

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

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Millions of people now access personal genetic risk estimates for diseases such as Alzheimer's, cancer and obesity¹. While this information can be informative^{2–4}, research on placebo and nocebo effects^{5–8} suggests that learning of one's genetic risk may evoke physiological changes consistent with the expected risk profile. Here we tested whether merely learning of one's genetic risk for disease alters one's actual risk by making people more likely to exhibit the expected changes in gene-related physiology, behaviour and subjective experience. Individuals were genotyped for actual genetic risk and then randomly assigned to receive either a 'high-risk' or 'protected' genetic test result for obesity via cardiorespiratory exercise capacity (experiment 1, $N=116$) or physiological satiety (experiment 2, $N=107$) before engaging in a task in which genetic risk was salient. Merely receiving genetic risk information changed individuals' cardiorespiratory physiology, perceived exertion and running endurance during exercise, and changed satiety physiology and perceived fullness after food consumption in a self-fulfilling manner. Effects of perceived genetic risk on outcomes were sometimes greater than the effects associated with actual genetic risk. If simply conveying genetic risk information can alter actual risk, clinicians and ethicists should wrestle with appropriate thresholds for when revealing genetic risk is warranted.

One in 25 American adults obtain personalized genetic test reports¹, and in 2017 alone, more people had their DNA analysed with direct-to-consumer genetic tests than in all previous years combined¹. Genetic risk estimates are now available for over 10,000 conditions and 16,000 genes⁹, including diseases such as Alzheimer's, breast cancer and obesity. As people increasingly opt to receive genetic risk information, understanding the psychological, behavioural and physiological impact of receiving that information becomes vital.

The momentum behind personalized genetic testing is driven by the hope that it will guide more precise medical treatments and motivate patient engagement in risk-reducing health behaviours². Although precision medicine has had some early successes (for example, genetically targeted cancer treatments³, safer cardiovascular medication dosing⁴), the effects of receiving genetic information on motivating risk-reducing health behaviours are more dubious. A recent meta-analysis of 18 studies found that the impact of communicating the genetic risk of disease had no effect on recipients' motivation to change behaviour or actual engagement in risk-reducing health behaviours¹⁰. Making matters worse, many studies suggest that people perceive conditions as less controllable when portrayed as genetically caused as opposed to environmentally caused, for a range of conditions and diseases^{11–17}.

Here we ask a more basic question: does merely receiving genetic risk information change an individual's risk? In other words, does receiving high-risk (or protective) genetic information make people more likely to exhibit the gene-related psychological, behavioural and physiological outcomes, specifically due to the mindset^{18,19} that their genes will make those outcomes more likely?

A mindset is a mental frame or lens that orients people to a particular set of expectations and guides them towards responses in line with those expectations^{18,19}. Mindsets change in response to receiving information, and a robust body of research suggests that mindsets can alter health-related behaviour, subjective experience and physiology in substantial ways^{5–7,19–28}. For example, providing older adults with positive messaging about aging improves cardiovascular health compared with messages that confirm negative mindsets²¹. Individuals informed about the enhancing nature of stress adopt the mindset that 'stress-is-enhancing' and, as a result, demonstrate improved work performance, health and wellbeing, and more adaptive cortisol responses to stressful situations compared with individuals informed that stress is harmful and should be avoided^{19,22}. Placebo effects, driven in large part by the conscious or embodied mindset that one is receiving a beneficial treatment, can improve physiological and subjective experience outcomes in a number of conditions, including Parkinson's disease, depression and allergies^{5–7,23}. Conversely, simply disclosing potential side effects of medications can increase their prevalence, even when providers emphasize that these side effects are occasional or uncommon^{26–28}.

Receiving genetic risk information has the potential to instill a potent mindset. Many studies show that providing people with a genetic causal explanation reduces perceived control compared with providing people with an environmental or lifestyle causal account for a range of conditions and situations, including mental illness, maths performance and obesity^{11–17}. Studies that have examined the impact of receiving genetic risk information about diseases such as Alzheimer's^{29,30}, alcoholism³¹, smoking-related diseases³² or a multi-panel of diseases^{33,34} show that individuals who learn that they are at high genetic risk compared with low genetic risk experience more negative emotions and distress^{29,31–34} and can sometimes exhibit deterministic behavioural responses and perceptions^{30,31,33}. Interestingly, the literature on receiving obesity-specific genetic risk information is more mixed. While a few studies reveal that learning of a higher genetic risk result for obesity can decrease perceived behavioural control^{35,36}, increase risk perceptions³⁷, increase negative affect³⁶ and lead to unhealthier dietary intake and decreased exercise three months later³³, other studies report that individuals who learned that they were at higher (versus lower) genetic risk of obesity did not exhibit decreased perceived control³⁸, intentions to eat healthier^{38–41} or healthy eating behaviours^{39–41}.

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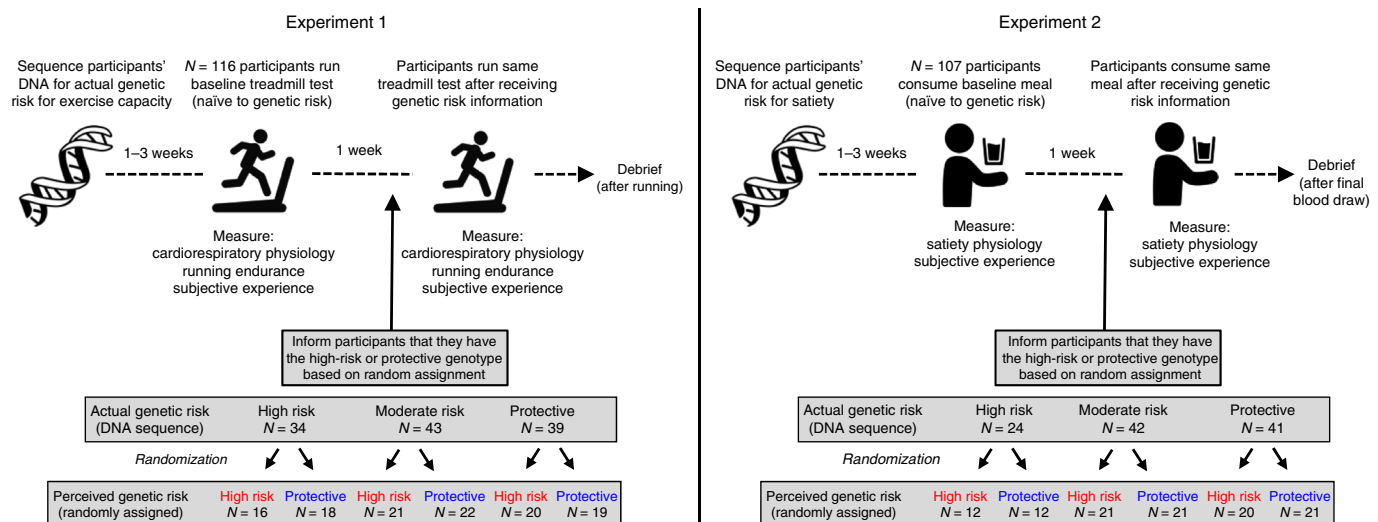


