Published in final edited form as:

Nat Hum Behav. 2019 January ; 3(1): 48–56. doi:10.1038/s41562-018-0483-4.

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

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Abstract

Millions of people now access personal genetic risk estimates for diseases such as Alzheimer's, cancer, and obesity[1]. While this information can be informative[2–4], research on placebo and nocebo effects[5–8] suggests that learning one's genetic risk may evoke physiological changes consistent with the expected risk profile. Here we tested whether merely learning 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 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 reports[1], and in 2017 alone, more people had their DNA analyzed with direct-to-consumer genetic tests than in all previous years combined[1]. Genetic risk estimates are now available for over 10,000 conditions and 16,000 genes[9], 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.

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Author Contributions: B.P.T. and A.J.C. conceived and designed the study. B.P.T., A.S., S.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.

Data Availability

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

Competing Interests Statement: The authors declare no competing interests.

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 behaviours[2]. Although precision medicine has had some early successes (e.g., genetically-targeted cancer treatments[3], safer cardiovascular medication dosing[4]), 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 genetic risk of disease had no effect on recipients' motivation to change behaviour or actual engagement in risk-reducing health behaviours[10]. 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 that guide people 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 elder adults with positive messaging about aging improves cardiovascular health compared to messages that confirm negative mindsets.[21] Individuals informed of 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 to individuals informed that stress is harmful and should be avoided[19,22]. Placebo effects, driven in large part by the 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 to providing people with an environmental or lifestyle causal account for a range of conditions, including mental illness, math performance, and obesity[11–17]. Studies that have examined the impact of actually receiving genetic risk information about diseases such as Alzheimer's[29,30], alcoholism[31], smoking-related diseases[32], or a multi-panel of diseases[33,34] show that individuals who learn that they are at high genetic risk compared to 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 receiving a higher genetic risk result for obesity can decrease perceived behavioural control[35,36], increase risk perceptions[37], increase negative affect[36], and lead to unhealthier dietary intake and decreased exercise three months later[33], other studies report

that individuals who learned that they were at higher (versus lower) genetic risk for obesity do not exhibit decreased perceived control,[38] intentions to eat healthier[38–41], or healthy eating behaviours[39–41].

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, and 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 one holds regarding their perceived genetic risk, can be distinct from actual genetic risk. However, properly assessing the effects of perceived genetic risk requires (a) DNA testing of participants in order to know whether each individual actually has the high-, moderate-, or low-risk/protective genotype for a disease, (b) randomly assigning half of 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 (c) measuring gene-relevant outcomes both prior to and again 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 to his/her own baseline when he/she was naïve of 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 genetic risk. Finally, this design makes comparing the relative effect sizes of perceived versus actual genetic risk on gene-relevant outcomes possible.

In spite of its benefits, this design is also 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 endeavored to overcome the methodological and ethical challenges. 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 held a potentially false belief about their genetic risk to approximately one hour 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 risk for 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 effects[26] 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 Figure 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 had on exercise capacity (Experiment 1) and satiety (Experiment 2) outcomes.

Experiment 1 explored the effect of perceived *CREB1* rs2253206 risk on exercise capacity. The *CREB1* rs2253206 high-risk genotype is associated with poorer aerobic exercise capacity[42–44], increased body temperature during aerobic exercise[42], and fewer cardiovascular improvements from participating in an exercise program[43,44] compared to 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 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 for poor exercise capacity compared to the other half of individuals who were informed that they had the protective *CREB1* genotype (M_{diff} = 3.46, 95% confidence interval (CI): [3.11, 3.81], $t(114) = 19.50$, $P < .001$, $d = 3.62$). 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* gene reported feeling more worry (M_{diff} = 1.88, 95% CI: [1.29, 2.47], $t(114) = 6.27$, $P < .001$, $d = 1.17$) and less control (M_{diff} = −0.79, 95% CI: [−1.25, −0.32], $t(105.5) = 3.35$, $P = .001$, $d = 0.63$) over their exercise capacity (Supplementary Figure 3).

