gas inhaled and exhaled from the lungs per minute[67] and rises as exercise intensity increases in an effort to supply the body with oxygen and remove carbon dioxide[66]. Thus maximum ventilatory flow rate represents an individual's maximum capacity for moving air through the respiratory system during strenuous exercise.

Measurement of physiological data in Experiment 2: In Experiment 2, blood samples were collected at the Stanford University Clinical Translational Research Center by intravenous catheter into 4 ml EDTA tubes, cooled on ice and pre-treated with 5,000 KIU aprotinin and 1 mg/ml pefabloc to prevent degradation of acylated ghrelin. After blood collection, samples were spun at 4 C for 10 min. Plasma was acidified to a final concentration of 0.05 N and stored at -80 C until analysis. Assays to determine the concentration of GLP-1 and acylated ghrelin in plasma were conducted at the Human Immune Monitoring Center at Stanford University. Kits were multiplex Premixed Human Metabolic Hormone Kit purchased from EMD Millipore Cat# SPRPMX41 and used according to the manufacturer's recommendations with modifications as described below. Samples were mixed with antibody-linked magnetic beads on a 96-well plate and incubated overnight at 4°C with shaking. Cold and room temperature incubation steps were performed on an orbital shaker at 500-600 rpm. Plates were washed twice with wash buffer in a Biotek ELx405 washer. Following 1 hour incubation at room temperature with biotinylated detection antibody, streptavidin-PE was added for 30 minutes with shaking. Plates were washed as described above and Sheath Fluid/PBS added to wells for reading in the Luminex Flex3D Instrument with a lower bound of 50 beads per sample

per peptide. Each sample was measured in duplicate. Custom assay Chex control beads by Radix Biosolutions were added to all wells.

Additional measures: Additional measures were obtained but are not reported in this manuscript because they will be the focus of a subsequent manuscript that explores psychological, affective, and stress responses to receiving genetic risk information. Additional measures include the following: the Dutch Eating Behaviour Questionnaire, the Dieting Beliefs Scale, Positive and Negative Affect Schedule, exercise self-efficacy, genetic and behavioural attributions for a range of conditions, desire to speak to a genetic counselor or learn more about genes, open ended thoughts about genetic risk information, intentions to eat healthier and exercise more, and stress-related biomarkers Interkleukin-6, TNF-alpha, and cortisol. Additionally many demographic and baseline health questions were asked upon participants' enrollment in the study (occupation, baseline fruit and vegetable consumption, baseline exercise behaviour, health history, family health history, CDC Healthy Days, Multidimensional Health Locus of Control, previous experience with genetic sequencing, education).

Statistical Analysis (cross-sectional)

For all analyses involving maxima reached (and the time to these maxima), we used a two-level multilevel regression model. The Level-1 model is within participants and specifies how the outcome differs between sessions, before (Session 1) and after (Session 2) receiving genetic risk information.

$$Y_{ij} = \pi_{0i} + \pi_{1i} SESSION_{ij} + \varepsilon_{ij}$$

The Level-2 model, between participants, predicts parameters of the Level-1 model as a function of condition, whether participants were informed that they were at high risk (AA genotype in both experiments) or protected (GG genotype in Experiment 1, TT genotype in Experiment 2).

$$\pi_{0i} = \gamma_{00} + \gamma_{01} PerceivedGENOTYPE_i + \delta_{0i}$$

$$\pi_{1i} = \gamma_{10} + \gamma_{11} PerceivedGENOTYPE_i + \delta_{1i}$$

We defined SESSION as 0 for Session 1 (baseline/pre-manipulation) and 1 for Session 2 (after receiving assigned genetic test result/post-manipulation). This meant that the main effects in the composite model yielded the parameters (intercept or slopes) for Session 1. To obtain the corresponding Level-1 parameters for Session 2, we reversed the coding, defining SESSION as 0 for Session 2 and +1 for Session 1.

We defined PerceivedGENOTYPE as 0 for individuals informed that they had the high-risk genotype (AA) and +1 for individuals informed that they had the protective genotype (GG for Experiment 1 or TT in Experiment 2). Consequently, the main effects in the composite model correspond to individuals informed that they had the high-risk genotype at Session 1. To obtain the relevant coefficients for those informed that they had the protective genotype, we reversed the coding, defining PerceivedGENOTYPE as 0 for this group and +1 for high-risk.

In the composite model, the SESSION × PerceivedGENOTYPE interaction indicates whether the difference in the outcome at Session 2 relative to Session 1 differs by informed genetic risk level. The main effect of SESSION indicates whether the outcome in Session 2 differs from the outcome in Session 1, for the condition group defined as 0. All cross-sectional outcomes are displayed in Supplementary Tables 1-3. Supplementary Table 4 displays the simple effects from these models for all outcomes in both experiments.

Additionally, to assess whether the SESSION x PerceivedGENOTYPE effects differed by individuals' actual genotypes, we assessed the above model when adding in a SESSION x PerceivedGENOTYPE x ActualGENOTYPE interaction term. Supplementary Table 5 presents the perceived genotype x session interactions for each of the actual genotypes individually, derived from the two-level regression model by coding each actual genotype condition as 0 and the other two actual genotypes as +1 and +2.

Effect Sizes: We computed effect size (see Table 1 in main text) as a proportion of the standard deviation of the raw outcome in the full sample in Session 1. The effect due to actual genotype is a between-subjects comparison (difference between actual protective and actual high-risk genotypes at the baseline session) and the effect due to

perceived genotype is a within-subjects comparison (changes in outcomes from baseline session to genetic risk session). To account for this inherent difference in design, the effect sizes for both actual genotype and perceived genotype were calculated as a proportion of the standard deviation in the full sample in the baseline session. The effect sizes for actual genotype represent the difference in mean outcomes from the baseline session between the actual protective genotype (GG in Experiment 1, TT in Experiment 2) and the actual high-risk genotype (AA) divided by the standard deviation of that outcome in the baseline session. The effect sizes for perceived genotype were calculated separately for individuals informed of high-risk and individuals informed that they had the protective genotype, and represented the change in the outcome between the baseline session and the genetic risk session divided by the standard deviation of that outcome in the full sample in the baseline session.

Statistical Analysis (longitudinal)

Analytic Approach for Supplementary Longitudinal Analyses in Experiment 1 (exercise)

To understand the effects on summary measures (those reported in the main text) in more detail, we used longitudinal multilevel regression models to assess changes in participants' exercise performance during the maximal treadmill test as a function of session and condition. For every longitudinal analysis, we fit a three-level multilevel model. The Level-1 model specified change in the outcome within a given session, the Level-2 model specified changes in the Level-1 parameters as a function of session (within-subjects), and the Level-3 model specified changes in the Level-2 parameters as a function of perceived genotype condition (between-subjects).

For the physiological outcomes respiratory exchange ratio and minute ventilation, the Level-1 submodel described how the outcome changed over time for a given participant. In addition to the main effect of time, it included time-varying predictors to allow for shifts in slope at key periods. Physiological outcomes were measured every 30 seconds, beginning at minute 0.5 (30 seconds after the walking warmup began). Session 1 and Session 2 were synchronized so that certain researcher-instigated events occurred at the same time in minutes in each session for each participant. We used percentage of the Session 1 test as the metric for time because participants finished the test at different times (often according to their baseline physical fitness levels) and thus had different amounts of data toward the end of the test. On average, participants' last recorded time in Session 1 occurred at 16.4 minutes (SD=2.3, range=9-24min) including the 4-minute walking warmup. The Session 2 outcomes occurring at the minutes to which these Session 1 percentages corresponded were used to assess the Session 2 trajectories. Because our primary question was a within-participant question (whether the intercept or slopes of Session 2 trajectories differed from those in Session 1 trajectories), this indexing of time to Session 1 was best for assessing this comparison.

We divided the test into phases using common observable events within each session and participants' ratings of perceived exertion. In this case, we mean-centered time on minute 4 of the Session 1 test (the variable PERC4 in the equations, see below). We anchored the time metric, PERC4, on 0 for minute 4 of the test (for all participants) and on 1 (representing 100%, as a proportion) for the last recorded time in Session 1 (different for each participant). Minute 4 corresponded to the time when participants transitioned from walking to running. Starting at minute 6, the treadmill incline was increased by 2.5% every 2 minutes. Minute 4 to Minute 6 was considered Phase 1 because it represented the time at which participants transitioned from walking to slowly increasing to their final set running speed. Regardless of the percentage of the Session 1 test to which they corresponded, these times were the same in minutes during both sessions. The primary threshold we were interested in occurred later in the test, when participants indicated their perceived exertion as 15 ("hard") on a 20-point scale (RPE 15). This RPE 15 threshold varied across participants (*M*=11.7min; *SD*=2.5min; range: 6 – 20 min). Phase 2 corresponded to the period from minute 6 to the time at which participants reached their RPE 15 threshold. The final, most challenging phase, Phase 3, was the time period after the RPE 15 threshold until the last recorded time. As before, all times and thresholds were from Session 1. The Level 1 model was modified as follows:

$$Y_{ijk} = \pi_{0ij} + \pi_{1ij} PERC4_{ijk} + \pi_{2ij} MIN6_{ijk} + \pi_{3ij} RPE15_{ijk} + \varepsilon_{ijk}$$

Four Level-2 submodels predicted key parameters of the Level-1 model as a function of session within participants (Session 1 versus Session 2):

$$\pi_{0ij} = \gamma_{00i} + \gamma_{01i} SESSION_{ij} + \delta_{0ij}$$

$$\pi_{1ij} = \gamma_{10i} + \gamma_{11i} SESSION_{ij} + \delta_{1ij}$$

$$\pi_{2ij} = \gamma_{20i} + \gamma_{21i} SESSION_{ij}$$

$$\pi_{3ij} = \gamma_{30i} + \gamma_{31i} SESSION_{ij}$$

$SESSION_{ij}$ is a dichotomous variable defined as 0 for Session 1 (pre-manipulation, before participants were told genetic information) and +1 for Session 2 (post-manipulation, after participants were told genetic information). This meant that the Level-1 parameters, the main effects in the longitudinal model, yielded the parameters (intercept or slopes) for Session 1. To obtain the corresponding Level-1 parameters for Session 2, we reversed the coding, defining $SESSION_{ij}$ as 0 for Session 2 and 1 for Session 1.

At Level 3, eight submodels predicted key parameters of the Level-2 model as a function of between-participant predictors, namely condition (informed of high-risk genotype versus protective genotype).

$$\gamma_{00i} = \alpha_{000} + \alpha_{001} PerceivedGENOTYPE_i + \delta_{00i}$$

$$\gamma_{01i} = \alpha_{010} + \alpha_{011} PerceivedGENOTYPE_i + \delta_{01i}$$

$$\gamma_{10i} = \alpha_{100} + \alpha_{101} PerceivedGENOTYPE_i + \delta_{10i}$$

$$\gamma_{11i} = \alpha_{110} + \alpha_{111} PerceivedGENOTYPE_i + \delta_{11i}$$

$$\gamma_{20i} = \alpha_{200} + \alpha_{201} PerceivedGENOTYPE_i$$

$$\gamma_{21i} = \alpha_{210} + \alpha_{211} PerceivedGENOTYPE_i$$

$$\gamma_{30i} = \alpha_{300} + \alpha_{301} PerceivedGENOTYPE_i$$

$$\gamma_{31i} = \alpha_{310} + \alpha_{311} PerceivedGENOTYPE_i$$

We defined $PerceivedGENOTYPE_i$ as 0 for participants informed that they had the high-risk genotype (AA genotype) and +1 for participants informed that they had the protective genotype (GG genotype). This meant that all Level-1 and Level-2 main effects and their interactions corresponded to individuals informed that they had the high-risk genotype. To obtain the same Level-1 and Level-2 parameters for individuals informed that they had the protective genotype, we reversed the coding, defining PerceivedGENOTYPE as 0 for individuals informed that they had the protective genotype and +1 for individuals informed they had the high-risk genotype.

When time was mean-centered at the beginning of Phase 1 (minute 4), π_{1ij} represented the slope in Phase 1. π_{2ij} represented the shift in slope from Phase 1 to Phase 2. π_{3ij} represented the shift in slope from Phase 2 to Phase 3. We changed the mean centering of time to obtain the slopes in the other phases. When time was centered

on the beginning of Phase 2 (minute 6), π_{1ij} now represented the slope in Phase 2. π_{2ij} now changed to represent the shift in slope from Phase 2 to Phase 1. π_{3ij} retained the same interpretation, the shift in slope from Phase 2 to Phase 3. When time was centered on the beginning of Phase 3 (RPE 15 threshold for each participant), π_{1ij} now represented the slope in Phase 3. π_{2ij} represented the shift in slope from Phase 2 to Phase 1, and π_{3ij} represented the shift in slope from Phase 3 to Phase 2. In each case, the intercept in the longitudinal model represented the mean level for the reference category (the condition group and session defined as 0) at the time defined as 0 (the beginning of Phase 1, Phase 2, or Phase 3, respectively).

In the composite longitudinal model, the $SESSION_{ij} \times PerceivedGENOTYPE_i$ interaction indicates whether the difference in intercept for individuals informed that they have the high-risk genotype versus protective genotype in a given phase (the phase where time is defined as 0) is different in Session 2 relative to Session 1. Given that participants were told randomly-assigned genetic information after Session 1 but before Session 2, any differences in outcomes between the two sessions should be due to receiving this genetic information. The three-way $SESSION_{ij} \times TIME_{ijk} \times PerceivedGENOTYPE_i$ interaction indicates whether the difference in slope for individuals informed that they have the high-risk genotype versus protective genotype during the given phase where time is defined as 0 differs in Session 2 relative to Session 1.