Fig. 1 | Experimental design.

Overall, while studies on responses to receiving personal genetic risk information have assessed affective, psychological and behavioural responses, no experimental designs to date have randomly assigned participants to learn of a high versus low genetic risk for a condition and then examined individuals' subjective experience and physiological functioning in a situation where the genetic risk is made salient. Furthermore, no studies to date have compared the effect sizes of perceived genetic risk to those of actual genetic risk on gene-relevant outcomes. Here we examine whether receiving genetic risk information changes an individual's actual risk by altering their gene-relevant subjective experience, behaviour and physiology. Furthermore, we compare the effect sizes of perceived genetic risk to actual genetic risk.

Isolating the effects of perceived genetic risk is methodologically challenging. Perceived genetic risk, defined as the mindset or set of expectations and associations a person holds regarding their perceived genetic risk, can be distinct from actual genetic risk. However, properly assessing the effects of perceived genetic risk requires (1) DNA testing of participants in order to know whether each individual actually has the high-, moderate- or low-risk/protective genotype for a disease, (2) randomly assigning half of the participants from each level of actual genetic risk to receive high-risk genetic information and the other half to receive low-risk/protective genetic information and (3) measuring gene-relevant outcomes both before and after individuals receive genetic risk information to determine whether gene-relevant outcomes worsen for individuals informed that they have an increased genetic risk, or improve for individuals informed that they have a decreased genetic risk. This design, which we developed for these experiments, has the benefit of within-participant comparisons of each individual's outcomes after receiving genetic risk information with his/her own baseline when they were naïve of the genetic risk. Additionally, this design allows for between-participant comparisons of the effects associated with individuals' actual genetic risk on gene-relevant outcomes at baseline when all individuals were naïve to the genetic risk. Finally, this design makes it possible to compare the relative effect sizes of perceived versus actual genetic risk on gene-relevant outcomes.

In spite of its benefits, this design is ethically challenging. Randomly assigning participants to learn that they have a high or low genetic risk necessitates deception, as some participants must be falsely informed of their genotype in an ethical, yet believable, manner. Therefore, potentially negative effects of this deception must be minimized and weighed against the potential value of the results.

Given the potential gravity of such implications in the context of rapidly increasing direct-to-consumer genetic testing, we endeavoured to overcome the methodological and ethical challenges. The ethical considerations were taken seriously, and we worked closely with the Stanford University IRB to minimize the potential risks in a number of ways. First, we chose to focus on the effects of genetic risk information for obesity because we believed that the results would be meaningful, yet not as emotionally charged as more life-threatening conditions, such as cancer or Alzheimer's disease. Second, we strictly limited the time under which participants would hold a potentially false belief about their genetic risk to approximately 1 h while under clinical supervision. Third, immediately after the outcomes were measured, participants were fully debriefed on the true purpose of the experiment and given an extensive debrief about the importance of behaviour and environment in shaping the risk of obesity. It was determined that the potential value of the information gleaned from this research would outweigh the necessary short-term deception, especially given that the potentially iatrogenic effects²⁶ of learning one's genetic risk are already occurring at scale.

Therefore, we conducted two experiments that were conceptual replications of one another to test whether receiving genetic risk information changes individuals' subjective experience, behaviour and physiology in a manner that is consistent with the expected risk (see Fig. 1). We hypothesized that individuals in both experiments who were informed that they had a high-risk genotype would exhibit maladaptive changes in subjective experience, behaviour and physiology because of the expectations given to them in their genetic test report, while individuals who were informed that their genotype was protective would experience improvements in those same measures. We also predicted that individuals informed of high genetic risk would experience increased feelings of worry and decreased feelings of control, based on the language used in the pamphlets and genetic test report that conveyed to participants the strong influence that a high-risk or protected genetic test result would have on exercise capacity (experiment 1) and satiety (experiment 2) outcomes.

Experiment 1 explored the effect of perceived *CREB1* rs2253206 (cAMP responsive element binding protein 1) risk on exercise capacity. The *CREB1* rs2253206 high-risk genotype is associated with poorer aerobic exercise capacity^{42–44}, increased body temperature during aerobic exercise⁴², and fewer cardiovascular improvements from participating in an exercise programme^{43,44} compared with individuals with the protective genotype (effect sizes for the

association between genotype and exercise outcomes range from 0.3–0.5 across studies)^{42–44}. Two-tailed *t*-tests revealed that immediately after receiving the genetic risk information, the random half of individuals at each level of actual genetic risk who were told that they had the high-risk *CREB1* genotype perceived themselves to be at higher risk of poor exercise capacity compared with the other half of individuals who were informed that they had the protective *CREB1* genotype ($M_{\text{diff}} = 3.46$, 95% confidence interval (CI): (3.11, 3.81), $t(114) = 19.50$, $P < 0.001$, $d = 3.62$). This confirmed that participants understood whether they had received high-risk or protective genetic information regarding the *CREB1* gene, and that participants understood the relationship between a high-risk *CREB1* result and the expected negative effects on exercise capacity. Participants also took this information seriously. Individuals who were informed that they had the high-risk *CREB1* genotype reported feeling more worry ($M_{\text{diff}} = 1.88$, 95% CI: (1.29, 2.47), $t(114) = 6.27$, $P < 0.001$, $d = 1.17$) and less control ($M_{\text{diff}} = -0.79$, 95% CI: (-1.25, -0.32), $t(105.5) = 3.35$, $P = 0.001$, $d = 0.63$) over their exercise capacity (Supplementary Fig. 3).