As hypothesized, perceived genetic risk changed participants' cardiorespiratory physiology in a manner that mirrored participants' expectations. Using multilevel regression models, we observed a significant perceived genotype × session effect on maximum CO_2:O_2 exchange rate ($B = 0.034$, 95% CI: [0.008, 0.059], $P = .010$). Individuals informed that they had the

high-risk genotype reached a significantly lower maximum capacity for CO_2:O_2 gas exchange compared to their own baseline session (B = −0.023, 95% CI: [−0.041, −0.005], P = .013), while individuals informed that they had the protective genotype did not significantly differ from baseline (B = 0.011, 95% CI: [−0.007, 0.029], P = .25; Fig. 2a; Supplementary Tables 1 and 4). Perceived risk also had a marginally significant effect on maximum ventilatory flow rate (perceived genotype × session effect: B = 2.60, 95% CI: [−0.25, 5.46], P = .074). Individuals informed that they had the high-risk genotype significantly decreased in maximum ventilatory flow rate by more than 2 liters of air per minute on average compared to their baseline session (B = −2.06, 95% CI: [−4.10, −0.02], P = .047), while individuals informed that they had the protective genotype did not significantly change from baseline (B = 0.54, 95% CI: [−1.46, 2.55], P = .59; Fig. 2b; Supplementary Tables 1 and 4). Effect size comparisons (in standard deviation units, or Cohen's d) revealed that the effect of perceived genotype was greater than the effect associated with actual *CREB1* genotype on CO_2:O_2 exchange rate ($d_{perceived}$ = 0.50 vs d_{actual} = −0.14), but not ventilatory flow rate ($d_{perceived}$ = 0.08 vs d_{actual} = 0.12). Longitudinal analyses of the trajectories of CO_2: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 to their baseline performance, while individuals informed that they had the protective genotype increased their rate of change in CO_2: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 = .019). Individuals informed that they had the high-risk genotype stopped running 0.36 minutes (22 seconds) earlier compared to their baseline session (B = −0.36, 95% CI: [−0.58, −0.13], P = .002), while individuals informed that they had the protective genotype did not change from baseline (B = 0.02, 95% CI: [−0.20, 0.23], P = .88; Fig. 2c; Supplementary Tables 2 and 4). The effect size of perceived genetic risk was smaller than the effect associated with actual genotype on running endurance ($d_{perceived}$ = 0.16 vs d_{actual} = 0.41).

Finally, perceived genetic risk changed subjective experience. We observed a significant perceived genotype × session effect on individuals' subjective experience of perceived exertion (B = 0.72, 95% CI: [0.12, 1.33], P = .020) and perceived heat (B = 0.92, 95% CI: [0.05, 1.80], P = .039), consistent with the expectations provided to them about how difficult exercise would be and how hot they would feel while exercising. Individuals informed that they had the protective genotype ran 0.79 minutes (47 seconds) longer before indicating that the test felt "hard" (B = 0.79, 95% CI: [0.37, 1.22], P < .001) and 1.12 minutes (67 seconds) longer before indicating that they felt "hot" (B = 1.12, 95% CI: [0.49, 1.74], P < .001) compared to their baseline session, despite running at the same speed and incline grade as their baseline session. Individuals 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 = .75) or perceived heat (B = 0.19, 95% CI: [−0.42, 0.81], P = .54; Fig. 2d–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 ($d_{perceived}$ = 0.29 vs d_{actual} = 0.40) but was greater

than the effect size associated with actual genetic risk for perceived heat ($d_{perceived}$ = 0.34 vs d_{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 × perceived genotype × 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's* > .10 for all pairwise comparisons of the perceived genotype × 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 seconds 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 6–7). 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 high-risk genotype, the best-studied and most highly associated genetic risk factor for obesity[45], 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 signaling after food consumption[47]. Effect sizes for the relationship between *FTO* genotype and outcomes range from 0.2 – 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 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 for poor satiety (M_{diff} = 2.84, 95% CI: [2.46, 3.22], $t(105)$ = 14.66, P < .001, d = 2.83), and felt more worry (M_{diff} = 1.53, 95% CI: [0.91, 2.15], $t(101.1)$ = 4.91, P < .001, d = 0.94) and less control over satiety (M_{diff} = −0.56, 95% CI: [−1.02, −0.10], $t(105)$ = 2.42, P = .017, d = 0.47) compared to individuals who were informed that they had the protective *FTO* genotype (Supplementary Figure 3).