The main effect of $PerceivedGENOTYPE_i$ represents the difference in intercept between individuals informed that they have the high-risk genotype versus protective genotype for the Session defined as 0. The main effect of $SESSION_{ij}$ represents the difference in intercept between Session 2 and Session 1 within participants, for the perceived genotype condition group defined as 0. The two-way $TIME_{ijk} \times PerceivedGENOTYPE_i$ interaction represents the difference in slope between individuals informed that they have the high-risk genotype vs. protective genotype, for the Session defined as 0. The primary slope parameter of interest was the $SESSION_{ij} \times TIME_{ijk}$ interaction, which represents the difference in slope between Session 2 and Session 1 within participants in the phase on which time is mean-centered, for the perceived genotype condition group defined as 0. In each case, as noted, the intercepts and slopes indicated by these parameters are for the phase (Phase 1, 2, or 3) on which time is centered.

In reporting the results, we focus on the rates of change (slopes) in each phase, and how these differed by session and perceived genotype condition. Supplementary Tables 6-8 display the longitudinal models for physiological data from Experiment 1.

Analytic Approach for Supplementary Longitudinal Analyses in Experiment 2 (satiety)

In Experiment 2, we also used longitudinal multilevel regression models to assess changes in participants' gut peptide levels as a function of session and condition. For every longitudinal analysis, we again fit a three-level multilevel model. However, the Level-1 submodel was simpler than in Experiment 1 because there were only three time points, immediately after consuming the shake, 15 minutes post-consumption, and 40 minutes post-consumption. This led to two phases: Phase 1 (the first 15 minutes post consumption) and Phase 2 (15 minutes post-consumption to 40 minutes post-consumption). The Level-1 submodel described how the outcome changed over time for a given participant. In addition to the main effect of time, it included a time-varying predictor to allow for a shift in slope in Phase 2 relative to Phase 1. We measured time in minutes since consumption. The threshold parameter allowed for a shift in slope at minute 15 post-consumption. Thus the Level-1 model was

$$Y_{ijk} = \pi_{0ij} + \pi_{1ij} MIN_{ijk} + \pi_{2ij} T15_{ijk} + \varepsilon_{ijk}$$

Three Level-2 submodels predicted key parameters of the Level-1 model as a function of session within participants (Session 1 versus Session 2):

$$\pi_{0ij} = \gamma_{00i} + \gamma_{01i} SESSION_{ij} + \delta_{0ij}$$

$$\pi_{1ij} = \gamma_{10i} + \gamma_{11i} SESSION_{ij} + \delta_{1ij}$$

$$\pi_{2ij} = \gamma_{20i} + \gamma_{21i} SESSION_{ij}$$

$SESSION_{ij}$ is a dichotomous variable defined as 0 for Session 1 (baseline/before participants were told genetic information) and +1 for Session 2 (post-manipulation, after participants were of their assigned genetic risk). This meant that the Level-1 parameters, the main effects in the longitudinal model, yielded the parameters (intercept or slopes) for Session 1. To obtain the corresponding Level-1 parameters for Session 2, we reversed the coding, defining $SESSION_{ij}$ as 0 for Session 2 and +1 for Session 1.

At Level-3, six submodels predicted key parameters of the Level-2 model as a function of between-participant predictors, namely perceived genotype condition (informed of high-risk genotype versus protective genotype).

$$\gamma_{00i} = \alpha_{000} + \alpha_{001} PerceivedGENOTYPE_i + \delta_{00i}$$

$$\gamma_{01i} = \alpha_{010} + \alpha_{011} PerceivedGENOTYPE_i$$

$$\gamma_{10i} = \alpha_{100} + \alpha_{101} PerceivedGENOTYPE_i + \delta_{10i}$$

$$\gamma_{11i} = \alpha_{110} + \alpha_{111} PerceivedGENOTYPE_i + \delta_{11i}$$

$$\gamma_{20i} = \alpha_{200} + \alpha_{201} PerceivedGENOTYPE_i$$

$$\gamma_{21i} = \alpha_{210} + \alpha_{211} PerceivedGENOTYPE_i$$

We defined $PerceivedGENOTYPE_i$ as 0 for participants informed that they had the high-risk genotype (AA genotype) and +1 for participants informed that they had the protective genotype (TT genotype). This meant that all Level-1 and Level-2 main effects and their interactions corresponded to individuals informed that they had the high-risk genotype. To obtain the same Level-1 and Level-2 parameters for individuals informed that they had the protective genotype, we reversed the coding, defining $PerceivedGENOTYPE_i$ as 0 for individuals informed that they had the protective genotype and +1 for individuals informed they had the high-risk genotype.

When time was mean centered at the beginning of Phase 1 (immediately after consuming the shake), π_{1ij} represented the slope in Phase 1. π_{2ij} represented the shift in slope from Phase 1 to Phase 2. When time was centered on the beginning of Phase 2 (15 minutes post-consumption), π_{1ij} now represented the slope in Phase 2. π_{2ij} now changed to represent the shift in slope from Phase 2 to Phase 1. In each case, the intercept in the longitudinal model represented the mean level for the reference category at the time defined as 0 (the beginning of Phase 1 or Phase 2, respectively).

In the composite longitudinal model, the $SESSION_{ij} \times PerceivedGENOTYPE_i$ interaction indicates whether the difference in intercept for individuals informed that they have the high-risk genotype versus protective genotype in a given phase (the phase where time is defined as 0) is different in Session 2 relative to Session 1. Given that participants were informed of randomly-assigned genetic risk after Session 1 but before Session 2, any differences should be due to receiving genetic risk information. The three-way $SESSION_{ij} \times TIME_{ijk} \times PerceivedGENOTYPE_i$ interaction indicates whether the difference in slope for individuals informed that they

had the high-risk genotype versus protective genotype during the given phase where time is defined as 0 differs in Session 2 relative to Session 1.

The main effect of Perceived$GENOTYPE_i$ represents the difference in intercept between individuals informed that they had the high-risk genotype versus protective genotype, for the Session defined as 0. The main effect of $SESSION_{ij}$ represents the difference in intercept between Session 2 and Session 1 within participants, for the perceived genotype condition defined as 0. The $TIME_{ijk}$ × Perceived$GENOTYPE_i$ interaction represents the difference in slope between individuals informed that they had the high-risk genotype versus protective genotype, for the Session defined as 0. The primary parameter of interest, the two-way $SESSION_{ij}$ × $TIME_{ijk}$ interaction, represents the difference in slope between Session 2 and Session 1 within participants, for the perceived genotype condition defined as 0. In each case, as noted, the intercepts and slopes indicated by these parameters are for the phase (Phase 1 or 2) on which time is centered. In reporting the results, we focus on the rates of change in each phase and how these differed by session and condition. Supplementary Tables 9-11 display the longitudinal models for physiological data from Experiment 2.

Stanford | Genomics
PERSONALIZED HEALTH & FITNESS

Genetic Test Report

Patient Name: Participant Name

Accession #: 06-3955
Test ID: SR0218359
Chip #: 434E387E9C

Test Performed: Personalized genotyping for metabolic genes
Test Results: High-risk CREB1 gene

Patient's CREB1 genotype: **AA**
Genetic Risk category: **High-Risk**
Risk: **70% increased risk**

After sequencing your DNA for genes involved in metabolism, your gene sequence confirms that you have the high-risk CREB1 gene (AA gene sequence). The CREB1 gene strongly influences a person's maximal exercise capabilities. Your high-risk CREB1 gene puts you at a disadvantage for aerobic exercise, decreasing the physiological and health benefits you may gain compared to most people. Individuals with your genotype are 70% more likely to develop obesity, heart disease, and diabetes.

The CREB1 gene determines an individual's ability to benefit from aerobic exercise by influencing heart function, oxygen processing, and body temperature during exercise. Individuals with your genotype experience increased body temperature, decreased exercise capacity, and lower heart rate capacity during exercise compared to people with the protective CREB1 gene.

An informational pamphlet regarding the CREB1 gene is included with this report. You should consult your physician for steps you can take to monitor your diet and exercise closely.

For further information about your genotype, please consult the Stanford Genomics Personalized Health & Fitness website at personalgenomics.stanford.edu.

MM/DD/YYYY
Date of Report

Dr. Jane S. Doe, MD, PhD
Director, Stanford Genomics

DISCLAIMER: "Stanford Genomics" is a fictional unit of Stanford that was created, with this genetic test report, for this research study. This fictional genetic test report is an artifact of the study and does not represent the views of Stanford University. This information does not constitute actual medical advice and was created for research purposes only.

Stanford | Genomics
PERSONALIZED HEALTH & FITNESS

Genetic Test Report

Patient Name: Participant Name

Accession #: 06-3955
Test ID: SR0218359
Chip #: 434E387E9C

Test Performed: Personalized genotyping for metabolic genes

Test Results: Protective CREB1 gene

Patient's CREB1 genotype: **GG**
Genetic Risk category: **Protective**
Risk: **70% decreased risk**

After sequencing your DNA for genes involved in metabolism, your gene sequence confirms that you have the protective version of the CREB1 gene (GG gene sequence). The CREB1 gene strongly influences a person's maximal exercise capabilities. Your protective CREB1 gene gives you a cardiovascular advantage for aerobic exercise, increasing the physiological benefits you gain from exercise compared to most people. Individuals with your genotype are 70% less likely to develop obesity, heart disease, and diabetes.

The CREB1 gene determines an individual's ability to benefit from aerobic exercise by influencing heart function, oxygen processing, and body temperature during exercise. Individuals with your genotype experience a more stable body temperature, increased exercise capacity, and increased heart rate capacity during exercise.

An informational pamphlet regarding how your protective CREB1 gene enhances your exercise capacity and decreases risk for developing chronic disease is included with this report.

For further information about your genotype, please consult the Stanford Genomics Personalized Health & Fitness website at personalgenomics.stanford.edu.

MM/DD/YYYY
Date of Report

Dr. Jane S. Doe, MD, PhD
Director, Stanford Genomics

DISCLAIMER: "Stanford Genomics" is a fictional unit of Stanford that was created, with this genetic test report, for this research study. This fictional genetic test report is an artifact of the study and does not represent the views of Stanford University. This information does not constitute actual medical advice and was created for research purposes only.

Stanford | Genomics
PERSONALIZED HEALTH & FITNESS

Genetic Test Report

Patient Name: Participant Name

Accession #: 06-3955
Test ID: SR0218359
Chip #: 434E387E9C

Test Performed: Personalized genotyping for metabolic genes

Test Results: High-risk FTO gene

Patient's FTO genotype: **AA**
Genetic Risk category: **High-Risk**
Risk: **70% increased risk**

After sequencing your DNA for genes involved in metabolism, your gene sequence confirms that you have the high-risk genotype (AA gene sequence) of the Fat Mass and Obesity-associated (FTO) gene. Clinical trials show that people with the high-risk genotype of FTO are 70% more likely to develop obesity than those with the protective FTO gene (TT gene sequence).

The FTO gene is linked to obesity because it affects how hungry a person feels. Individuals with your genetic sequence have more persistent hunger signals after consuming a meal. This leads to chronic overeating and a decreased ability to feel full.

An informational pamphlet regarding how your high-risk FTO gene causes excess hunger signals is included with this report. You should consult your physician for steps you can take to monitor your diet and exercise closely.

For further information about your genotype, please consult the Stanford Genomics Personalized Health & Fitness website at personalgenomics.stanford.edu.

MM/DD/YYYY
Date of Report

Dr. Jane S. Doe, MD, PhD
Director, Stanford Genomics

DISCLAIMER: "Stanford Genomics" is a fictional unit of Stanford that was created, with this genetic test report, for this research study. This fictional genetic test report is an artifact of the study and does not represent the views of Stanford University. This information does not constitute actual medical advice and was created for research purposes only.

Stanford | Genomics
PERSONALIZED HEALTH & FITNESS

Genetic Test Report

Patient Name: Participant Name

Accession #: 06-3955
Test ID: SR0218359
Chip #: 434E387E9C

Test Performed: Personalized genotyping for metabolic genes

Test Results: Protective FTO gene

Patient's FTO genotype: **TT**
Genetic Risk category: **Protective**
Risk: **70% decreased risk**

After sequencing your DNA for genes involved in metabolism, your gene sequence confirms that you have the protective genotype (TT gene sequence) of the Fat Mass and Obesity-associated (FTO) gene. Clinical trials show that people with the protective FTO gene are 70% less likely to develop obesity than those with the high-risk FTO gene (AA gene sequence).

The FTO gene is linked to obesity because it affects how hungry a person feels. People with your genotype respond appropriately to their hunger signals and experience lasting feelings of fullness after a meal. In comparison to individuals with the high-risk FTO genotype, those with your FTO genotype are more satisfied with their meals, eat less, and are less tempted by indulgent foods.

An informational pamphlet regarding how the FTO gene affects hunger is included with this report. Please read this short pamphlet to better understand how your FTO genotype protects you from inappropriate hunger signaling.

For further information about your genotype, please consult the Stanford Genomics Personalized Health & Fitness website at personalgenomics.stanford.edu.

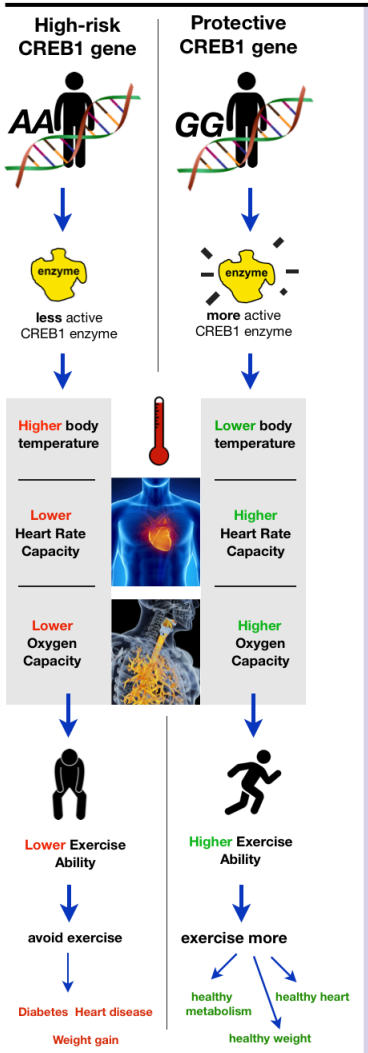
MM/DD/YYYY
Date of Report

Dr. Jane S. Doe, MD, PhD
Director, Stanford Genomics

DISCLAIMER: "Stanford Genomics" is a fictional unit of Stanford that was created, with this genetic test report, for this research study. This fictional genetic test report is an artifact of the study and does not represent the views of Stanford University. This information does not constitute actual medical advice and was created for research purposes only.