As hypothesized, the perceived genetic risk changed participants' cardiorespiratory physiology in a manner that mirrored participants' expectations. Using multilevel regression models, we observed a significant perceived genotype \times session effect on maximum $\text{CO}_2\text{:O}_2$ exchange rate ($B = 0.034$, 95% CI: (0.008, 0.059), $P = 0.010$). Individuals who were informed that they had the high-risk genotype reached a significantly lower maximum capacity for $\text{CO}_2\text{:O}_2$ gas exchange compared with their own baseline session ($B = -0.023$, 95% CI: (-0.041, -0.005), $P = 0.013$), while individuals who were informed that they had the protective genotype did not significantly differ from baseline ($B = 0.011$, 95% CI: (-0.007, 0.029), $P = 0.25$; Fig. 2a; Supplementary Tables 1 and 4). Perceived risk also had a marginally significant effect on maximum ventilatory flow rate (perceived genotype \times session effect: $B = 2.60$, 95% CI: (-0.25, 5.46), $P = 0.074$). Individuals who were informed that they had the high-risk genotype showed a significantly decreased maximum ventilatory flow rate by more than 2 litres of air per minute on average compared with their baseline session ($B = -2.06$, 95% CI: (-4.10, -0.02), $P = 0.047$), while individuals who were informed that they had the protective genotype did not significantly change from baseline ($B = 0.54$, 95% CI: (-1.46, 2.55), $P = 0.59$; Fig. 2b; Supplementary Tables 1 and 4). Effect size comparisons (in standard deviation units or Cohen's *d*) revealed that the effect of the perceived genotype was greater than the effect associated with the actual *CREB1* genotype on $\text{CO}_2\text{:O}_2$ exchange rate ($d_{\text{perceived}} = 0.50$ vs $d_{\text{actual}} = -0.14$), but not the ventilatory flow rate ($d_{\text{perceived}} = 0.08$ vs $d_{\text{actual}} = 0.12$). Longitudinal analyses of the trajectories of $\text{CO}_2\text{:O}_2$ exchange rate and ventilatory flow rate over time (presented in the Supplementary Notes and Supplementary Tables 6–8) demonstrated that individuals who were informed that they had the high-risk genotype experienced a plateau effect during the final challenging minutes of the exercise test compared with their baseline performance, while individuals who were informed that they had the protective genotype increased their rate of change in $\text{CO}_2\text{:O}_2$ gas exchange and ventilatory flow rate during this same time period.

Also as hypothesized, perceived risk significantly altered participants' running endurance, the amount of time that participants ran before giving up ($B = 0.38$, 95% CI: (0.06, 0.69), $P = 0.019$). Individuals who were informed that they had the high-risk genotype stopped running 0.36 min (22 s) earlier compared with their baseline session ($B = -0.36$, 95% CI: (-0.58, -0.13), $P = 0.002$), while individuals who were informed that they had the protective genotype did not change from baseline ($B = 0.02$, 95% CI: (-0.20, 0.24), $P = 0.88$; Fig. 2c; Supplementary Tables 2 and 4). The effect size of perceived genetic risk was smaller than the effect associated with the actual genotype on running endurance ($d_{\text{perceived}} = 0.16$ vs $d_{\text{actual}} = 0.41$).

In addition to the physiological and behavioural effects, perceived genetic risk changed subjective experience. We observed a significant perceived genotype \times session effect on individuals' subjective experience of perceived exertion ($B = 0.72$, 95% CI: (0.12, 1.33), $P = 0.020$) and perceived heat ($B = 0.92$, 95% CI: (0.05, 1.80), $P = 0.039$), consistent with the expectations provided to them about how difficult exercise would be and how hot they would feel while exercising. Individuals who were informed that they had the protective genotype ran 0.79 min (47 s) longer before indicating that the test felt 'hard' ($B = 0.79$, 95% CI: (0.37, 1.22), $P < 0.001$) and 1.12 min (67 s) longer before indicating that they felt 'hot' ($B = 1.12$, 95% CI: (0.49, 1.74), $P < 0.001$) compared with their baseline session, despite running at the same speed and incline grade as their baseline session. Individuals who were informed that they had the high-risk genotype did not change from baseline on perceived exertion ($B = 0.07$, 95% CI: (-0.36, 0.50), $P = 0.75$) or perceived heat ($B = 0.19$, 95% CI: (-0.42, 0.81), $P = 0.54$; Figs. 2d and 2e; Supplementary Tables 2 and 4). The effect size of perceived genetic risk was smaller than that associated with actual genetic risk on perceived exertion ($d_{\text{perceived}} = 0.29$ vs $d_{\text{actual}} = 0.40$) but was greater than the effect size associated with actual genetic risk for perceived heat ($d_{\text{perceived}} = 0.34$ vs $d_{\text{actual}} = 0.14$).

Taken together, these results indicate that informing individuals of high versus low genetic risk led to changes in metabolic gas exchange and ventilatory physiology that exacerbated the perceived risk. These physiological changes were mirrored by changes in subjective experience (perceived exertion, heat) and behaviour (total time run). Furthermore, the size of the effects due to perceived genetic risk were sometimes greater than effect sizes associated with actual *CREB1* genetic risk on outcomes (see Table 1 for summary). Analyses of actual genotype \times perceived genotype \times session interactions demonstrated that the effects of perceived genotype on all outcomes did not significantly differ by individuals' actual *CREB1* genotype, though analyses of these three-way interactions have less power to detect effects and are only suggestive based on the available sample ($P > 0.10$ for all pairwise comparisons of the perceived genotype \times session effect between actual high-risk, moderate-risk and protective genotypes for all outcomes; Supplementary Table 5).

In this context of maximal exercise testing, where there was little room for improvement from one's baseline performance, physiological and behavioural differences due to perceived risk were primarily driven by the negative effects of being informed of increased risk. Though individuals informed that they had the high-risk genotype ran for 22 s less than their baseline on average, longitudinal analyses that control for the change in time run indicate that perceived risk affected the trajectories of both metabolic and ventilatory physiology in the final phase of the test (Supplementary Tables 6 and 7). These results illustrate the impact of learning one's genetic risk alone, regardless of actual genetic risk, and show that the mindset that genetic risk information creates can have meaningful consequences.