As hypothesized, perceived genetic risk changed physiological satiety in a manner that mirrored participants' expectations. We observed a significant perceived genotype × 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 = .028). Individuals informed that they had the protective genotype experienced a 2.5-fold greater increase in GLP-1 after food intake compared to their baseline (B = 17.75, 95% CI: [8.04, 27.46], P < .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 = .63; Fig. 3a, Supplementary Tables 3–4, 9–11). The effect size of perceived genetic risk on GLP-1 response was much greater than the effect associated with actual *FTO* genotype ($d_{perceived}$ = 0.66 vs d_{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 × session effect: B = 0.58, 95% CI: [0.07, 1.08], P = .025). Individuals informed that they had the protective genotype reported a 1.4-fold increase in fullness post-consumption compared to their baseline session (B = 0.55, 95% CI: [0.19, 0.90], P = .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 3–4). 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 ($d_{perceived}$ = 0.46 vs d_{actual} = −0.07).

Similar to Experiment 1, analyses of actual genotype × perceived genotype × 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's > .30 for all pairwise comparisons of the perceived genotype × 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 = .32; Supplementary Tables 3–4, 9–11). However, there was a significant actual genotype × perceived genotype × 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 = .027). Individuals who actually 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 actually had the protective *FTO* genotype exhibited the opposite trend (Supplementary Table 5). It is not clear why actual genotype impacted 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 beneficial effects of being told that one was protected rather than detrimental effects of being informed of high-risk.

These experiments examined whether learning 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 CO_2:O_2 gas exchange, decreased the amount of air with which participants supplied their lungs by more than 2 liters per minute, and decreased how long participants ran before giving up during strenuous aerobic exercise compared to their own performance one week prior 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 leveled 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 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 to when they consumed the same meal one week prior 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 (e.g., 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 show 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 to his/her baseline. Another potential mechanism is stress. It is possible that 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 mindset that is shaped almost immediately upon learning genetic risk[8,11,19,26,52]. The individual is, of course, genetically identical before and after receiving genetic information, yet the information they have been 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, 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 likely differs depending on the gene of interest and experimental paradigm. For example, the exercise test in Experiment 1 was a maximal exertion test. Therefore, there was little room for improvement. These results are consistent with results from an analogous cognitive performance paradigm demonstrating that elder adults who were informed that they had an increased genetic risk for Alzheimer's disease performed worse on memory tasks and judged their memory performance more harshly than elder adults who were also at increased genetic risk but were unaware of it.[30] 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 for a disease. Broadly, 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 risk[35] 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 to lower risk genetic information did not undermine, and sometimes increased, motivation to engage in healthier behaviours[35–38].The few randomized trials of disclosing genetic risk information for obesity to date found no difference in intentions to eat healthier or actual healthy eating at follow-up 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 increased risk for obesity was associated with unhealthier dietary intake and less exercise three months later[33]. 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 control[34]. Whereas the pamphlets that 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 to other information that may also impact expectations, such as information gleaned from one's family history, lifestyle risk (e.g., exercise, diet, sedentary behaviour), pharmacological risk (e.g., side effects of medications or procedures), metabolic risk (e.g., hormone levels, insulin sensitivity) or other biological indicators of health (e.g., 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 sufficient to change psychological, behavioural, and physiological outcomes1[5–7,19–28]. Several studies have specifically compared how individuals respond to receiving genetic risk information to non-genetic risk information. The limited evidence suggests that genetic risk information may have a greater impact on perceived risk level and emotions compared to either family history information[53] or metabolite levels[54], but does not differentially affect weight loss compared to lifestyle feedback[40] or information about family history and glucose levels[55]. 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 whether genetic risk information is differentially likely to instill self-fulfilling effects compared to 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, an important consequence 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]. Effects of perceived genetic risk on physiology are likely greater for conditions in which these systems are highly involved and less so for those that are not (e.g., tumor growth)[5]. The challenge of 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 manifest through different body systems than 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, policy makers, clinicians, genetic counselors and the genetic testing industry. Medical ethicists and policy makers 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 have largely ignored the potential influence of mindset effects. Clinicians, genetic counselors, and direct-to-consumer testing organizations should also 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 with best practices 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 one's genetic risk for 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 upon both.