Study Materials (Informational Pamphlets)

Experiment 1 Pamphlet (pages 1 and 4).



Applying your Knowledge

If you have the protective CREB1 gene (GG sequence), consider yourself lucky! You should consider pushing yourself with your fitness goals, especially when it comes to aerobic exercise, as you have a higher capacity for exercise and can make improvements in your fitness faster than individuals with the high-risk CREB1 gene.

For individuals with the high-risk CREB1 gene (AA gene sequence), exercise sessions will need to be of relatively long duration to reap benefits because of your genetic disadvantage. Individuals with the high-risk CREB1 gene should strive for running sessions (or aerobic exercise of equivalent intensity) lasting 45 minutes per day 4-5 days per week. Those with the high-risk CREB1 gene may also benefit from high-intensity interval training - alternating between sprinting at maximum speed for 60 seconds and jogging at medium intensity for 30 seconds for at least 30 minutes a day on 4-5 days per week. Although the exercise routines described above may help improve a range of risk factors such as weight gain, diabetes, and heart disease within ten weeks, it may take longer to make improvements.

Individuals with the high-risk version of the CREB1 gene should not be discouraged if they do not see results or even experience weight gain despite exercise. Rather, high-risk CREB1 individuals should aim to set achievable goals when exercising. According to Dr. Kumar, "This should not be an excuse, but it is an explanation why intelligent and motivated individuals struggle so much, because they are fighting their biology and it's uncomfortable to fight your own biology."

Individuals with the high-risk CREB1 gene should consult their doctor to construct a diet and exercise plan to suit their abilities.

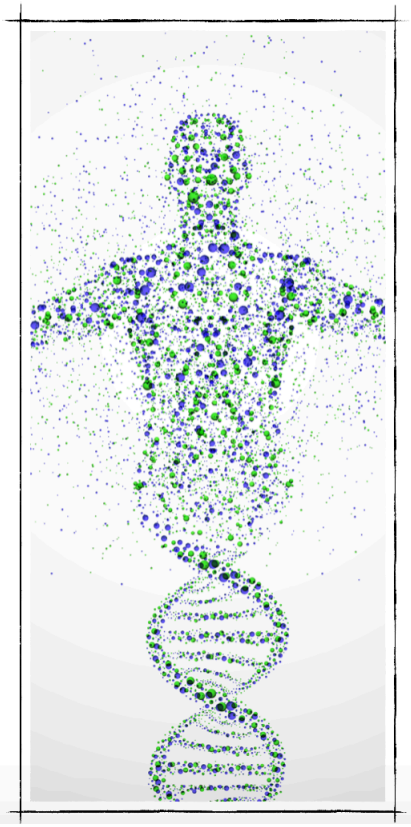
Stanford | Genomics
PERSONALIZED HEALTH & FITNESS

DISCLAIMER: "Stanford Genomics" is a fictional unit of Stanford that was created, with this brochure, for this research study. This brochure is an artifact of the study and does not represent the views of Stanford University. This information does not constitute actual medical advice and was created for research purposes only.

Stanford | Genomics
PERSONALIZED HEALTH & FITNESS

The CREB1 Gene

Personal Information Pamphlet



Overview

The CREB1 gene, nicknamed "the exercise gene", was discovered in 2010 as the first gene to reliably predict aerobic exercise ability and how much a person can benefit from exercise. The reason the CREB1 gene influences exercise is because it directly determines a person's maximal oxygen capacity, heart rate, and body temperature during exercise.

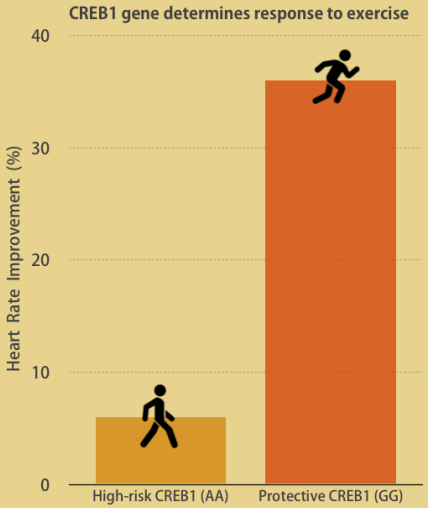
Individuals with the high-risk CREB1 gene have lower oxygen capacity, decreased heart rate capacity, and elevated body temperature during exercise compared to people with the protective CREB1 gene.

Experiment 1 Pamphlet (pages 2 and 3).

Exercise Responders and Non-Responders

Research has confirmed that physiological responses to exercise vary widely from person to person. Some lucky men and women take up jogging, for example, and quickly become much fitter. Others complete the same program and develop little if any additional endurance.

A landmark research study in 2013 involving over 1,000 individuals at Harvard University Medical School found that people varied enormously in how much or how little they improved in response to an exercise program. Initially, researchers thought the disparity between "exercise responders" and "exercise non-responders" was caused by individual differences in diet. However, upon closer examination, the cause of such varying responses turned out to be genetic. In particular, an individual's response to the aerobic exercise program depended on one important gene: the CREB1 gene. Individuals with the protective CREB1 gene responded to exercise, whereas those with the high-risk CREB1 gene did not. Over the course of the 10-week study, those with the protective CREB1 gene improved their heart rate capacity 6 times as much as individuals with the high-risk CREB1 gene.

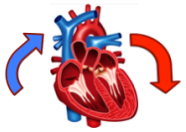
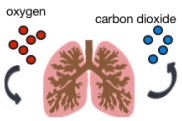
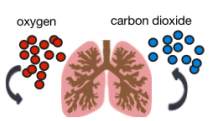


According to Dr. Kumar, Chief of Cardiology, *"This shows that if two people—one who is genetically endowed and the other who isn't—are doing the same workout at the same intensity, they will not get the same results. It's unfortunate, but individuals with the high-risk CREB1 gene just do not show much improvement in their cardiovascular health in response to exercise training."*

Cardiovascular Health and Exercise Ability

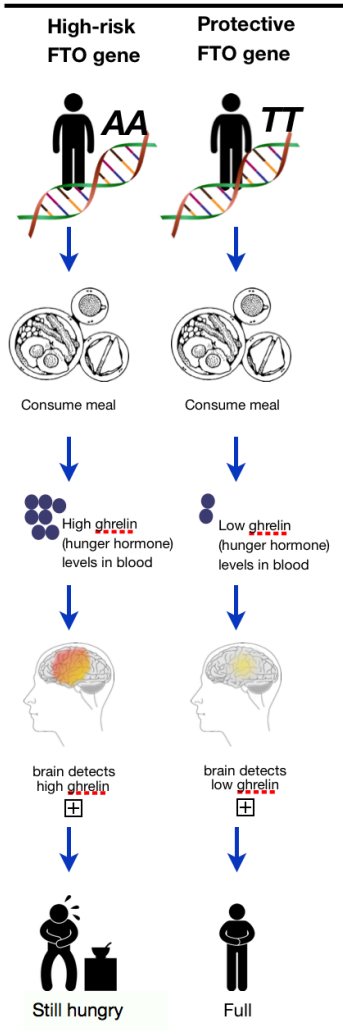
The CREB1 gene codes for the CREB1 enzyme, which controls the heart's ability to keep up with oxygen demands and the lungs' ability to exchange oxygen for carbon dioxide. The high-risk CREB1 gene encodes a less active enzyme than the protective CREB1 gene. This less active enzyme leads to decreased strengthening of cardiac muscle in the heart. Since the major purpose of aerobic exercise is to train cardiac muscle to maintain low heart rates during rest but accommodate high heart rates during exercise, those with the high-risk version of the CREB1 gene miss out on a significant portion of the heart rate benefits of exercise.

The activity of the CREB1 enzyme also determines maximal exercise capacity, the highest intensity of exercise your body is physically capable of performing. Above your maximal exercise capacity, your lungs can no longer keep up with oxygen exchange and your heart fails to keep up with blood flow to meet the increased oxygen demands. Due to lower enzyme activity, people with the high-risk CREB1 gene have a lower maximal oxygen capacity than people with the protective CREB1 gene. This means that those with the high-risk CREB1 gene are not able to reach exercise intensities that they could if they had the protective CREB1 gene.

High-risk CREB1 gene		Protective CREB1 gene	
	**less** active CREB1 enzyme		**more** active CREB1 enzyme
	**lower** maximal heart rate facilitates **less** blood flow		**higher** maximal heart rate facilitates **more** blood flow
	**lower** maximal exercise capacity delivers **less** oxygen to muscles		**higher** maximal exercise capacity delivers **more** oxygen to muscles
	**higher** body temperature during exercise leads to feelings of frustration and stopping		**lower** body temperature during exercise leads to feelings of enjoyment and perseverance

Body Temperature Effects - People with the high-risk CREB1 gene variation not only have lower exercise capacity, but also have an increased body temperature during exercise. On average, people with the high-risk CREB1 gene are 1.2 degrees hotter than those with the protective CREB1 gene during aerobic exercise. Their heart and lungs have to work harder as intensity increases and their less active form of the enzyme can't keep up as well. This makes exercise less sustainable as intensity increases, increasing feelings of negative emotions and wanting to stop to cool down. "For people with the high-risk CREB1 gene, it's a doubly bad effect that's not in their control; it's in their genes", says Dr. Yamada, co-author of the study. "You become vulnerable to that higher body temperature as a "stop exercising" cue, and these are the same people who already have poor ability to make cardiac improvements from exercise."

Experiment 2 Pamphlet (pages 1 and 4).



Applying Your Knowledge

If you have the protective FTO gene (TT gene sequence), consider yourself lucky! To use your genetic advantage, you should work to stay mindful while eating. Since your ghrelin levels properly communicate fullness to you, your body will tell you when you've had enough to eat.

Unfortunately for those with the high-risk FTO gene (AA gene sequence), you will have to fight your body to maintain your weight. We recommend carefully monitoring your caloric intake. Since your ghrelin continues signaling even when you are full, you will have to end your meals before you 'feel' full.

High-risk FTO individuals should not be discouraged if they do not see results or even experience weight gain despite exercising regularly and maintaining a healthy diet. To maintain motivation, high-risk FTO individuals should develop achievable goals for their fitness and body image, and should consult their doctor to construct a diet and exercise plan to suit their abilities.

Recent studies have shown that the high-risk FTO gene makes it easier to regain weight that is lost during an exercise program or dieting. Due to excess ghrelin signaling, hunger effects may persist despite lifestyle changes. As Dr. Kumar explains, "The FTO gene should not be an excuse, but it is an explanation why intelligent and motivated individuals struggle so much. They are fighting their biology and it's uncomfortable to fight your own biology."

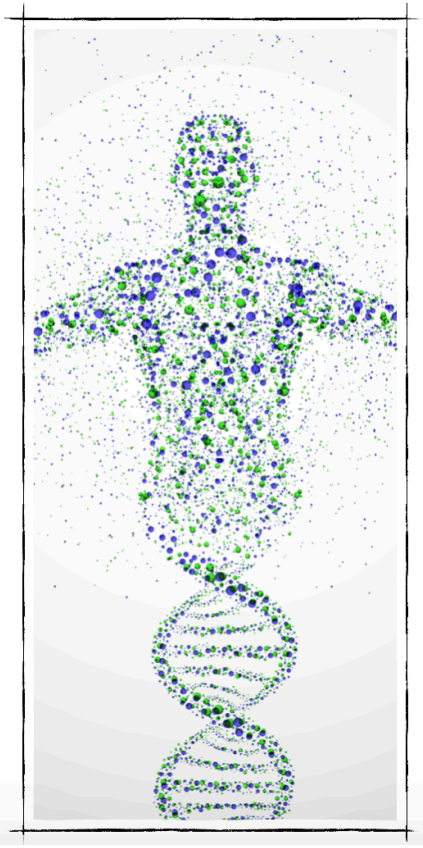
Stanford | Genomics
PERSONALIZED HEALTH & FITNESS

DISCLAIMER: "Stanford Genomics" is a fictional unit of Stanford that was created, with this brochure, for this research study. This brochure is an artifact of the study and does not represent the views of Stanford University. This information does not constitute actual medical advice and was created for research purposes only.

Stanford | Genomics
PERSONALIZED HEALTH & FITNESS

The FTO Gene

Personal Information Pamphlet

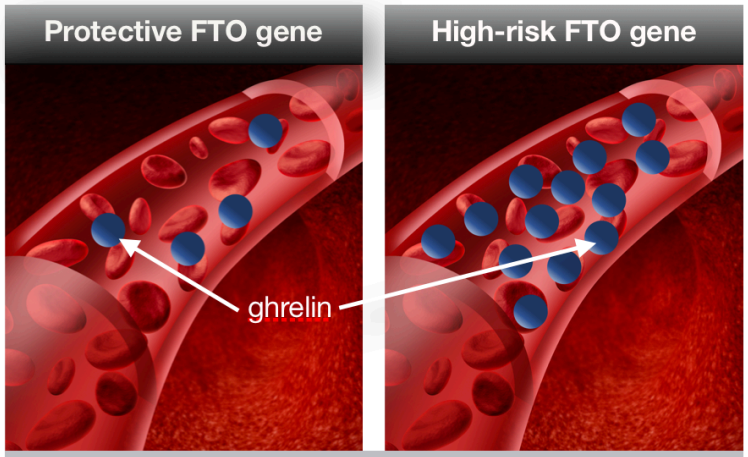


Overview

The FTO gene, nicknamed "the hunger gene", was discovered in 2007 as the first gene to reliably predict weight gain and hunger cues. The FTO gene influences satiety because it is linked to activity of the hormone that signals hunger to the brain, a hormone called ghrelin. People with the high-risk FTO gene do not suppress ghrelin properly after a meal, so they remain hungry despite eating. In contrast, people with the protective FTO gene have ghrelin levels that decrease properly after a meal, and experience fullness in proportion to the calories they consumed.