Would the effects of perceived genetic risk generalize to a different gene and context? Experiment 2 was designed to extend the results of experiment 1 using the most established candidate gene for obesity. The *FTO* rs9939609 (fat mass and obesity-associated gene) high-risk genotype, the best-studied and most highly associated genetic risk factor for obesity⁴⁵, is associated with lower self-reported satiety^{46–48}, stronger neural responses to images of food in brain regions that regulate appetite and reward^{47,49}, and decreased physiological satiety, as measured by gut peptide signalling after food consumption⁴⁷. Effect sizes for the relationship between the *FTO* genotype and outcomes range from 0.2 to 1.1, with smaller effect sizes reported in studies with a greater number of participants^{46–50}. Experiment 2 tested whether perceived *FTO* rs9939609 genetic risk for obesity affects post-consumption gut peptide physiology and subjective satiety. It was also designed to limit

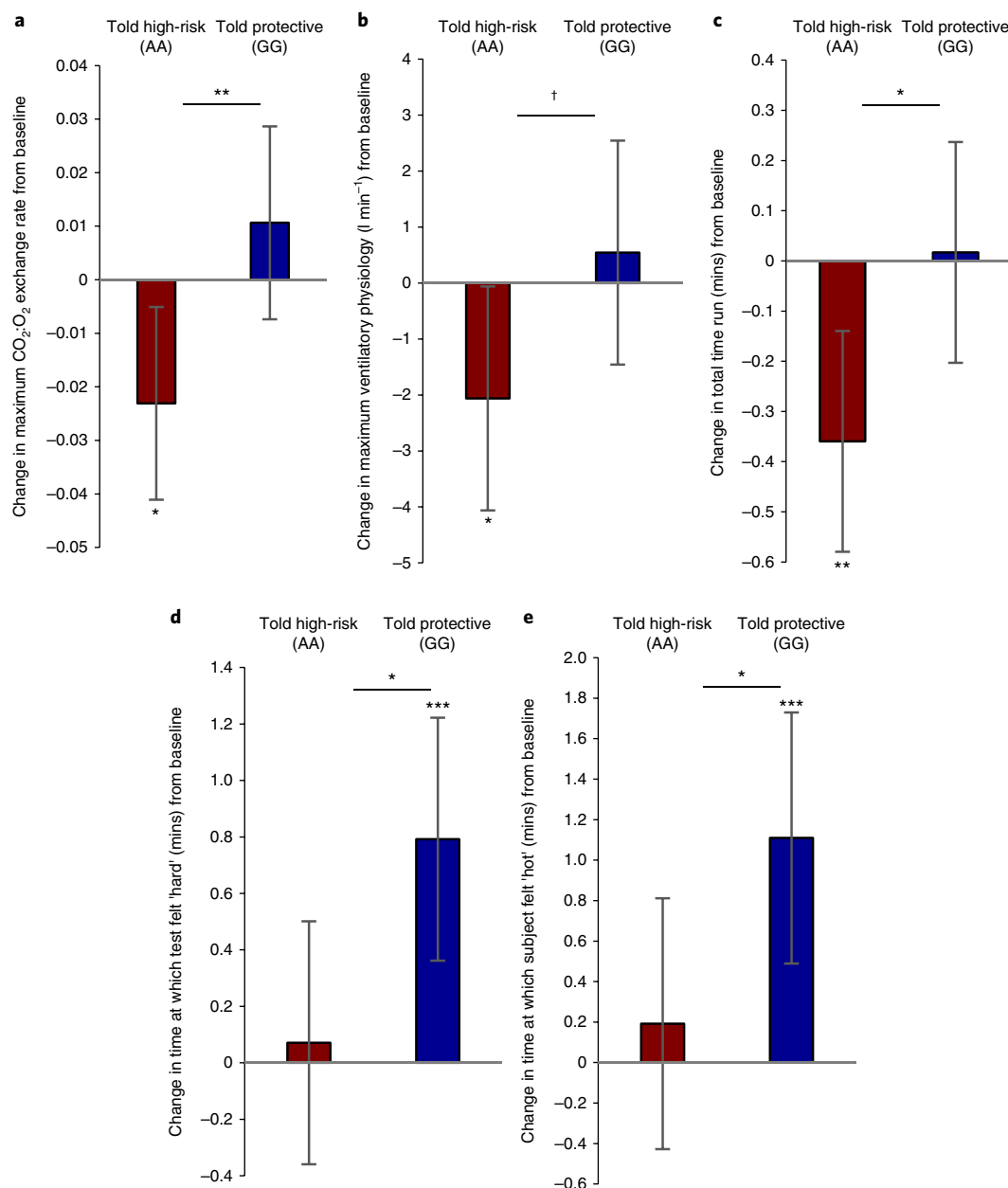


Fig. 2 | Receiving genetic risk information for exercise capacity alters cardiorespiratory physiology, running endurance and subjective experience.

a–e, Effects of receiving high-risk (red) versus protective (blue) genetic test results for *CREB1* rs2253206 on cardiorespiratory physiology (**a,b**), running endurance (**c**) and subjective experience (**d,e**) during strenuous exercise in experiment 1 ($N=116$). AA represents the high-risk genotype and GG the protective genotype for *CREB1* rs2253206. Bars represent estimates for the effect of perceived genotype \pm 95% CI from the multilevel regression model of the difference in participants' outcomes from their baseline session (naïve to genetic risk) and after receiving the genetic risk information that was randomly assigned to them. **a**, Maximum respiratory exchange ratio, metabolic measure of $\text{CO}_2\text{:O}_2$ gas exchange. **b**, Maximum ventilation (VE), flow rate of inhaled and exhaled gas. **c**, Running endurance (total time run) in minutes. **d**, Perceived exertion, measured by the time at which participants indicated that the test felt 'hard'. **e**, Perceived heat, measured by the time at which participants indicated that their body temperature felt 'hot'. Significance of both between-group and within-group effects is indicated as follows: † $P < 0.10$, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

changes in behaviour so as to isolate the effect of perceived genotype on physiology.