METHODS

The experimental design for Experiments 1 and 2 is illustrated in Figure 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 that 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) × 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 have the protective genotype.

A total of 271 participants [$M = 25.3$ ($SD = 6.0$) 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* rs9939609 (Experiment 2; $N = 107$). In both experiments, participants within each of the three risk groups (high-risk, moderate-risk, protective) completed a baseline session prior to 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 participants within each actual 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 actual 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 report and pamphlets emphasized that the *CREB1* and *FTO* genes are quite predictive of exercise- and satiety-related outcomes, respectively. Participants then followed the same protocol as the baseline session, allowing for comparison of how each individual's outcomes changed from the baseline session depending upon whether he/she received high-risk or protective genetic risk information. This also allowed for the calculation of the effect size of perceived genetic risk alone on outcomes so that we could compare them to the effect sizes associated with actual genetic risk from the baseline session.

In Experiment 1, exploring 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 Figure 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 two 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 to 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, different paradigm, different outcomes, and different participants, Experiment 2 explored the effect of perceived *FTO* rs9939609 risk on satiety. Participants consumed the same 480-calorie meal at both sessions and had blood samples drawn pre-consumption, and 15 and 40 minutes post-consumption (Supplementary Figure 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 to 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 to 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 analyzed and no data were excluded from the analyses. 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. Detailed methods including detailed 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

This research is supported by the Foundation for the Science of the Therapeutic Encounter, the National Science Foundation GRFP Grant No. DGE-114747, and the National Institutes of Health DP2 AT009511 and U54EB020405. The funders had no role in the conceptualization, design, data collection, analysis, decision to publish, or preparation of the manuscript. Correspondence and requests for materials should be addressed to turnwald@stanford.edu or crum@stanford.edu. We thank Yael Rosenberg-Hasson, the Clinical Translational Research Unit, Human Immune Monitoring Center, Human Performance Lab and Protein and Nucleic Acid Facility at Stanford University for assistance in collection and processing of biological samples. We thank colleagues Carol Dweck, Hazel Markus, Kathryn Hall, and Greg Walton for comments on versions of this manuscript.

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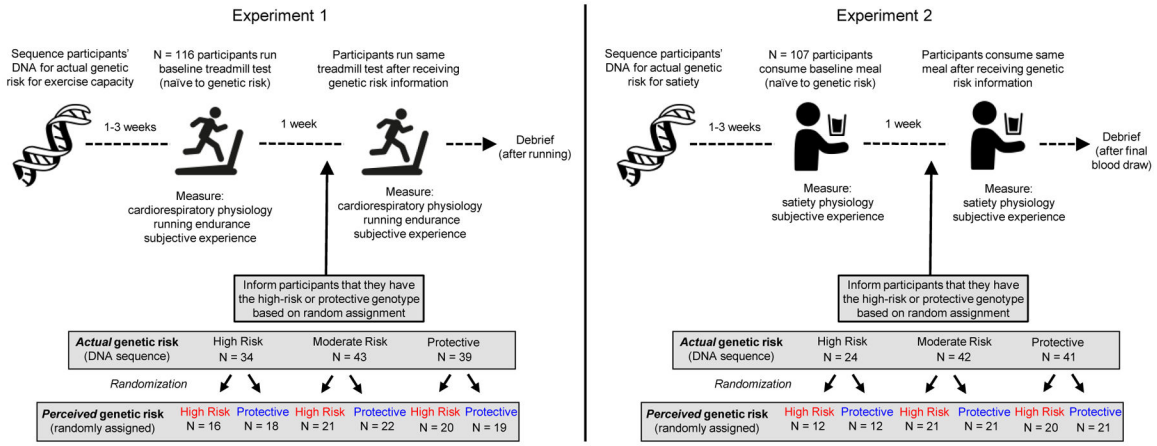

Fig. 1. Experimental design.