In addition to increasing hunger directly, high levels of ghrelin also slow down metabolism. The combination of increased hunger and slower metabolism can lead to weight gain. According to the National Institutes of Health, people with the high-risk version of the FTO gene usually begin gaining weight in their twenties. Over their lifetime, they are 70% more likely to become obese and develop conditions associated with weight gain, such as diabetes, than those with the protective version of the gene.

Experiment 2 Pamphlet (pages 2 and 3).



After a meal, ghrelin levels in the bloodstream typically fall and cause hunger signals to subside. This is the case for individuals with the protective FTO gene (left). However, people with the high-risk FTO gene (right) have high levels of ghrelin in the blood even after a meal, prolonging the communication of hunger signals to the brain. ● = ghrelin

FTO, Ghrelin, and Hunger

Ghrelin is the hormone that signals hunger and stimulates appetite. When blood concentrations of ghrelin are low, people feel full. When blood concentrations of ghrelin are high, people feel hungry. In individuals with the protective FTO gene, blood ghrelin levels fall after eating, so they feel satisfied. On the other hand, in high-risk FTO individuals, ghrelin levels do not fall as far after a meal. Since the blood concentration of ghrelin remains elevated in people with the high-risk FTO gene, hunger cues persist despite calorie intake (see figure above), according to a study by Dr. Karra and colleagues at University College London.

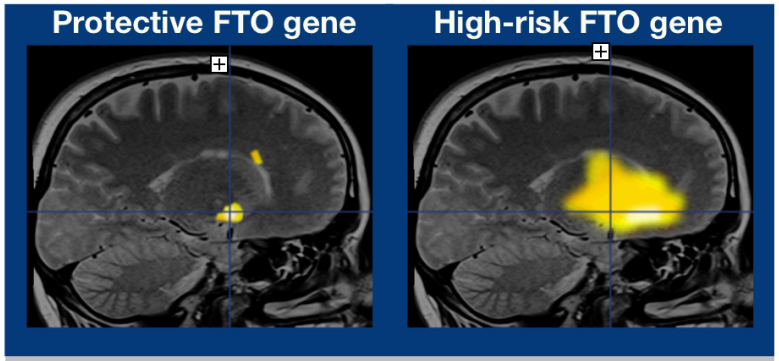
As a result of persistent and more frequent hunger, people with the high-risk FTO gene consume an extra 280 calories per day compared to people with the protective FTO gene. This adds up to 100,000 extra calories per year for those with the high-risk FTO gene.

The Double Hunger Effect

In addition to having higher levels of ghrelin in their blood, people with the high-risk FTO gene also have an increased sensitivity to ghrelin in their brain. This means that people with the high-risk FTO gene experience more hunger signals *and* their brain responds more strongly to those hunger signals.

In a 2014 study at Harvard University, researchers found higher activity in reward areas of the brain in response to food for people with the high-risk FTO gene compared to people with the protective FTO gene. "People who carry the high-risk version of FTO show an increased reward response to food cues and are more drawn to foods high in sugar and fat," said Dr. Kumar, Chief of Psychiatry.

In fact, brain activity scans showed that people with the high-risk FTO gene have the same brain activation pattern to food cues as do addicts asked to think about their next drink or scoring their next hit at a casino. This increased brain sensitivity makes resisting food more difficult for high-risk FTO individuals. Moreover, because they experience a heightened neurological reward response from food, high-risk FTO individuals are consistently more motivated to eat.



Functional magnetic resonance imaging (fMRI) brain scans from people with protective (left) and high-risk (right) FTO genes. As indicated by the yellow activation pattern, people with the high-risk FTO gene have much stronger brain activation in response to food. In this study, brain activation was 4 times higher in response to food for people with high-risk FTO genes compared to people with protective FTO genes.

Supplementary Notes

Time to Reach Physiological Maxima in Experiment 1

How does receiving genetic information affect the time at which maximum physiological performance is reached?

Time to Maximum Respiratory Exchange Ratio (CO_2:O_2 exchange rate). We observed a negative impact on time to reach maximum CO_2:O_2 exchange rate for individuals informed that they had the high-risk genotype. While the overall session × perceived genotype interaction was not significant (*B*=0.50, 95% CI: [-0.53, 1.53], *P*=0.34), participants informed that they had the high-risk genotype reached their maximum marginally significantly earlier (*M*=14.38 min) relative to their baseline test (*M*=15.08 min) (*B*=-0.70, 95% CI: [-1.43, 0.03], *P*=0.060] (Supplementary Tables 1 and 4). For individuals informed that they had the protective genotype, the time to maximum CO_2:O_2 exchange rate was not significantly different (*M*=15.29 min) compared to baseline (*M*=15.49 min) (*B*=-0.20, 95% CI: [-0.92, 0.52], *P*=0.58). We observed no significant difference by actual *CREB1* genotype at the baseline session in time to reach maximum CO_2:O_2 exchange rate (*B*=-0.05, 95% CI: [-1.98, 1.87], *P*=0.96] (Supplementary Table 4).

Time to Maximum Respiratory Minute Ventilation (VE). We observed a negative impact on time to reach maximum VE for individuals informed that they had the high-risk genotype. There was a marginally significant session × perceived genotype interaction (*B*=0.32, 95% CI: [-0.02, 0.65], *P*=0.063), such that individuals informed that they had the high-risk genotype reached their maximum VE earlier (*M*=15.40 min) than during their baseline test (*M*=15.70 min) (*B*=-0.30, 95% CI: [-0.53, -0.06], *P*=0.014) (Supplementary Tables 1 and 4). For individuals informed that they had the protective genotype, the time to maximum VE was not significantly different (*M*=16.31 min) compared to their baseline test (*M*=16.29 min) (*B*=0.017, 95% CI: [-0.22, 0.25], *P*=0.89). We observed no significant difference by actual *CREB1* genotype at the baseline session in time to reach maximum VE (*B*=0.81, 95% CI: [-0.26, 1.88], *P*=0.14] (Supplementary Table 4).

Experiment 1 (exercise) Longitudinal Analyses

Did receiving genetic information affect the rate of change in participants' Respiratory Exchange Ratio (CO_2:O_2 exchange rate) in each phase of the maximal exercise treadmill test?

Phase 1. Details from the longitudinal model for all three reported phases below are in Supplementary Table 6, and the simple effects are in Supplementary Table 7. Phase 1 consisted of minute 4 to minute 6 of the Session 1 test. This corresponded to 22.9% to 35.3% of the Session 1 test. Minute 4 marked the transition from the walking warmup to running. Minute 6 was when participants achieved their final running speed (these events occurred at the same time for Session 2). For this phase, the session × time × perceived genotype interaction was marginally significant (*B*=0.084, 95% CI: [-0.008, 0.175], *P*=0.072). The three-way interaction was driven by individuals informed that they had the high-risk genotype. This group had a lower Phase 1 slope in Session 2 relative to Session 1 (Session 1: 0.494 units/100% of test versus Session 2: 0.427 units/100% of test) (*B*=-0.067, 95% CI: [-0.006, 0.139], *P*=0.041). For individuals informed that they had the protective genotype, the session × time interaction was not significant (*B*=0.017, 95% CI: [-0.048, 0.082], *P*=0.61). This group had similar Phase 1 rates of change in CO_2:O_2 exchange rate in both Session 1 (0.557 units/100% of test) and Session 2 (0.574 units/100% of test).

Phase 2. Phase 2 consisted of the period from minute 6 to the time when each participant reached his or her RPE 15 threshold (when they indicated that the test felt "hard") in Session 1. Minute 6 was the time at which participants reached their final running speed. After minute 6, the incline of the treadmill was increased by 2.5% every 2 minutes. The RPE 15 threshold was the time in minutes when participants rated their perceived exertion as 15 on a 20-point scale in Session 1; for Session 2, the outcome value was the measurement at the same time in minutes as the Session 1 RPE 15 threshold. On average, this Phase 2 period was from 35.3% to 70.6% of the Session 1 test, as a percentage of each participant's last recorded Session 1 time. As in Phase 1, the three-way session × time × perceived genotype interaction was marginally significant (*B*=-0.027, 95% CI: [-0.055, 0.002], *P*=0.064). However, in Phase 2 the three-way interaction was driven by individuals informed that they had the

protective genotype. For this group, the session × time interaction was significant (*B*=-0.029, 95% CI: [-0.049, -0.008], *P*=0.006), indicating that those informed that they had the protective genotype showed a decrease in slope in Session 2 [0.191 units/100% of test] relative to Session 1 [0.219 units/100% of test] during this phase. For individuals informed that they had the high-risk genotype, the two-way session ×time interaction was not significant (*B*=-0.002, 95% CI: [-0.022, 0.018], *P*=0.86). This group exhibited similar Phase 2 slopes in both Session 1 [0.216 units/100% of test] and Session 2 [0.214 units/100% of test].

Phase 3. We were most interested in Phase 3, the most challenging end-phase of the exercise. We expected that, if informing participants of a high-risk genotype resulted in differences in physiological performance relative to those informed that they had the protective genotype, these differences would likely emerge during the most difficult part of the test. Phase 3 consisted of the period from the time when participants reached their RPE 15 threshold to their last recorded time in Session 1, the time when they indicated to the experimenter they were too exhausted to continue the test. This was the period from 70.6% to 100% of the Session 1 test on average, i.e., the last 30% of the Session 1 test, when it was most challenging. The Session 2 outcome values were those measured at the same time in minutes as the RPE 15 threshold and the last recorded time for each participant in Session 1. In Phase 3, the three-way session × time × perceived genotype interaction was significant (*B*=0.037, 95% CI: [0.0003, 0.073], *P*=0.048). This interaction was driven by individuals informed that they had the protective genotype exhibiting a higher slope (greater increase in CO_2:O_2 exchange rate) in Session 2 (0.387 units/100% of test) relative to Session 1 (0.365 units/100% of test) (*B*=0.023, 95% CI: [-0.002, 0.047], *P*=0.066). Individuals informed that they had the high-risk genotype exhibited a slightly lower Phase 3 slope in Session 2 (0.353 units/100% of test) relative to Session 1 (0.368 units/100% of test), but the two-way session × time interaction was not significant (*B*=-0.014, 95% CI: [-0.042, 0.013], *P*=0.31). This suggests that perceived genetic risk significantly affected whether individuals increased or decreased their rate of change in metabolic respiratory physiology to meet the most difficult physical demands of the end phase of the test, with the interaction particularly driven by individuals informed that they had the protective genotype enhancing their rate of change in RER compared to baseline performance. Actual *CREB1* genotype had no effect on the rate of change in RER during the Session 1 maximal exercise treadmill test, in any of the three phases (*P*s>0.53; Supplementary Table 8).

Did receiving genetic information affect the rate of change in participants' ventilatory flow rate (VE) in each phase of the maximal exercise treadmill test?

Phase 1. Details from the longitudinal model for all three reported phases below are in Supplementary Table 6 and the simple effects are in Supplementary Table 7. The Phase 1 (22.9% to 35.3% of the Session 1 test) three-way session × time × perceived genotype interaction was non-significant (*B*=5.41, 95% CI: [-9.85, 20.68], *P*=0.49). In this phase, both individuals informed that they had the high-risk (Session 1: 160.5 units/100% of test; Session 2: 162.0 units/100% of test) and protective (Session 1: 173.7 units/100% of test; Session 2: 180.6 units/100% of test) genotypes had similar Phase 1 rates of change in ventilation in Session 2 relative to Session 1.

Phase 2. The Phase 2 (35.3% to 70.6% of the Session 1 test) three-way session × time × perceived genotype interaction was significant (*B*=-5.52, 95% CI: [-10.12, -0.91], *P*=0.019). The three-way interaction was driven by individuals informed that they had the protective genotype experiencing a decrease in rate of change in ventilation in Session 2 [42.6 units/100% of test] relative to Session 1 [48.2 units/100% of test] during this phase (*B*=-5.61, 95% CI: [-8.92, -2.30], *P*=0.001). Individuals informed that they had the high-risk genotype did not significantly differ in slope during this phase (*B*=-0.089, 95% CI: [-3.29, 3.11], *P*=0.96) in Session 2 [49.2 units/100% of test] relative to Session 1 [49.3 units/100% of test].

Phase 3. Similar to RER, we were most interested in Phase 3, the most challenging end-phase of the exercise. The Phase 3 (70.6% to 100% of the Session 1 test) three-way session × time × perceived genotype interaction was not significant (*B*=3.16, 95% CI: [-3.04, 9.36], *P*=0.32). However, individuals informed that they had the protective genotype exhibited a higher slope (greater increase in VE) in Session 2 (112.9 units/100% of test) relative to Session 1 (106.3 units/100% of test) (*B*=6.62, 95% CI: [2.57, 10.67], *P*=0.001). Individuals informed that they had the high-risk genotype also had a higher Phase 3 slope in in Session 2 (95.6 units/100% of test) relative to Session 1 (92.1 units/100% of test) but, in contrast to individuals informed protective, this difference did not reach significance (*B*=3.46, 95% CI: [-1.23, 8.15], *P*=0.15). This suggests that, similar to metabolic physiology in the end stage of the treadmill test, individuals informed that they had the protective genotype significantly enhanced their rate of change in ventilatory flow rate physiology compared to baseline performance. Actual *CREB1* genotype had no effect on the rate of change in VE during the Session 1 maximal exercise treadmill test, in any of the three phases (*P*s>0.16; Supplementary Table 8).

Did participants display a shift in slope in physiological outcomes before and after the second psychological threshold (Phase 3 versus Phase 2), and did this shift differ by session and condition?