Similar to experiment 1, the random half of individuals at each level of actual genetic risk in experiment 2 who were informed that they had the high-risk *FTO* genotype immediately perceived themselves to be at higher risk of poor satiety ($M_{\text{diff}}=2.84$, 95% CI: (2.46, 3.22), $t(105)=14.66$, $P < 0.001$, $d=2.83$), and felt more worry ($M_{\text{diff}}=1.53$, 95% CI: (0.91, 2.15), $t(101.1)=4.91$, $P < 0.001$, $d=0.94$) and less control over satiety ($M_{\text{diff}}=-0.56$, 95% CI: (-1.02,

-0.10), $t(105)=2.42$, $P=0.017$, $d=0.47$) compared with individuals who were informed that they had the protective *FTO* genotype (Supplementary Fig. 3).

As hypothesized, perceived genetic risk changed physiological satiety in a manner that mirrored participants' expectations. We observed a significant perceived genotype \times session effect on physiological satiety, as measured by glucagon-like peptide 1 (GLP-1) response ($B=15.39$, 95% CI: (1.66, 29.12), $P=0.028$). Individuals informed that they had the protective genotype experienced a

Table 1 | Effect sizes for actual genetic risk versus perceived genetic risk in experiments 1 and 2

	Actual genotype	Perceived genotype
	<i>d</i>	<i>d</i>
Experiment 1		
Maximum CO ₂ :O ₂ exchange rate	−0.14	0.50
Maximum ventilatory flow rate	0.12	0.08
Running endurance	0.41	0.16
Perceived exertion	0.40	0.29
Perceived heat	0.14	0.34
Experiment 2		
GLP-1 (physiological satiety)	0.09	0.66
Acyl-ghrelin (physiological hunger)	−0.21	0.25
Perceived satiety (fullness)	−0.07	0.46

Effect sizes (Cohen's *d*) for both actual genotype and perceived genotype on all outcomes. Effect sizes with positive values indicate that the effects were in the hypothesized direction, except for acyl-ghrelin (for which negative values represent the hypothesized direction). Bolded numbers indicate where the effect of perceived genotype was greater than the effect of actual genotype. The total effect size of perceived genotype represents the effect size for individuals told protective minus the effect size for individuals told high-risk (see Supplementary Table 4 for effect sizes split by perceived genotype group). 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 design, 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. *d* is effect size (standard deviation units).

2.5-fold greater increase in GLP-1 after food intake compared with their baseline ($B = 17.75$, 95% CI: (8.04, 27.46), $P < 0.001$), while individuals informed that they had the high-risk genotype did not significantly change from baseline ($B = 2.36$, 95% CI: (−7.35, 12.07), $P = 0.63$; Fig. 3a, Supplementary Tables 3 and 4, 9–11). The effect size of perceived genetic risk on GLP-1 response was much greater than the effect associated with the actual *FTO* genotype ($d_{\text{perceived}} = 0.66$ vs $d_{\text{actual}} = 0.09$).

As hypothesized and corresponding to the observed changes on GLP-1 physiological satiety, perceived risk significantly altered self-reported satiety (perceived genotype \times session effect: $B = 0.58$, 95% CI: (0.07, 1.08), $P = 0.025$). Individuals informed that they had the protective genotype reported a 1.4-fold increase in fullness post-consumption compared with their baseline session ($B = 0.55$, 95% CI: (0.19, 0.90), $P = 0.003$), while individuals informed that they had the high-risk genotype did not significantly change from baseline ($B = -0.03$, 95% CI: (−0.39, 0.33), $P = 0.86$; Fig. 3b; Supplementary Tables 3 and 4). Similar to the effect sizes on physiological satiety, the effect size of perceived genetic risk on self-reported satiety was much greater than the effect associated with actual *FTO* genotype ($d_{\text{perceived}} = 0.46$ vs $d_{\text{actual}} = -0.07$).

Similar to experiment 1, analyses of actual genotype \times perceived genotype \times session interactions on physiological satiety and self-reported satiety demonstrated that the effects of perceived genotype did not significantly differ by individuals' actual *FTO* genotype ($P > 0.30$ for all pairwise comparisons of the perceived genotype \times session effect between actual high-risk, moderate-risk and protective genotypes; Supplementary Table 5).

We observed no significant effect of informed risk on physiological hunger levels, as measured by acyl-ghrelin response ($B = 6.95$, 95% CI: (−6.82, 20.73), $P = 0.32$; Supplementary Tables 3 and 4, 9–11). However, there was a significant genotype \times perceived genotype \times session interaction for acyl-ghrelin response between individuals who actually had the high-risk and protective *FTO* genotypes ($B = 40.28$, 95% CI: (4.57, 75.99), $P = 0.027$). Individuals who

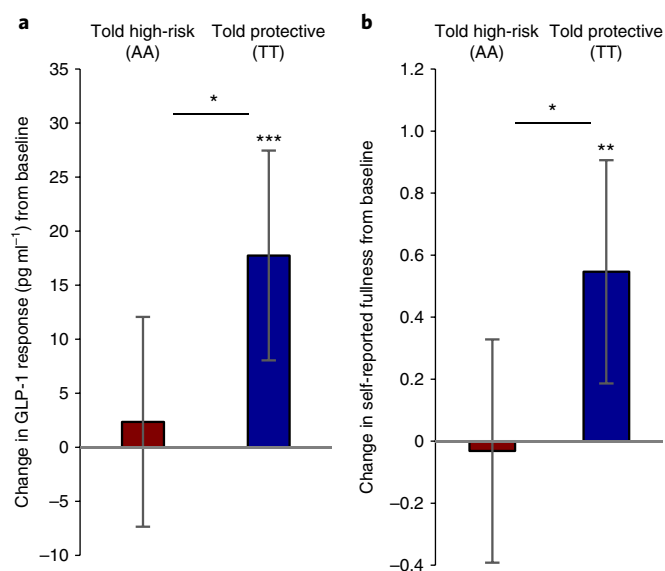


Fig. 3 | Receiving protective genetic risk information for satiety increases physiological and self-reported satiety. a, b, Effects of receiving high-risk (red) versus protective (blue) genetic test results for *FTO* rs9939609 on physiological satiety (**a**) and subjective experience of satiety (**b**) immediately before and 15 min after consuming a 480-calorie meal in experiment 2 ($N = 107$). AA represents the high-risk genotype and TT the protective genotype for *FTO* rs9939609. Bars represent estimates for the effect of perceived genotype \pm 95% CI from the multilevel regression model of the difference in participants' outcomes from their baseline session (naïve to genetic risk) and after receiving the genetic risk information that was randomly assigned to them. **a**, GLP-1 response, physiological biomarker of satiety. **b**, Self-reported satiety (fullness). Significance of both between-group and within-group effects is indicated as follows: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