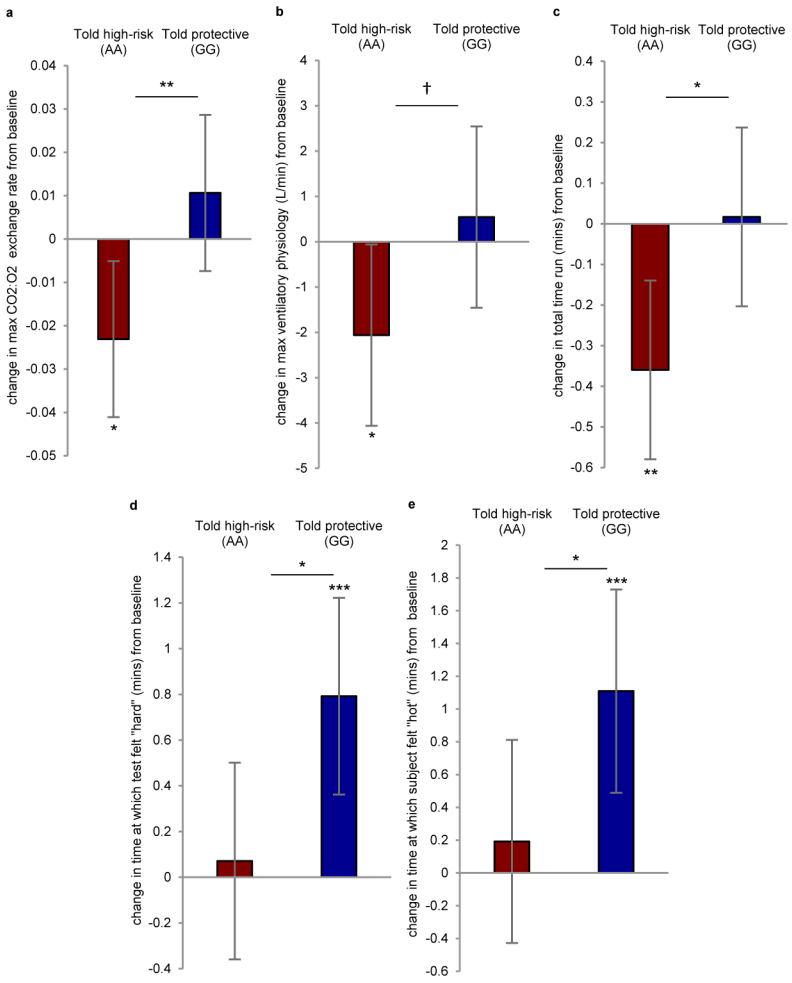

Fig. 2. Receiving genetic risk information for exercise capacity alters cardiorespiratory physiology, running endurance, and subjective experience.

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 strenous exercise in Experiment 1 (N=116). Bars represent means ± 95% CI from the multilevel regression model of the difference in participants' outcomes from their baseline session (naïve to genetic risk) to after receiving the genetic risk information that was randomly assigned to them. (**a**) Maximum respiratory exchange ratio, metabolic measure of CO_2: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.