CO_2:O_2 exchange rate. We observed a positive effect of shift in slope in CO_2:O_2 exchange rate for individuals informed that they had the protective genotype. In the model centered on minute 4 (Phase 1), there was a significant three-way session × perceived genotype × shift in slope parameter, reflecting a shift in slope between Phase 2 and Phase 3 (*B*=0.072, 95% CI: [0.022, 0.122], *P*=0.005). In this model, the shift in slope parameter is defined as the Phase 3 slope minus the Phase 2 slope for the group defined as the reference category (Supplementary Table 6). This shift in slope was driven by individuals informed that they had the protective genotype. These individuals experienced a significant session × shift in slope interaction (*B*=0.055, 95% CI: [0.021, 0.089], *P*=0.002), indicating a greater shift in slope in Session 2 [Δ=0.185 units/100% of test] relative to Session 1 [Δ=0.130 units/100% of test]. In Session 2, the slope changed from 0.191 units/100% of test in Phase 2 to 0.376 units/100% of test in Phase 3. In Session 1, the slope changed from 0.218 units/100% of test in Phase 2 to 0.348 units/100% of test in Phase 3. Thus, for individuals informed that they had the protective genotype, the acceleration from Phase 2 to Phase 3 (rate of change in the slopes) was greater in Session 2. Individuals informed that they had the high-risk genotype did not significantly change in the shift in slope between Phase 2 and 3 (*B*=-0.017, 95% CI: [-0.053, 0.019], *P*=0.36). Their shift in slope from Phase 2 to Phase 3 was similar in Session 1 [Δ=0.139 units/100% of test] and Session 2 [Δ=0.122 units/100% of test]. In Session 1, the slope changed from 0.215 units/100% of test in Phase 2 to 0.354 units/100% of test in Phase 3. In Session 2, the change in slope across phases was similar, from a slope of 0.215 units/100% of test in Phase 2 to a slope of 0.337 units/100% of test in Phase 3.

VE. We also observed a positive effect of shift in slope in VE for individuals informed that they had the protective genotype. In the model centered on minute 4 (Phase 1), the three-way session × perceived genotype × shift in slope parameter interaction was significant (*B*=9.91, 95% CI: [1.37, 18.45], *P*=0.023) (Supplementary Table 6). As with CO_2:O_2 exchange rate, the session × shift in slope was significant for individuals informed that they had the protective genotype (*B*=13.09, 95% CI: [7.24, 18.94], *P*<0.0001), such that they experienced a greater shift in slope in Session 2 [Δ=71.4 units/100% of test] relative to Session 1 [Δ=58.3 units/100% of test] from Phase 2 to Phase 3. In Session 2, the slope changed from 42.8 units/100% of test in Phase 2 to 114.2 units/100% of test in Phase 3. In Session 1, the slope changed from 48.1 units/100% of test in Phase 2 to 106.4 units/100% of test in Phase 3. Thus, for individuals informed that they had the protective genotype, the acceleration from Phase 2 to Phase 3 (rate of change in the slopes) was greater in Session 2, similar to as observed for CO_2:O_2 exchange rate.

As with CO_2:O_2 exchange rate, the session × shift in slope parameter was not significant for individuals informed that they had the high-risk genotype (*B*=3.18, 95% CI: [-3.04, 9.41], *P*=0.32). Their shift in slope from Phase 2 to Phase 3 was similar in Session 1 [Δ=44.2 units/100% of test] and Session 2 [Δ=47.4 units/100% of test]. In Session 1, the slope changed from 49.2 units/100% of test in Phase 2 to 93.4 units/100% of test in Phase 3. In Session 2, the change in slope across phases was similar, from a slope of 49.4 units/100% of test in Phase 2 to a slope of 96.8 units/100% of test in Phase 3.

Taken together, the shift in slope from Phase 2 to Phase 3 suggests that in addition to perceived genotype changing maximum CO_2:O_2 exchange rate and maximum VE and the slope of CO_2:O_2 exchange rate and VE during the challenging third phase of the treadmill test in a self-fulfilling manner, individuals informed that they had the protective genotype also increased their acceleration of CO_2:O_2 exchange rate and VE, such that they increased the most during the most challenging phase of the test. These longitudinal results further support the results reported in the main text and suggest that individuals informed that they had the protective genotype optimally increased their physiology to meet the highly challenging demands at the end of the treadmill test.

Experiment 2 (satiety) Longitudinal Analyses

Did receiving genetic information affect the rate of change in participants' level of GLP-1 in each phase of the test?

Phase 1. Details from the longitudinal model for both reported phases below are in Supplementary Table 9, and the simple effects are in Supplementary Table 10. The slope during the first phase from minute 0 to minute 15 was predicted by a significant session × time × perceived genotype interaction (*B*=1.03, 95% CI: [0.09, 1.96], *P*=0.032), such that individuals informed that they had the protective genotype had a greater increase in GLP-1 response than individuals informed that they had the high-risk genotype. This effect was driven by individuals informed that they had the protective genotype significantly increasing their GLP-1 response in Session 2 (1.95

pg/ml/min) relative to Session 1 (0.77 pg/ml/min) (*B*=1.18, 95% CI: [0.52, 1.85], *P*<0.001). Individuals informed that they had the high-risk genotype did not significantly change in GLP-1 response (*B*=0.16, 95% CI: [-0.51, 0.82], *P*=0.64) from Session 1 (1.35 pg/ml/min) to Session 2 (1.51 pg/ml/min).

Phase 2. In Phase 2 (15 minutes post-consumption to 40 minutes post-consumption) the three-way session × time × perceived genotype interaction was not significant (*B*=-0.44, 95% CI: [-1.02, 0.15], *P*=0.14). However, while the rate of change in GLP-1 during Phase 2 was not significantly different for individuals informed that they had the high-risk genotype in Session 2 relative to Session 1 (*B*=-0.25, 95% CI: [-0.67, 0.16], *P*=0.23), the rate of change in GLP-1 during Phase 2 significantly declined from Session 1 (0.21 pg/ml/min) to Session 2 (-0.49 pg/ml/min) for individuals informed that they had the protective genotype (*B*=-0.69, 95% CI: [-1.11, -0.28], *P*=0.001). This indicated that overall the GLP-1 response for all participants occurred primarily in the first phase (first 15 minutes post-consumption) and leveled off or declined from 15 minutes to 40 minutes post-consumption, consistent with the expected rapid response of GLP-1. More importantly, for individuals informed that they had the protective genotype, the GLP-1 response shifted to be more rapid after they learned their genetic risk compared to their baseline, occurring almost entirely in the first 15 minutes post-consumption as evidenced by the 2.5-fold greater increase in Phase 1, followed by the decay of GLP-1 signal in Phase 2.

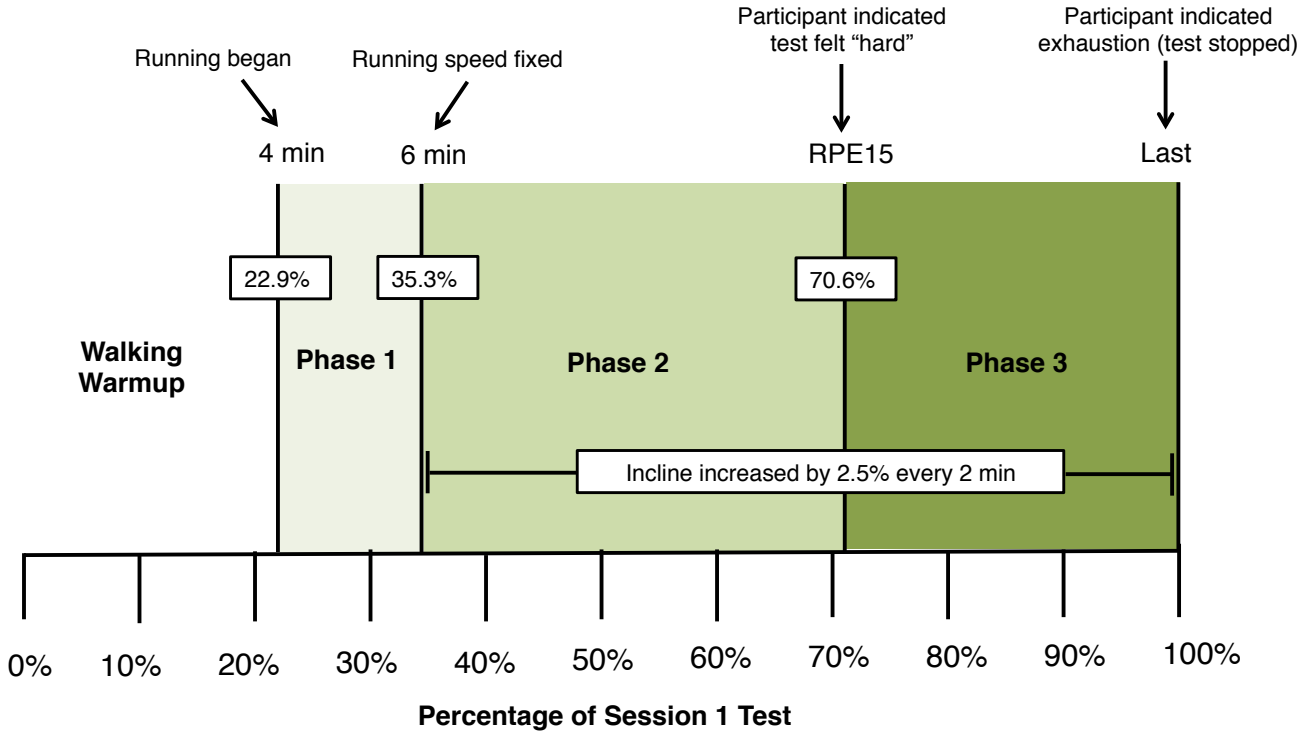
Did receiving genetic information affect the rate of change in participants' level of acyl-ghrelin in each phase of the test?

Phase 1. Details from the longitudinal model for both reported phases below are in Supplementary Table 9, and the simple effects are in Supplementary Table 10. In contrast with GLP-1, perceived risk had no effect on acyl-ghrelin rate of change. The session × time × perceived genotype interaction was not a significant predictor of the slope during the first phase from minute 0 to minute 15 (*B*=0.46, 95% CI: [-0.59, 1.51], *P*=0.39). The session × time interaction was also not significant for either group (*Ps*>0.19).

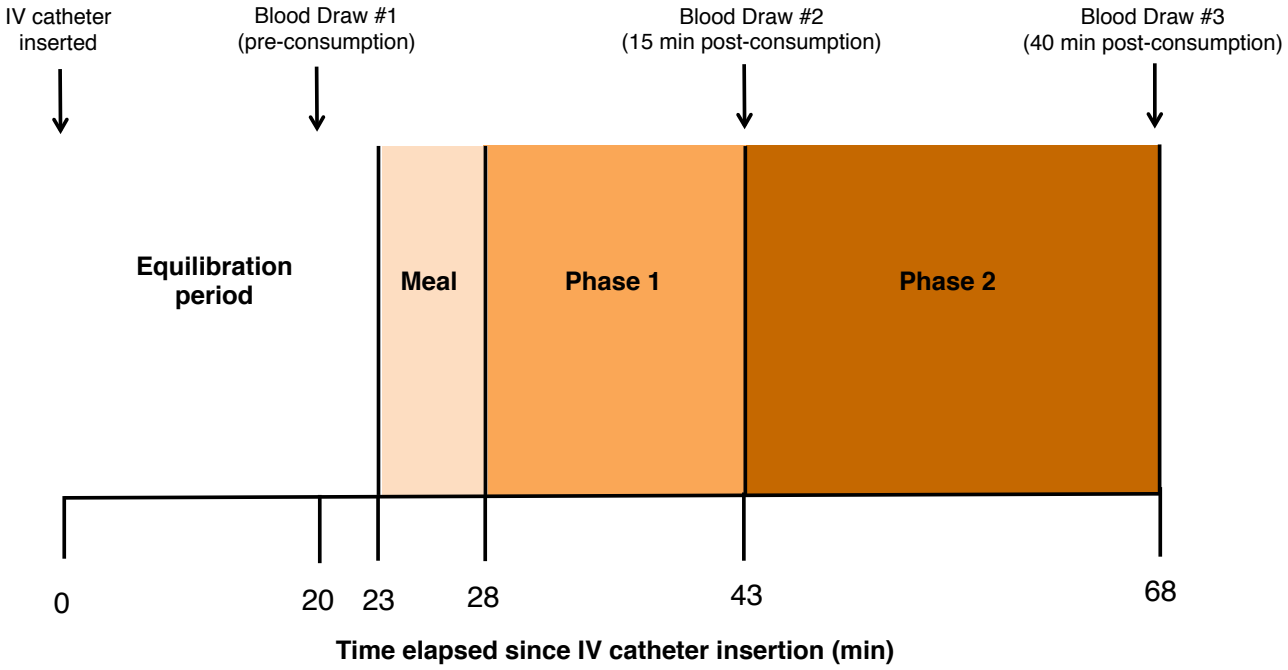
Phase 2. In Phase 2, the three-way session × time × perceived genotype interaction was not significant [*B*=-0.18, 95% CI: [-0.78, 0.43], *P*=0.56]. The two-way session × time interactions also remained non-significant for each group (*Ps*>0.29).

Actual *FTO* genotype had no effect on the rate of change in GLP-1 or acyl-ghrelin in either the first (minute 0 to minute 15) or second phases (minute 15 to minute 40) during Session 1 (*P*s>0.42; Supplementary Table 11).