had the high-risk *FTO* genotype exhibited the hypothesized trend of results (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), while individuals who had the protective *FTO* genotype exhibited the opposite trend (Supplementary Table 5). It is not clear why actual genotype impacted the participants' acyl-ghrelin response but no other outcomes in either experiment. The sample sizes for both experiment 1 and experiment 2 were designed to have 80% power to detect medium effect sizes between individuals informed that they had the high-risk genotype and individuals informed that they had the protective genotype, and therefore were not sufficiently powered to test the effects of perceived risk *within* each of the three levels of actual genetic risk separately. Thus, any results based on this subgroup analysis (presented in Supplementary Table 5) are only suggestive at this stage based on the available sample. Future research with a greater number of participants is warranted to test these three-way interactions with more statistical power.

Taken together, the results of experiment 2 conceptually replicate and extend experiment 1, using the most well-studied candidate gene for obesity. Informing individuals that they were genetically predisposed to feel more full after eating led to a greater increase in physiological satiety, as measured by GLP-1 response. This change in physiology was mirrored by changes in participants' feelings of fullness, both of which occurred independently of participants' actual *FTO* genetic risk. Furthermore, the size of the effects due to perceived genetic risk on physiological satiety and self-reported satiety were greater than the effects associated with actual *FTO* genetic

risk on satiety outcomes. Overall, in this experimental context, the differences due to perceived risk were primarily driven by the beneficial effects of being told that one was protected rather than the detrimental effects of being informed of high risk.

These experiments examined whether learning of one's genetic risk (regardless of actual genetic risk) influences behaviour, physiology and subjective experience in a manner that alters gene-relevant outcomes and, therefore, actually changes one's risk. Indeed, our results show that perceived genetic risk independently alters physiology, subjective experience and behaviour in ways that may exacerbate actual risk. In experiment 1, informing individuals of high versus low genetic risk for exercise capacity led to poorer maximum capacity for CO₂:O₂ gas exchange, decreased the amount of air with which participants supplied their lungs by more than 2 litres per minute, and decreased how long participants ran before giving up during strenuous aerobic exercise compared with their own performance one week earlier when they were naïve to genetic risk. Longitudinal analyses revealed that the differences in cardiorespiratory physiology by perceived genotype emerged during the final, challenging minutes of the treadmill test, at which point those informed of high risk levelled off in their cardiorespiratory capacity while those informed that they had the protective genotype increased. These changes were mirrored by changes in subjective experience of how difficult the exercise felt and participants' self-reported body heat while exercising. All of these changes were present regardless of whether the information they had received about genetic risk was true, illustrating the impact of the genetic risk information itself and the mindset that the information created.

In experiment 2, informing individuals that they were genetically protected from poor satiety led them to demonstrate a 2.5-fold increase in physiological satiety and a 1.4-fold increase in self-reported fullness compared with when they consumed the same meal one week earlier but were naïve to genetic risk. Again, these changes were present regardless of whether the information they received about genetic risk was true. Perhaps most interestingly, our findings show that the effect of perceived genotype on outcomes was sometimes greater than the effects associated with actual genetic risk.

How does perceived genetic risk alter physiology? One potential explanation is behaviour. Although perceived genetic risk can change behaviour (for example, running endurance), our results suggest that changes in behaviour are not necessary to evoke changes in physiology. In experiment 2, food consumption behaviour was fixed for all subjects, and in experiment 1, longitudinal analyses showed that differences in physiology by perceived risk persisted when controlling for the difference in time that a participant ran in his/her second session compared with their baseline. Another potential mechanism is stress. It is possible that the individuals informed of high genetic risk experienced more stress than those informed of a protective genotype^{29,33,51}. While stress can affect the gastrointestinal tract, the physiological changes in satiety occurred in participants informed that they had the protective genotype, not high-risk, making stress an unlikely mechanism. We speculate that the overarching mechanism at play is the effect of the mindset that is shaped almost immediately on learning of the genetic risk^{8,11,19,26,52}. The individual is, of course, genetically identical before and after receiving the genetic information, yet the information they are given is not innocuous. The information itself provides a distinct psychological framework through which the individual interprets their current experience and prepares for future experiences and, as a result, this new mindset influences attention, motivation and, most interestingly, physiology in a manner that confirms their expectations^{8,11,19,26,52}.

While perceived genetic risk mattered in both experiments, the effects were sometimes driven by negative changes for those who were told that they were at high risk, and sometimes driven by

benefits for those who were told that they had the protective genotype. Whether perceived risk elicits a negative effect or perceived protection elicits a positive effect is likely to differ depending on the gene of interest and the experimental paradigm. For example, the exercise test in experiment 1 was a maximal exertion test and there was therefore little room for improvement. These results are consistent with results from an analogous cognitive performance paradigm demonstrating that older adults who were informed that they had an increased genetic risk of Alzheimer's disease performed worse on memory tasks and judged their memory performance more harshly than older adults who were also at increased genetic risk but were unaware of it³⁰. In contrast, the benefits in physiological and perceived satiety for individuals informed that they had the protective genotype in experiment 2 were substantial and highlight the potential of protective genetic information to improve health outcomes for individuals who are not at genetic risk of a disease. Overall, however, few studies report that individuals who receive lower-risk information actually do experience psychological benefits^{30,38,53} or change health behaviours, with some studies reporting that individuals exhibit less healthy behaviours or intentions after learning that they are not at risk^{35,41}.