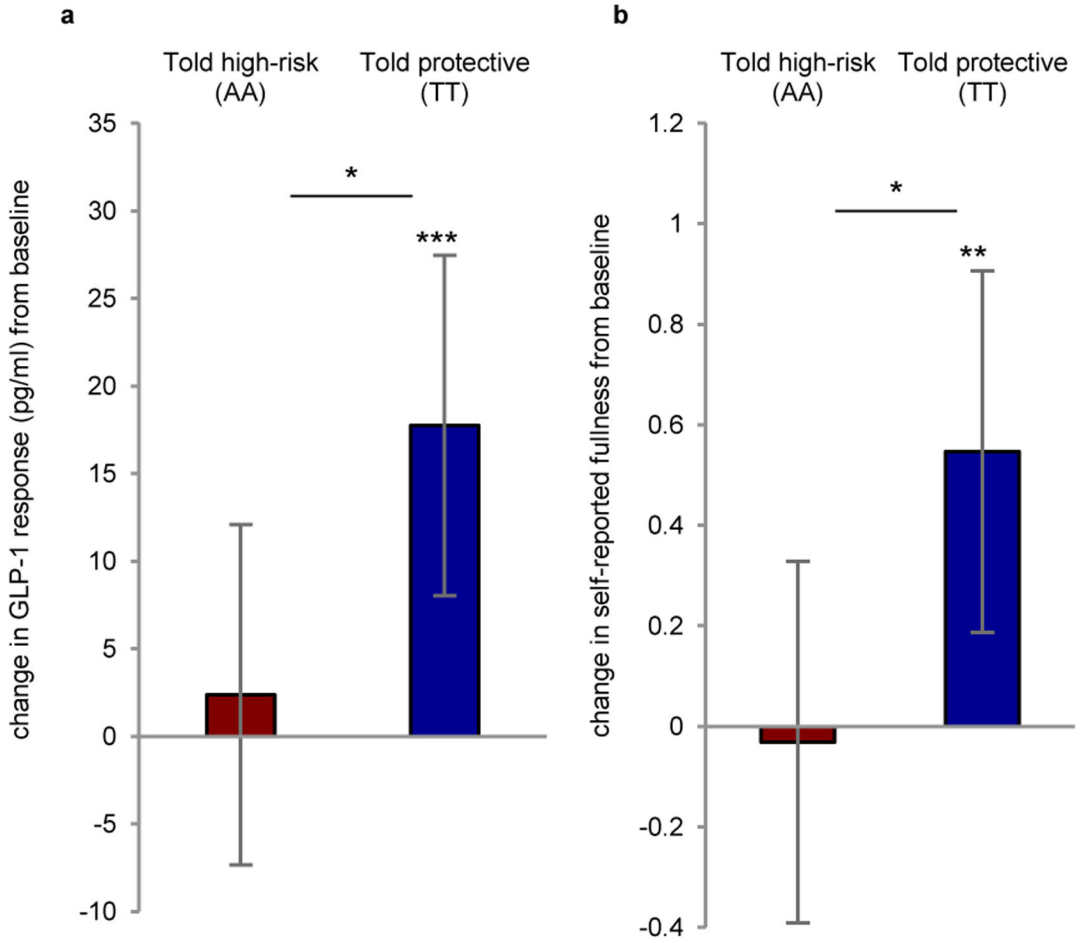

Fig. 3. Receiving protective genetic risk information for satiety increases physiological and self-reported satiety.

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 minutes after consuming a 480-calorie meal in Experiment 2 (N=107). Bars represent means ± 95% CI from the multilevel regression model of the difference in participants' outcomes from their baseline session (naïve to genetic risk) to after receiving the genetic risk information that was randomly assigned to them. (**a**) Glucagon-like peptide 1 (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.

Table 1.

Effect sizes for actual genetic risk versus perceived genetic risk in Experiments 1 and 2.

	Actual genotype	Perceived genotype
	d	***d***
Experiment 1		
Max CO_2:O_2 exchange rate	**−.14**	**.50**
Max ventilatory flow rate	.12	.08
Running endurance	.41	.16
Perceived exertion	.40	.29
Perceived heat	**.14**	**.34**
Experiment 2		
GLP-1 (physiological satiety)	**.09**	**.66**
Acyl-ghrelin (physiological hunger)	.21	−.25
Perceived satiety (fullness)	**−.07**	**.46**

Note: 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, and 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. 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* = effect size (standard deviation units), GLP-1 = glucagon-like peptide 1.