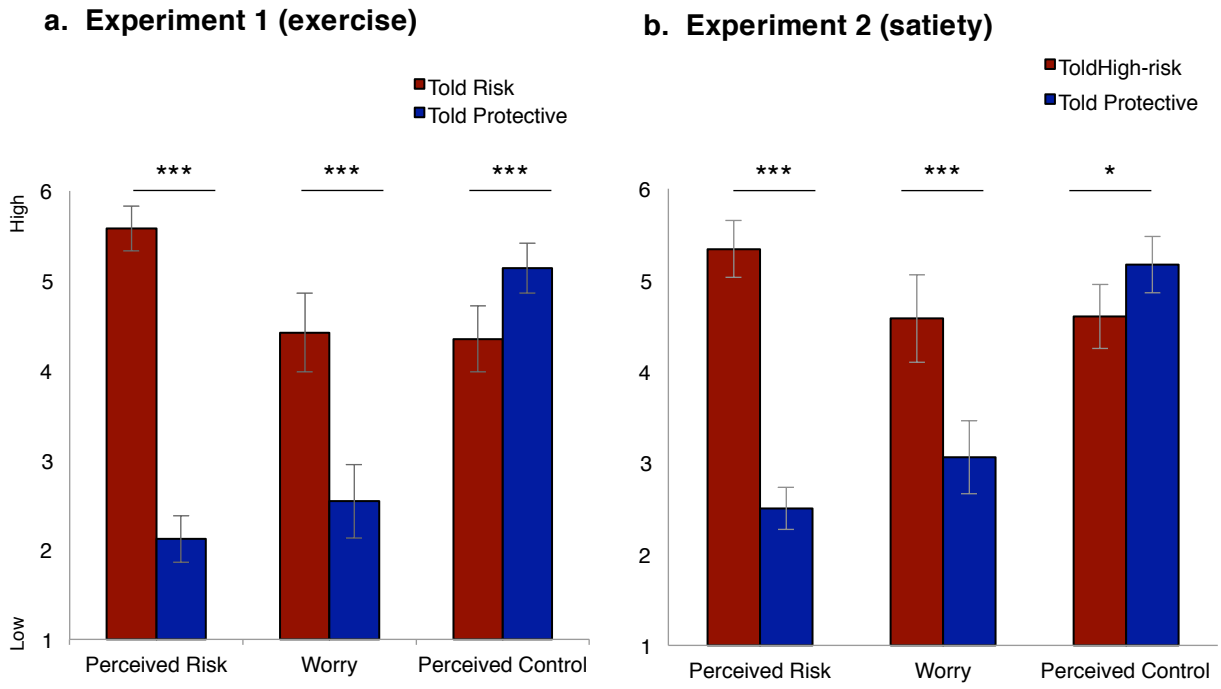
Supplementary Figure 1. Schematic of maximal effort exercise treadmill test in Experiment 1



Supplementary Figure 2. Schematic of satiety protocol in Experiment 2



Supplementary Figure 3. Receiving high-risk genetic test results increases perceived risk and worry, decreases perceived control in Experiments 1 and 2



Effects (means ± 95% CI) of receiving genetic information on perceived risk, worry, and perceived control immediately after receiving randomly assigned high-risk vs. protective genetic test results in (a) Experiment 1 and (b) Experiment 2. *P<0.05, ***P<0.001 (t test).

Supplementary Table 1. Cross-sectional physiological outcomes by perceived *CREB1* rs2253206 genotype in Experiment 1

	Experiment 1 (Exercise): Cross-Sectional Physiological Outcomes							
	Maximum Reached				Time to Maximum			
	CO_2:O_2 exchange		VE (L/min)		CO_2:O_2 exchange (min)		VE (min)	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI
Fixed Effects								
Level-1: Intercept	1.169***	[1.152, 1.186]	114.56***	[106.34, 122.78]	15.08***	[14.01, 16.15]	15.70***	[15.11, 16.30]
Level-2: Perceived Genotype	-0.009	[-0.033, 0.016]	7.98	[-3.55, 19.51]	0.41	[-1.08, 1.91]	0.59	[-0.25, 1.42]
Level-1: Session	-0.023**	[-0.041, -0.005]	-2.06*	[-4.10, -0.02]	-0.70~	[-1.43, 0.03]	-0.30**	[-0.53, -0.06]
Level-2: Perceived Genotype	0.034**	[0.008, 0.059]	2.60~	[-0.25, 5.46]	0.50	[-0.53, 1.53]	0.32~	[-0.02, 0.65]
Random Effects								
Level-1: within person	0.001		23.46		2.06~		0.42***	
Level-2: In Level-1 intercept	0.004		979.44*		14.80***		5.31***	
Level-2: In session within person	0.003		14.65		3.85~			
Level-2: Covariance	-0.001		8.69					
Goodness-of-fit								
Deviance	-611.142		1937.54		1223.07		835.01	
AIC	-595.143		1953.54		1237.07		847.01	
BIC	-573.114		1975.57		1256.34		863.53	
N	116		116		116		116	

Note. ~$p \leq 0.10$, *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$. Regression coefficients, 95% CI's, and goodness-of-fit statistics for a two-level linear regression model predicting the maximum reached and the time taken to reach this maximum during a maximal exercise treadmill test, for two physiological indices of performance, respiratory exchange ratio (CO_2:O_2 exchange rate) and ventilation (VE), as a function of session and perceived genotype. Session (within-subjects) was specified at Level-1 (0=baseline session, +1=Session 2, after receiving genetic information), and perceived genotype condition (between-subjects) was specified at Level-2 [0=told high-risk (AA), +1=told protective (GG)]. The model also included a random intercept, random slope for session, and their covariance (these were sometimes omitted to achieve model convergence). The composite model featured interactions between the given Level-1 parameter in column 1 and the Level-2 parameter indented directly below it. Given this coding strategy, the Level-1 intercept is the Session 1 mean for participants informed that they had the high-risk genotype. The main effect of perceived genotype represents the contrast between the Session 1 mean for individuals informed that they had the protective genotype and the Session 1 mean for those informed of high-risk. The main effect of session represents the contrast between the Session 2 (post genetic risk disclosure) and Session 1 (pre genetic risk disclosure) means for individuals informed of high-risk. The perceived genotype × session interaction reflects whether the difference in Session 2 versus Session 1 means in turn differs by condition. Deviance=-2 * log likelihood. AIC=Akaike Information Criterion. BIC=Bayesian Information Criterion.

Supplementary Table 2. Cross-sectional subjective experience and behavioural outcomes by perceived *CREB1* rs2253206 genotype in Experiment 1

	Experiment 1 (Exercise): Cross-Sectional Subjective Experience and Behaviour Outcomes					
	Time Taken to Reach (min)					
	RPE Level 15 ("hard")		Heat Level 4 ("hot")		Endurance (total time run)	
	B	95% CI	B	95% CI	B	95% CI
Fixed Effects						
Level-1: Intercept	11.86***	[11.23, 12.49]	10.73***	[10.00, 11.46]	16.19***	[15.60, 16.78]
Level-2: Perceived Genotype	-0.20	[-1.09, 0.69]	0.53	[-0.48, 1.55]	0.48	[-0.34, 1.31]
Level-1: Session	0.07	[-0.36, 0.50]	0.19	[-0.42, 0.81]	-0.36**	[-0.58, -0.13]
Level-2: Perceived Genotype	0.72*	[0.12, 1.33]	0.92*	[0.05, 1.80]	0.38*	[0.06, 0.69]
Random Effects						
Level-1: within person	0.62		2.10***		0.24	
Level-2: In Level-1 intercept	5.31		5.29***		4.91	
Level-2: In session within person	1.49		0.84		0.27	
Level-2: Covariance	-0.58				0.36	
Goodness-of-fit						
Deviance	962.85		970.95		815.22	
AIC	978.85		984.95		831.22	
BIC	1000.88		1003.98		853.25	
N	116		112		116	

Note. ~$p \leq 0.10$, *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$. Regression coefficients, 95% CIs, and goodness-of-fit statistics for a two-level linear regression model predicting the time (min) taken to reach (left panel) a perceived exertion rating of "hard" (15 on a 6-20 Borg rating of perceived exertion scale[64]), (middle panel) perceived heat rating of "hot" (4 on a 1-7 rating of perceived heat scale), and (right panel) endurance (total time run), during a maximal exercise treadmill test, as a function of session and perceived genotype. Session (within-subjects) was specified at Level-1 (0=baseline session, +1=Session 2, after receiving genetic information), and perceived genotype condition (between-subjects) was specified at Level-2 [0=told high-risk (AA), +1=told protective (GG)]. The model also included a random intercept, random slope for session, and their covariance (these were sometimes omitted to achieve model convergence). The composite model featured interactions between the given Level-1 parameter in column 1 and the Level-2 parameter indented directly below it. Given this coding strategy, the Level-1 intercept is the Session 1 mean for participants informed that they had the high-risk genotype. The main effect of perceived genotype represents the contrast between the Session 1 mean for individuals informed that they had the protective genotype and the Session 1 mean for individuals informed that they had the high-risk genotype. The main effect of session represents the contrast between the Session 2 (post genetic risk disclosure) and Session 1 (pre genetic risk disclosure) means for individuals informed of high-risk. The perceived genotype × session interaction reflects whether the difference in Session 2 versus Session 1 means in turn differs by condition. Deviance=-2 * log likelihood. AIC=Akaike Information Criterion. BIC=Bayesian Information Criterion.

Supplementary Table 3. Cross-sectional outcomes by perceived *FTO* rs9939609 genotype in Experiment 2

	Experiment 2 (Satiety): Cross-Sectional Outcomes					
	Difference in Level During First 15 Minutes After Consumption					
	GLP-1 (pg/ml)		Acyl-ghrelin (pg/ml)		Fullness	
	B	95% CI	B	95% CI	B	95% CI
Fixed Effects						
Level-1: Intercept	20.32***	[14.15, 26.50]	-7.99*	[-15.30, -0.67]	1.612***	[1.29, 1.95]
Level-2: Perceived Genotype	-8.77*	[-17.51, -0.04]	-6.34	[--16.68, 4.01]	-0.39~	[-0.85, 0.08]
Level-1: Session	2.36	[-7.35, 12.07]	-7.37	[-17.11, 2.37]	-0.03	[-0.39, 0.33]
Level-2: Perceived Genotype	15.39*	[1.66, 29.12]	6.95	[-6.82, 20.73]	0.58*	[0.07, 1.08]
Random Effects						
Level-1: within person	464.81***		599.97***		0.71***	
Level-2: In Level-1 intercept	60.99		138.33~		0.79***	
Level-2: In session within person	370.69**		108.91		0.36	
Level-2: Covariance						
Goodness-of-fit						
Deviance	1985.51		2013.05		689.54	
AIC	1999.51		2027.05		703.54	
BIC	2018.15		2045.69		722.25	
N	106		106		107	

Note. ~$p \leq 0.10$, *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$. Regression coefficients, 95% CIs, and goodness-of-fit statistics for a two-level linear regression model predicting the change in satiety during the first 15 minutes after consuming a shake in the satiety experiment, as a function of session and perceived genotype. The left and middle panels represent effects on physiological measures (the change in levels of the hormones GLP-1 and acyl-ghrelin, respectively). The right panel represents the effects on a sensory experience measure, self-reported fullness (1 = not at all full, 7 = extremely full), representing an aggregate measure of the response to three questions: How full do you feel, How hungry do you feel (reverse scored), and How much could you eat right now (reverse scored). Session (within-subjects) was specified at Level-1 (0=baseline session, +1=Session 2, after receiving genetic information), and perceived genotype condition (between-subjects) was specified at Level-2 [0=told high-risk (AA), +1=told protective (TT)]. The model also included a random intercept, random slope for session, and their covariance (these were sometimes omitted to achieve model convergence). The composite model featured interactions between the given Level-1 parameter in column 1 and the Level-2 parameter indented directly below it. Given this coding strategy, the Level-1 intercept is the Session 1 mean for participants informed that they had the high-risk genotype. The main effect of perceived genotype represents the contrast between the Session 1 mean for individuals informed that they had the protective genotype and the Session 1 mean for individuals informed that they had the high-risk genotype. The main effect of session represents the contrast between the Session 2 (post genetic risk disclosure) and Session 1 (pre genetic risk disclosure) means for individuals informed of high-risk. The perceived genotype × session interaction reflects whether the difference in Session 2 versus Session 1 means in turn differs by condition. Deviance=-2 * log likelihood. AIC=Akaike Information Criterion. BIC=Bayesian Information Criterion.

Supplementary Table 4. Simple effects for cross-sectional outcomes by perceived and actual genotypes in Experiments 1 and 2

	Simple Effects for Cross-Sectional Outcomes in Both Experiments (Exercise and Satiety)								
	Session 1 Actual (GG/TT vs. AA)			Told Risk (AA)			Told Protective (GG or TT)		
	B	95% CI	d	B	95% CI	d	B	95% CI	d
					Physiology				
Experiment 1									
Maximum CO_2:O_2 exchange	-0.009	[-0.033, 0.016]	-0.14	-0.023**	[-0.042, -0.005]	-0.34	0.011	[-0.007, 0.029]	0.16
Maximum VE	3.88	[-11.06, 18.81]	0.12	-2.06*	[-4.10, -0.02]	-0.06	0.54	[-1.46, 2.55]	0.02
Time to Max CO_2:O_2 exchange	-0.05	[-1.98, 1.87]	-0.01	-0.70~	[-1.43, 0.03]	-0.17	-0.20	[-0.92, 0.52]	-0.05
Time to Max VE	0.81	[-0.26, 1.88]	0.35	-0.30**	[-0.53, -0.06]	-0.13	0.02	[-0.22, 0.25]	0.01
Experiment 2									
15-min Change in GLP-1	2.21	[-9.69, 14.12]	0.09	2.36	[-7.35, 12.07]	0.10	17.75***	[8.04, 27.46]	0.76
15-min Change in Acyl-ghrelin	-5.78	[-19.69, 8.13]	-0.21	-7.37	[-17.11, 2.37]	-0.27	-0.42	[-10.16, 9.32]	-0.02
					Subjective Experience and Behaviour				
Experiment 1									
Time to RPE Level 15	0.97~	[-0.16, 2.10]	0.40	0.07	[-0.36, 0.50]	0.03	0.79***	[0.37, 1.22]	0.32
Time to Heat Level 4	0.39	[-0.95, 1.74]	0.14	0.19	[-0.42, 0.81]	0.07	1.12***	[0.49, 1.74]	0.41
Total Time Run	0.94~	[-0.11, 2.00]	0.41	-0.36**	[-0.58, -0.13]	-0.16	0.02	[-0.20, 0.24]	0.01
Experiment 2									
Self-Reported Fullness	-0.09	[-0.72, 0.54]	-0.07	-0.03	[-0.39, 0.33]	-0.02	0.55**	[0.19, 0.90]	0.44

Note. ~$p \leq 0.10$, *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$. Regression coefficients, 95% CIs, and effect sizes for simple effects of actual genotype (left panel) and session within perceived genotype condition (middle and right panels), on both physiological, subjective experience, and behavioural outcomes across both the exercise and satiety experiments. The parameters in the left panel represent the linear effect of actual genotype in Session 1, for the given outcome in column 1, using an additive model of decreasing risk [0=high-risk (AA), +1=moderate risk (exercise=AG; diet=AT), +2 = protective (exercise=GG; diet=TT)]. Actual genotype refers to the participants' genotype for the *CREB1* rs2253206 single nucleotide polymorphism in the exercise experiment and the *FTO* rs9939609 single nucleotide polymorphism in the satiety experiment. The main effects of session presented in the middle and right panels are derived from the two-level regression models presented in Supplementary Tables 1-3 by coding each perceived genotype condition as 0 and the other condition as +1. Effect sizes for all effects are expressed as a proportion of the raw standard deviation of each outcome in Session 1.