While receiving high-risk genetic information can increase perceptions of risk³⁵ and decrease perceived control^{35,36}, as we observed in the present research, some vignette studies or pilot studies on disclosing obesity-specific genetic risk found that receiving high-risk compared with lower-risk genetic information did not undermine, and sometimes increased, the motivation to engage in healthier behaviours^{35–38}. The few randomized trials of disclosing genetic risk information for obesity have so far found in the follow-up no difference in intentions to eat healthier or actual healthy eating between individuals who learned of elevated genetic risk and those who learned of lower genetic risk^{39,40}. However, the largest study of participants who received direct-to-consumer test results reported that learning of their increased risk of obesity was associated with unhealthier dietary intake and less exercise three months later³³. One potential reason for differences among studies in these psychological and behavioural outcomes may be in the manner in which the genetic risk information was communicated. Recent work indicates that the perceived seriousness of the disease is associated with greater distress responses to high-risk results and decreased perceived control³⁴. While the pamphlets we designed emphasized that the *CREB1* and *FTO* genes strongly contribute to obesity, and underemphasized the importance of environmental contributions to obesity, information that presents genetic risks as being relatively unimportant in shaping outcomes might be less likely to produce the same effects that we observed here on perceived risk, worry and control or on the primary outcomes.

One important question that the current experiments did not test was how the impact of receiving genetic information compares with other information that may also impact expectations, such as information gleaned from one's family history, lifestyle risk (for example, exercise, diet, sedentary behaviour), pharmacological risk (for example, side effects of medication or procedures), metabolic risk (for example, hormone levels, insulin sensitivity) or other biological indicators of health (for example, heart rate, blood pressure, BMI). While the present results demonstrate that receiving genetic risk information can change subjective experience, behaviour and physiology in self-fulfilling ways, the effects of receiving information on related outcomes is not unique to genetic information. Indeed, research on mindsets, expectations and placebo effects demonstrates that many types of non-genetic information are capable of changing psychological, behavioural and physiological outcomes^{5–7,19–28}. Several studies have specifically compared how individuals respond to receiving genetic risk information with receiving non-genetic risk information. The limited evidence suggests that genetic risk information may have a greater impact on

perceived risk levels and emotions compared with either family history information⁵³ or metabolite levels⁵⁴, but does not differentially affect weight loss compared with lifestyle feedback⁴⁰ or information about family history and glucose levels⁵⁵. Future research is needed to test these comparisons more systematically for a range of non-genetic types of risk information and for gene-relevant outcomes to help inform the precision medicine movement as to whether genetic risk information is differentially likely to instil self-fulfilling effects compared with other types of risk information. However, regardless of whether genetic risk information has similar or greater impacts on gene-relevant outcomes, the present results show that receiving genetic risk information can change gene-relevant outcomes, which is important to consider as the reach of personalized genetic testing increases exponentially.

More research is also needed to test the extent to which perceptions of risk alter health outcomes for a range of different conditions. Existing research documents that expectations can trigger changes in the cardiovascular, endocrine, immune and nervous systems^{5–7,19,21,23}. The effects of perceived genetic risk on physiology are likely to be greater for conditions in which these systems are highly involved and less so for those that are not (for example, tumour growth)⁵. The challenge for future research will be to test the longitudinal effects of perceived genetic risk in a manner that minimizes patient deception but still effectively uncovers how perceived genetic risk may influence outcomes for a range of diseases that are manifested through different body systems from those tested in the present research. Research of this nature will bring up ethical challenges that must be weighed seriously when considering experimental design.

This research has important implications for medical ethicists, policymakers, clinicians, genetic counsellors and the genetic testing industry. Medical ethicists and policymakers already face the challenging task of determining the thresholds at which revealing genetic risk is warranted. These determinations may be based on a variety of factors, but to date they have largely ignored the potential influence of mindset effects. Clinicians, genetic counsellors and direct-to-consumer testing organizations should thus be mindful that the mere act of delivering genetic information can influence actual risk. Additional research and policy is needed to equip those entities with guidelines regarding when genetic risk disclosure is appropriate as well as best practice for communicating genetic information in ways that increase the benefit to patients while decreasing potential costs. Ideally, genetic risk disclosure would activate a placebo-like boost for individuals who are not at risk while minimizing the negative psychological and physiological impacts for individuals who are at risk.

Although much remains to be explored, the present research represents a major advance in our understanding of the impact of genetic risk disclosure and suggests that learning of one's genetic risk of obesity may in fact exacerbate one's risk. As our biological understanding of genetic risk increases at an unprecedented rate, the results herein underscore the critical need to accompany biological advances in genetics with an equally sophisticated understanding of the impact of receiving genetic risk information on patient health outcomes. Effective implementation of 'precision medicine' depends on both.

Methods

The experimental design for experiments 1 and 2 is illustrated in Fig. 1. Briefly, participants from the San Francisco Bay Area were recruited over the course of 1 year for a 'personalized health' study in which they believed they would learn which exercises and diets were best suited for them given their genetic profile. In both experiments, we set out to recruit 120 participants such that we had approximately $N = 20$ participants in each cell for the 3 (actual genotype: high-risk, moderate-risk, protective) \times 2 (perceived genotype: high-risk, protective) design. These numbers were determined based on sample sizes used in previous research^{29–31}, and power analyses indicating that this sample size would have

approximately 80% power to detect medium-sized effects between those informed of high risk and those informed that they had the protective genotype.

A total of 271 participants ($M = 25.3$ (s.d. = 6.0) years old, 62.8% female) were genotyped to retain roughly equal numbers of participants with the high-risk, moderate-risk and protective (low-risk) genotypes for the genes of interest in each experiment, *CREB1* rs2253206 (experiment 1; $N = 116$) and *FTO* rs9393609 (experiment 2; $N = 107$). In both experiments, participants within each of the three risk groups (high-risk, moderate-risk, protective) completed a baseline session before receiving genetic risk information, allowing for the calculation of effect sizes associated with actual genetic risk on baseline outcomes.