Supplementary Table 5. Perceived genotype x session interaction effects for cross-sectional outcomes in Experiments 1 and 2, controlling for actual genotype and split by actual genotype

	Original		Controlling for actual genotype (linear)		High-risk actual genotype		Moderate-risk actual genotype		Protective actual genotype	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI
Experiment 1										
Max CO_2:O_2 exchange	0.034**	[0.008, 0.059]	0.034**	[0.008, 0.059]	0.034	[-0.013, 0.080]	0.058**	[0.016, 0.099]	0.009	[-0.035, 0.052]
Max VE	2.60~	[-0.25, 5.46]	2.60~	[-0.25, 5.46]	3.24	[-1.80, 8.27]	0.95	[-3.52, 5.42]	4.08~	[-0.61, 8.77]
Total Time Run	0.38*	[0.06, 0.69]	0.38*	[0.06, 0.69]	0.23	[-0.34, 0.79]	0.58*	[0.08, 1.08]	0.30	[-0.23, 0.82]
Time to RPE Level 15	0.72*	[0.12, 1.33]	0.72*	[0.11, 1.33]	0.88	[-0.23, 1.98]	0.76	[-0.23, 1.76]	0.53	[-0.52, 1.57]
Time to Heat Level 4	0.92*	[0.05, 1.80]	0.92*	[0.05, 1.80]	1.93*	[0.34, 3.51]	0.87	[-0.56, 2.31]	0.13	[-1.32, 1.57]
Experiment 2										
GLP-1	15.39*	[1.66, 29.12]	15.39*	[1.66, 29.12]	20.58	[-8.03, 49.20]	15.32	[-6.31, 36.95]	12.34	[-9.82, 34.50]
Acyl-ghrelin	6.95	[-6.82, 20.73]	6.95	[-6.82, 20.73]	-22.11[a]	[-50.34, 6.12]	12.87	[-8.47, 34.21]	18.17[a]	[-40.04, 3.70]
Fullness	0.58*	[0.07, 1.08]	0.58*	[0.07, 1.08]	0.65	[-0.41, 1.71]	0.27	[-0.53, 1.07]	0.85*	[-1.66, -0.04]

Note. ~$p \leq 0.10$, *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, [a]column estimates for the perceived genotype x session interaction significantly differ from one another at the $p \leq 0.05$ level. Regression coefficients and 95% CIs for the perceived genotype (high-risk = 0, protective = +1) x session interactions for cross-sectional outcomes in Experiments 1 and 2. Throughout the Table, positive values indicate that the perceived genotype x session interaction was in the hypothesized direction (representing improvements in the outcome for individuals informed that they have the protective genotype relative to their own baseline outcomes and negative effects on the outcome for individuals informed that they have the high-risk genotype relative to their own baseline), except for acyl-ghrelin, for which negative values were hypothesized for the perceived genotype x session interaction (with negative values representing a larger decrease in acyl-ghrelin, a biomarker associated with physiological hunger). The Original column reports the regression coefficients for the perceived genotype x session interactions as reported in the main text and presented in Supplementary Tables 1-3. The Controlling for actual genotype (linear) column reports the regression coefficients for the perceived genotype x session interactions, controlling for actual *CREB1* rs2253206 genotype in Experiment 1 or for actual *FTO* rs9939609 genotype in Experiment 2, using an additive model of decreasing risk [0=high-risk (AA), +1=moderate risk (*CREB1*=AG; *FTO* =AT), +2 = protective (*CREB1*=GG; *FTO*=TT)]. The final three columns report the perceived genotype x session interactions for each of the actual genotypes individually, derived from the two-level regression model that explored the three-way actual genotype x perceived genotype x session interactions for all cross-sectional outcomes, by coding each actual genotype condition as 0 and the other two actual genotypes as +1 and +2. The change in acyl-ghrelin was the only outcome for which there was a significant actual genotype x perceived genotype x session interaction between any two actual genotypes [actual genotype (AA vs. TT) x perceived genotype x session interaction for acyl-ghrelin change: (*B*=40.28, 95% CI: [4.57, 75.99], *P*=0.027). Simple effects of this three-way interaction for acyl-ghrelin revealed that individuals who actually had the high-risk *FTO* genotype exhibited the hypothesized trend of results for the perceived genotype x session interaction (attenuated reduction in acyl-ghrelin post-consumption when informed of high-risk, increased reduction in acyl-ghrelin post-consumption when informed of the protective genotype; *B*=-22.11, 95% CI: [-50.34, 6.12], *P*=0.125), while individuals who actually had the protective *FTO* genotype exhibited the opposite trend (*B*=18.17, 95% CI: [-40.04, 3.70], *P*=0.103).

Supplementary Table 6. Longitudinal physiological outcomes by perceived *CREB1* rs2253206 genotype in Experiment 1

		Experiment 1 (Exercise): Longitudinal Physiological Outcomes			
		Respiratory Exchange Ratio (CO_2:O_2 exchange)		Ventilation (VE)	
	Parameter	B	95% CI	B	95% CI
Fixed Effects					
Level-1 Intercept [Mean at Minute 4]					
Level-2: Intercept	000	0.837***	[0.819, 0.855]	29.47***	[27.06, 31.87]
Level-3: Perceived Genotype	001	-0.012	[-0.037, 0.013]	0.22	[-3.14, 3.59]
Level-2: Session	010	0.008	[-0.007, 0.023]	-0.17	[-1.79, 1.45]
Level-3: Perceived Genotype	011	-0.006	[-0.027, 0.015]	-0.37	[-2.63, 1.89]
Slope from Minute 4 to Minute 6					
Level-2: Intercept	100	0.494***	[0.443, 0.544]	160.50***	[149.13, 171.87]
Level-3: Perceived Genotype	101	0.064~	[-0.008, 0.135]	13.19	[-2.88, 29.25]
Level-2: Session	110	-0.067*	[-0.131, -0.003]	1.47	[-9.28, 12.21]
Level-3: Perceived Genotype	111	0.084~	[-0.008, 0.175]	5.41	[-9.85, 20.68]
Shift in Slope at Minute 6					
Level-2: Intercept	200	-0.279***	[-0.333, -0.225]	-111.25***	[-120.42, -102.09]
Level-3: Perceived Genotype	201	-0.060	[-0.137, 0.017]	-14.34*	[-27.42, -1.27]
Level-2: Session	210	0.067~	[-0.006, 0.139]	-1.29	[-13.56, 10.98]
Level-3: Perceived Genotype	211	-0.110*	[-0.214, -0.007]	-10.88	[-28.39, 6.63]
Shift in Slope at RPE 15 Threshold					
Level-2: Intercept	300	0.139***	[0.112, 0.167]	44.18***	[39.37, 48.99]
Level-3: Perceived Genotype	301	-0.010	[-0.048, 0.029]	14.09***	[7.49, 20.68]
Level-2: Session	310	-0.017	[-0.053, 0.019]	3.18	[-3.04, 9.41]
Level-3: Perceived Genotype	311	0.072**	[0.022, 0.122]	9.91*	[1.37, 18.45]
Random Effects					
Level-1: within person		0.001***		29.49***	
Level-2: In Level-1 intercept		0.001***		4.28***	
Level-2: In rate of change		0.001***		14.47***	
Level-2: Covariance		-0.001***		0.47	
Level-3: In Level-1 intercept		0.003***		65.81***	
Level-3: In rate of change		0.005***		1000.61***	
Level-3: Covariance		-0.002***		38.20	
Goodness-of-fit					
Deviance		-22460.1		38235	
AIC		-22414.1		38281.01	
BIC		-22350.8		38344.34	
N		116		116	

Note. ~$p \leq 0.10$, *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$. Regression coefficients, 95% CIs, and goodness-of-fit statistics for a three-level linear regression model predicting the change in respiratory exchange ratio (CO_2:O_2 exchange rate) and ventilation (VE) over time during a maximal exercise treadmill test, as a function of session and perceived genotype, using the time at which the running speed was reached and the time at which a perceived exertion rating of "hard" was reached as thresholds to model shifts in slope. Time within session was modeled at Level-1, session within-subjects was modeled at Level-2, and perceived genotype condition (between-subjects) was modeled at Level-3, separately for each outcome. The Level-1 model specified two shifts in slope: at minute 6 (when the walking warm-up ended and participants reached their fixed running speed) and at RPE Level 15 (when participants indicated that the test felt "hard", or 15 on the Borg 6-20 perceived exertion scale[64]) to divide the treadmill test into three phases. Each outcome was measured continuously and averaged across 30-second intervals. At Level-1, time was expressed as a percentage of the Session 1 test. Session 2 outcomes were those that occurred at the same time in minutes as the Session 1 percentages. Time was centered on (defined as 0% for) minute 4. A value of 100% was assigned to each participant's last recorded time for Session 1; (the coefficients shown are the Betas for a time variable that ranged from 0 to 1). Session was defined as 0 for the baseline session and +1 for Session 2; and perceived genotype condition was defined as 0 for individuals informed that they had the high-risk genotype (AA) and +1 for the individuals informed that they had the protective genotype (GG). Consequently, the Level-1 parameters shown represent the means for individuals informed high-risk in Session 1. Each of the four Level-1 parameters is in turn predicted by a main effect of session, a main effect of perceived genotype condition, and their interaction. Each model also included the random effects shown. Deviance=-2 * log likelihood. AIC=Akaike Information Criterion. BIC=Bayesian Information Criterion.

Supplementary Table 7. Longitudinal simple effects for physiological outcomes in Experiment 1

	Experiment 1 (Exercise): Longitudinal Simple Effects					
	Phase 1		Phase 2		Phase 3	
	Told high-risk (AA)	Told protective (GG)	Told high-risk (AA)	Told protective (GG)	Told high-risk (AA)	Told protective (GG)
	Respiratory Exchange Ratio (CO_2:O_2 exchange rate)					
Slope in Phase for Ref Category	0.494*** [0.443, 0.544]	0.557*** [0.507, 0.608]	0.216*** [0.192, 0.239]	0.219*** [0.196, 0.243]	0.368*** [0.340, 0.396]	0.365*** [0.338, 0.391]
Perceived Genotype × Slope	0.064~ [-0.008, 0.135]	-0.064~ [-0.135, 0.008]	0.004 [-0.030, 0.037]	-0.004 [-0.037, 0.030]	-0.003 [-0.042, 0.036]	0.003 [-0.036, 0.042]
Session × Slope	-0.067* [-0.131, -0.003]	0.017 [-0.048, 0.082]	-0.002 [-0.022, 0.018]	-0.029** [-0.049, -0.008]	-0.014 [-0.042, 0.013]	0.023~ [-0.002, 0.047]
Perceived × Session × Slope	0.084~ [-0.008, 0.175]	-0.084~ [-0.175, 0.008]	-0.027~ [-0.055, 0.002]	0.027~ [-0.002, 0.055]	0.037* [0.0003, 0.073]	-0.037* [-0.073, -0.0003]
	Ventilation (VE)					
Slope in Phase for Ref Category	160.50*** [149.13, 171.87]	173.69*** [162.34, 185.03]	49.33*** [40.75, 57.92]	48.22*** [39.76, 56.68]	92.11*** [83.31, 100.9]	106.31*** [97.77, 114.8]
Perceived × Slope	13.19 [-2.88, 29.25]	-13.19 [-29.25, 2.88]	-1.12 [-13.17, 10.93]	1.12 [-10.93, 13.17]	14.19* [1.94, 26.45]	-14.19* [-26.45, -1.94]
Session × Slope	1.47 [-9.28, 12.21]	6.88 [-3.96, 17.72]	-0.09 [-3.29, 3.11]	-5.61*** [-8.92, -2.30]	3.46 [-1.23, 8.15]	6.62*** [2.57, 10.67]
Perceived × Session × Slope	5.41 [-9.85, 20.68]	-5.41 [-20.68, 9.85]	-5.52* [-10.12, -0.92]	5.52* [0.91, 10.12]	3.16 [-3.04, 9.36]	-3.16 [-9.36, 3.04]

Note. ~$p \leq 0.10$, *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$. Regression coefficients and 95% CIs for the slope in respiratory exchange ratio (CO_2:O_2 exchange) and ventilation (VE) associated with each phase of the maximal exercise treadmill test, using the time at which the running speed was fixed and the time at which a perceived exertion rating of "hard" was reached as thresholds, for each condition. Coefficients were obtained from the same longitudinal regression model (left panel of Supplementary Table 6) using simple effects, by recentering time on the beginning of the given phase, and by defining each perceived genotype condition as 0 and the other as +1. The key parameter is the session × slope interaction, which indicates whether the slope in Session 2 (after receiving genetic information) differs from the slope in Session 1 (baseline, before receiving genetic information), for a given perceived genotype condition. The perceived genotype × session interaction has the same magnitude for each condition within a given phase because simple slopes were obtained from the same regression model. Thresholds refer to the slope from minute 4 to minute 6 (Phase 1), the slope from minute 6 to the time when participants indicated a perceived exertion of 15 out of 20 (Phase 2), and the slope from RPE Level 15 to the end of the Session 1 test, the time when they indicated that they could no longer continue running (Phase 3). For a visual depiction of the different phases using each threshold type, see Supplementary Figure 1. Ref = reference, Perceived = perceived genotype.

Supplementary Table 8. Longitudinal physiological outcomes by actual *CREB1* rs2253206 genotype in Experiment 1

	Experiment 1 (Exercise): Longitudinal Physiological Outcomes			
	Respiratory Exchange Ratio (CO_2:O_2 exchange)		Ventilation (VE)	
	B	95% CI	B	95% CI
Fixed Effects				
Level-1 Intercept [Mean at Minute 4 in Session 1]				
Level-2 Intercept	0.830***	[.810, .851]	30.34***	[27.56, 33.11]
Level-2 Actual Genotype (Linear)	0.001	[-0.014, 0.017]	-0.60	[-2.72, 1.52]
Slope from Minute 4 to Minute 6 in Session 1				
Level-2 Intercept	0.528***	[0.470, 0.587]	164.05***	[150.63, 177.46]
Level-2 Actual Genotype (Linear)	-0.005	[-0.051, 0.041]	1.75	[-8.63, 12.14]
Shift in Slope at Minute 6 in Session 1				
Level-2 Intercept	-0.321***	[-0.386, -0.256]	-120.93***	[-132.40, -109.45]
Level-2 Actual Genotype (Linear)	0.012	[-0.038, 0.063]	3.83	[-5.06, 12.71]
Shift in Slope at RPE 15 Threshold in Session 1				
Level-2 Intercept	0.146***	[0.111, 0.181]	52.76***	[46.46, 59.06]
Level-2 Actual Genotype (Linear)	-0.007	[-0.034, 0.019]	-1.56	[-6.30, 3.18]
Random Effects				
Level-1: within person	0.001***		31.53***	
Level-2: In Level-1 intercept	0.004***		67.88***	
Level-2: In rate of change	0.006***		1004.70***	
Level-2: Covariance	-0.003***		29.91	
Goodness-of-fit				
Deviance	-11252.06		19850.39	
AIC	-11228.06		19874.39	
BIC	-11195.01		19907.44	
N	116		116	

Note. ~$p \leq 0.10$, *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$. Regression coefficients, 95% CIs, and goodness-of-fit statistics for a two-level linear regression model predicting the change in respiratory exchange ratio (CO_2:O_2 exchange) and ventilation (VE) over time during a maximal exercise treadmill test in the baseline session (Session 1), as a function of actual genotype (between-subjects), using thresholds to model shifts in slope. The purpose of this analysis was to compare the effect of actual genotype to perceived genotype. This analysis used the same Level-1 model as was used to predict the effect of perceived genotype within subjects, but only accounted for a single predictor at Level-2, the effect of actual genotype using an additive model of decreasing risk [0=high-risk (AA), 1=moderate risk (AG), 2=protective (GG)]. As before, time within session was modeled at Level-1 (for Session 1 only), separately for each outcome. The Level-1 model specified two shifts in slope: at minute 6 (when the walking warm-up ended and participants reached their fixed running speed) and at RPE Level 15 (when participants indicated that the test felt "hard", or 15 on the Borg 6-20 perceived exertion scale[64]) to divide the treadmill test into three phases. Each outcome was measured continuously and averaged across 30-second intervals. Time was centered on (defined as 0% for) minute 4. A value of 100% was assigned to each participant's last recorded time for Session 1; (the coefficients shown are the Betas for a time variable that ranged from 0 to 1). Each model also included the random effects shown. Deviance=-2 * log likelihood. AIC=Akaike Information Criterion. BIC=Bayesian Information Criterion. The slope in each phase for a given genotype could be obtained by recentering time on the beginning of that phase, and by defining that genotype as 0 (for AG, defining actual genotype as -1, 0, 1; for GG, defining actual genotype as -2, -1, 0, for the AA, AG, and GG genotypes, respectively).

Supplementary Table 9. Longitudinal physiological outcomes by perceived *FTO* rs9939609 genotype in Experiment 2

	Experiment 2 (Satiety): Longitudinal Physiological Outcomes			
	GLP-1 (pg/ml/min)		Acyl-ghrelin (pg/ml/min)	
	B	95% CI	B	95% CI
Fixed Effects				
Level-1 Intercept [Mean at Minute 0]				
Level-2: Intercept	15.90***	[8.44, 23.36]	68.12***	[57.30, 78.94]
Level-3: Perceived Genotype	10.68*	[0.14, 21.23]	3.34	[-11.96, 18.64]
Level-2: Session	3.71	[-6.30, 13.72]	3.20	[-8.44, 14.83]
Level-3: Perceived Genotype	-6.75	[-20.91, 7.41]	-1.65	[-18.10, 14.81]
Slope from Minute 0 to Minute 15				
Level-2: Intercept	1.36***	[0.89, 1.82]	-0.53*	[-1.06, -0.01]
Level-3: Perceived Genotype	-0.58~	[-1.25, 0.08]	-0.42	[-1.17, 0.32]
Level-2: Session	0.16	[-0.51, 0.82]	-0.49	[-1.23, 0.25]
Level-3: Perceived Genotype	1.03*	[0.09, 1.96]	0.46	[-0.59, 1.51]
Shift in Slope at Minute 15				
Level-2: Intercept	-1.18***	[-1.82, -0.53]	-0.36	[-1.10, 0.37]
Level-3: Perceived Genotype	0.61	[-0.29, 1.52]	0.63	[-0.41, 1.67]
Level-2: Session	-0.41	[-1.32, 0.50]	0.72	[-0.32, 1.76]
Level-3: Perceived Genotype	-1.46*	[-2.75, -0.18]	-0.64	[-2.11, 0.83]
Random Effects				
Level-1: within person	327.48***		428.62***	
Level-2: In Level-1 intercept	363.78***		504.92***	
Level-2: In rate of change	0.12**			
Level-3: In Level-1 intercept	75.83		681.34***	
Goodness-of-fit				
Deviance	5886.36		6090.70	
AIC	5918.36		6122.70	
BIC	5960.98		6165.31	
N	106		106	

Note. ~$p \leq 0.10$, *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$. Regression coefficients, 95% CIs, and goodness-of-fit statistics for a three-level linear regression model predicting the change in gut peptides GLP-1 and acyl-ghrelin following consumption of the meal, as a function of session and perceived genotype. Each hormone was measured three times within a session: immediately pre-consumption (time 1), and 15 (time 2) and 40 minutes post-consumption (time 3). Time within session was modeled at Level-1, session within-subjects was modeled at Level-2, and perceived genotype condition (between-subjects) was modeled at Level-3, separately for each outcome. The Level-1 model specified a shift in slope at minute 15, to allow for different slopes between time 1 and 2 and between time 2 and 3. Session was defined as 0 for the baseline session and +1 for Session 2 (after receiving genetic information); and perceived genotype condition was defined as 0 for individuals informed that they had the high-risk genotype (AA) and +1 for individuals informed that they had the protective genotype (TT). Consequently, the Level-1 parameters shown represent the means for individuals informed of high-risk in Session 1. Each of the three Level-1 parameters is in turn predicted by a main effect of session, a main effect of perceived genotype condition, and their interaction. Each model also included the random effects shown. Deviance=-2 * log likelihood. AIC=Akaike Information Criterion. BIC=Bayesian Information Criterion.

Supplementary Table 10. Longitudinal simple effects for physiological outcomes in Experiment 2

	Phase 1 (Minute 0 to 15)		Phase 2 (Minute 15 to 40)	
Reference Category	Told high-risk (AA)	Told protective (TT)	Told high-risk (AA)	Told protective (TT)
		GLP-1 (pg/ml/min)		
Slope in Phase for Ref Category	1.36*** [0.89, 1.82]	0.77*** [0.30, 1.24]	0.18 [-0.11, 0.47]	0.21 [-0.08, 0.50]
Perceived × Slope	-0.58~ [-1.25, 0.08]	0.58~ [-0.08, 1.25]	0.03 [-0.38, 0.44]	-0.03 [-0.44, 0.38]
Session × Slope	0.16 [-0.51, 0.82]	1.18*** [0.52, 1.85]	-0.25 [-0.67, 0.16]	-0.69*** [-1.11, -0.28]
Perceived × Session × Slope	1.03* [0.09, 1.96]	-1.03* [-1.96, -0.09]	-0.44 [-1.02, 0.15]	0.44 [-0.15, 1.02]
		Acyl-ghrelin (pg/ml/min)		
Slope in Phase for Ref Category	-0.53* [-1.06, -0.01]	-0.96*** [-1.48, -0.43]	-0.90*** [-1.20, -0.59]	-0.69*** [-0.99, -0.39]
Perceived × Slope	-0.42 [-1.17, 0.32]	0.42 [-0.32, 1.17]	0.21 [-0.22, 0.6	-0.21 [-0.63, 0.22]
Session × Slope	-0.49 [-1.23, 0.25]	-0.03 [-0.77, 0.72]	0.23 [-0.20, 0.6	0.05 [-0.38, 0.48]
Perceived × Session × Slope	0.46 [-0.59, 1.51]	-0.46 [-1.51, 0.59]	-0.18 [-0.78, 0.4	0.18 [-0.43, 0.78]

Note. ~$p \leq 0.10$, *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$. Regression coefficients and 95% CIs for the slope in GLP-1 (top panel) and acyl-ghrelin (bottom panel) associated with the two phases of the satiety experiment. Phase 1 occurred from minute 0 to minute 15, and Phase 2 from minute 15 to minute 40. Coefficients were obtained from the same longitudinal regression model using simple effects, by recentering time on the beginning of the given phase, and by defining each perceived genotype condition as 0 and the other as +1. The key parameter is the session × slope interaction, which indicates whether the slope in Session 2 (after receiving genetic information) differs from the slope in Session 1 (baseline, before receiving genetic information), for a given perceived genotype condition. Because these hormones respond rapidly to nutrient intake, effects were primarily expected in Phase 1. The perceived genotype × session interaction has the same magnitude for each condition within a given phase because simple slopes were obtained from the same regression.

Supplementary Table 11. Longitudinal physiological outcomes by actual *FTO* rs9939609 genotype in Experiment 2

	Experiment 2 (Satiety): Longitudinal Physiological Outcomes			
	GLP-1 (pg/ml/min)		Acyl-ghrelin (pg/ml/min)	
	B	95% CI	B	95% CI
Fixed Effects				
Level-1 Intercept [Mean at Minute 0]				
Level-2 Intercept	20.00***	[11.45, 28.55]	67.31***	[54.99, 79.63]
Level-2 Actual Genotype (Linear)	1.08	[-5.12, 7.27]	2.16	[-6.77, 11.08]
Slope from Minute 0 to Minute 15				
Level-2 Intercept	0.98***	[0.44, 1.51]	-0.52	[-1.18, 0.14]
Level-2 Actual Genotype (Linear)	0.07	[-0.32, 0.46]	-0.19	[-0.67, 0.29]
Shift in Slope at Minute 15				
Level-2 Intercept	-0.84*	[-1.55, -0.14]	-0.38	[-1.31, 0.55]
Level-2 Actual Genotype (Linear)	-0.02	[-0.54, 0.49]	0.29	[-0.38, 0.96]
Random Effects				
Level-1: within person	243.15***		414.30***	
Level-2: In Level-1 intercept	371.67***		863.06***	
Level-2: In rate of change	0.27***		0	
Goodness-of-fit				
Deviance	2910.19		3028.88	
AIC	2928.19		3046.88	
BIC	2952.16		3070.85	
N	106		106	

Note. ~$p \leq 0.10$, *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$. Regression coefficients, 95% CIs, and goodness-of-fit statistics for a two-level linear regression model predicting the change in gut peptides GLP-1 and acyl-ghrelin following consumption of the meal in Session 1, as a function of actual genotype (between-subjects). Each hormone was measured three times: immediately pre-consumption (time 1), and 15 (time 2) and 40 minutes post-consumption (time 3). Time within Session 1 was modeled at Level-1, using the same shifts in slope as in Supplementary Table 9. The model specified only a single-predictor at Level-2, the effect of actual genotype using an additive model of decreasing risk [0=high-risk (AA), 1=moderate risk (AT), 2=protective (TT)]. The purpose of this analysis was to compare the effect of actual genotype to perceived genotype (see Supplementary Table 9). Consequently, the Level-1 parameters shown represent the Session 1 means for individuals with the AA genotype for *FTO* rs9939609. The intercept and slope in each phase for a given genotype could be obtained by recentering time on the beginning of that phase, and by defining that genotype as 0 (for AT, by defining actual genotype as -1, 0, 1; for TT, by defining actual genotype as -2, -1, 0, for the AA, AT, and TT genotypes, respectively). Each model also included the random effects shown. Deviance=-2 * log likelihood. AIC=Akaike Information Criterion. BIC=Bayesian Information Criterion.

References

63 Astrand P., & Rodahl, K. *Textbook of Work Physiology* (New York, NY: McGraw-Hill, 1970).

64 Borg, G.A. Psychophysical bases of perceived exertion. *Med. Sci. Sports. Exerc.* **14,** 377-381 (1982).

65 Goedecke, J.H., et al. Determinants of the variability in respiratory exchange ratio at rest and during exercise in trained athletes. *Am. J. Physiol. Endocrinol. Metab.* **279,** E1325-E1334 (2000).

66 Howley, E.T., Bassett, D.R., & Welch, H.G. Criteria for maximal oxygen uptake: review and commentary. *Med. Sci. Sports. Exerc.* **27,** 1292-1301 (1995).

67 Edvardsen, E., Hem, E., & Anderssen, S.A. End criteria for reaching maximal oxygen uptake must be strict and adjusted to sex and age: a cross-sectional experiment. *PloS One* **9,** e85276 (2014).