At a second session, half of the participants within each genotype were randomly assigned to be informed that they had the high-risk genotype and half were randomly assigned to be informed that they had the protective genotype, using a 1:1 ratio, such that approximately equal numbers of each of the three genotypes (high-risk, moderate-risk and protective) received high-risk and protective genetic test results. To convey this information, each participant received a genetic test report detailing his/her risk level and a pamphlet (constructed from published scientific and popular press articles about the *CREB1* or *FTO* gene) explaining the gene's effects on subjective experience, behaviour and physiology, and the scientific evidence^{42–50} for its link to obesity through exercise capacity (*CREB1*) or satiety (*FTO*) (see Supplementary Methods). The genetic test reports and pamphlets emphasized that the *CREB1* and *FTO* genes were predictive of exercise- and satiety-related outcomes, respectively. Participants then followed the same protocol as in the baseline session, allowing for comparison of how each individual's outcomes changed from the baseline session depending on whether he/she received high-risk or protective genetic risk information. This also allowed for calculation of the effect size of perceived genetic risk alone on outcomes so that we could compare them with the effect sizes associated with actual genetic risk from the baseline session.

In experiment 1, examining the effect of perceived *CREB1* rs2253206 risk on exercise capacity, participants completed a maximal effort treadmill test at both sessions (taking place at the same time of day) in which breath-by-breath metabolic and ventilatory data were collected (Supplementary Fig. 1). Two summary measures of cardiorespiratory physiology were examined: (a) the CO_2/O_2 exchange rate (the oxidative capacity to supply muscles with energy) as the summary measure of metabolic respiratory physiology, and (b) the ventilatory flow rate (the volume of gas inhaled and exhaled from a person's lungs per minute), as the summary measure of physical respiratory physiology. Because participants were specifically informed in their genetic test report and pamphlet that the high-risk *CREB1* gene not only conferred poorer physiological exercise capacity but also negative effects on subjective experience (feeling hotter during exercise and experiencing exercise as more difficult) and behaviour (poorer running endurance), we asked participants to self-report their perceived body heat and perceived exertion levels every 2 minutes, and recorded their running endurance. We compared changes in cardiorespiratory physiology, subjective experience (perceived exertion and perceived heat) and behaviour (running endurance) from the baseline session with the genetic risk disclosure session for individuals informed that they had the high-risk versus the protective genotype.

To conceptually replicate the design of experiment 1 using a different gene, a different paradigm, different outcomes and different participants, experiment 2 explored the effect of perceived *FTO* rs9393609 risk on satiety. Participants consumed the same 480-calorie meal at both sessions and had blood samples drawn pre-consumption, and at 15 and 40 min post-consumption (Supplementary Fig. 2). Both sessions took place at the same time in the morning after an overnight fast. Participants were informed that the high-risk *FTO* genotype conferred poorer feelings of satiety and poorer physiological satiety compared with the protective *FTO* genotype, and two measures of physiological satiety were examined: glucagon-like peptide 1 (GLP-1) as a physiological signature of satiety, and acyl-ghrelin as a physiological signature of hunger. GLP-1, rapidly released from the intestines after meal intake, is a satiety peptide that slows gastric emptying, agonizes brain receptors associated with food intake and energy balance, and inhibits subsequent food intake^{56–60}. Acyl-ghrelin is a peptide that stimulates appetite by modulating activity in brain regions associated with reward and energy balance^{61,62}. We compared changes in physiological satiety (gut peptides GLP-1 and acyl-ghrelin) and subjective experience (self-reported satiety) from the baseline session with the genetic risk disclosure session for individuals informed that they had the high-risk versus the protective genotype.

Only data from participants who completed the full study were analysed and no data were excluded from the analyses. In both experiments, the experimenters were blind to the participants' actual genotype and outcomes from the participants' baseline session. The experimenters were also blind to participants' randomly assigned genotype until participants received their genetic test report and pamphlets at the genetic risk session (thereafter, blinding to the 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 processed and analysed the physiological data were blind to participants' actual and assigned genetic risk level. Detailed methods including experimental

protocols, measurement of physiological data, DNA sequencing, participant characteristics, study allocation and attrition, additional measures, cross-sectional and longitudinal statistical analyses, and supplementary results, figures, and tables are presented in the Supplementary Information.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Data is available on the Open Science Framework at the following link: https://osf.io/gz57m/?view_only=71292e851b754bacbd89dc07c8113829.

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Author contributions

B.P.T. and A.J.C. conceived and designed the study. B.P.T., A.S., S.L.D. and A.J.C. designed protocol details. B.P.T. and D.Z.B. were responsible for consenting participants, running participants through the protocol and debriefing participants. A.S. was responsible for processing physiological data, B.P.T. and D.Z.B. were in charge of data management and J.P.G. was in charge of data analysis. B.P.T. wrote the first draft, and all authors contributed critical revisions of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Physiological data Experiment 1 were collected using software from Quark b2, version 8.2 (COSMED, Rome, Italy).

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Data were analyzed using Stata SE 15.0.

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Sample size	Participants from the San Francisco Bay Area were recruited over the course of 1 year. In both experiments, we set out to recruit 120 participants such that we had approximately n=20 participants in each cell for the 3 (actual genotype: high-risk, moderate-risk, protective) x 2 (perceived genotype: high-risk, protective) design. This sample size yielded approximately 80% power to detect medium effect size differences between those informed of high-risk and those informed that they have the protective genotype.
Data exclusions	Only data from participants who completed the full study were analyzed and no data were excluded from the analyses.
Replication	Experiment 2 provides a conceptual replication of Experiment 1.
Randomization	As described in the paper, all participants in both experiments were randomly assigned to receive either high-risk or protective genetic test results using a 1:1 ratio, so that approximately equal numbers of each of the three actual genotypes (high-risk, moderate-risk, and protective) received high-risk and protective genetic test results.
Blinding	In both experiments, experimenters were blind to participants' actual genotype and outcomes from participants' baseline session. Experimenters were also blind to participants' randomly assigned genotype 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 processed and analyzed the physiological data were blind to participants' actual and assigned genetic risk level.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> Unique biological materials
<input checked="" type="checkbox"/>	<input type="checkbox"/> Antibodies
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology
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Methods

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<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics	Participants were individuals from the San Francisco Bay Area, 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.
Recruitment	Participants were recruited via flyer that 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 and were aware that they would be paid \$85 for participation. This recruited population was likely biased towards people who are

interested in learning about their genetic risks and how to use genetic information to inform health behaviors and decisions.