Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

A Randomized Trial Examining the Impact of Communicating Genetic and Lifestyle Risks for Obesity

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Objective: Genetic testing for obesity is available directly to consumers, yet little is understood about its behavioral impact and its added value to nongenetic risk communication efforts based on lifestyle factors.

Methods: A randomized trial examined the short-term impact of providing personalized obesity risk information, using a 2 × 2 factorial design. Participants were recruited from the Coriell Personalized Medicine Collaborative (CPMC) and randomized to receive (1) no risk information (control), (2) genetic risk, (3) lifestyle risk, or (4) combined genetic/lifestyle risks. Baseline and 3-month follow-up survey data were collected. Analyses examined the impact of risk feedback on intentions to lose weight and self-reported weight.

Results: A total of 696 participants completed the study. A significant interaction effect was observed for genetic and lifestyle information on intent to lose weight ($P = 0.0150$). Those who received genetic risk alone had greater intentions at follow-up, compared with controls ($P = 0.0034$). The impact of receiving elevated risk information on intentions varied by source and combination of risks presented. Non-elevated genetic risk did not lower intentions. No group differences were observed for self-reported weight.

Conclusions: Genetic risk information for obesity may add value to lifestyle risk information depending on the context in which it is presented.

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Introduction

Obesity is known to have multiple contributing factors, yet with heritability estimates ranging from 81% to 92%, the contribution of genetics is indisputable (1,2). Reviews have identified more than 50 genes associated with obesity as defined by increased body mass index (BMI) or waist-to-hip ratio (3,4). Despite ongoing discoveries, the *FTO* gene continues to garner attention in the obesity research community. The rs9939609 variant of the *FTO* gene is located at 16q12.2 and associated with body weight increase by 1.2 kg per A-allele (5). Approximately 16% of adults are homozygous for the high-risk allele (AA), which is associated with higher odds of obesity (OR = 1.47 in males; 1.46 in females) (6). Exercise can successfully blunt the effects of the rs9939609 variant, suggesting that additional efforts to motivate individual behavior change to offset genetic influences are important for weight management (7-9).

Consistent with U.S. national efforts to usher in a new era of precision medicine (10), efforts to convey genetic risk for common complex conditions have been undertaken in attempts to identify those at greater risk and motivate lifestyle behavior change (11). To date, the clinical utility of genetic testing for obesity has been largely

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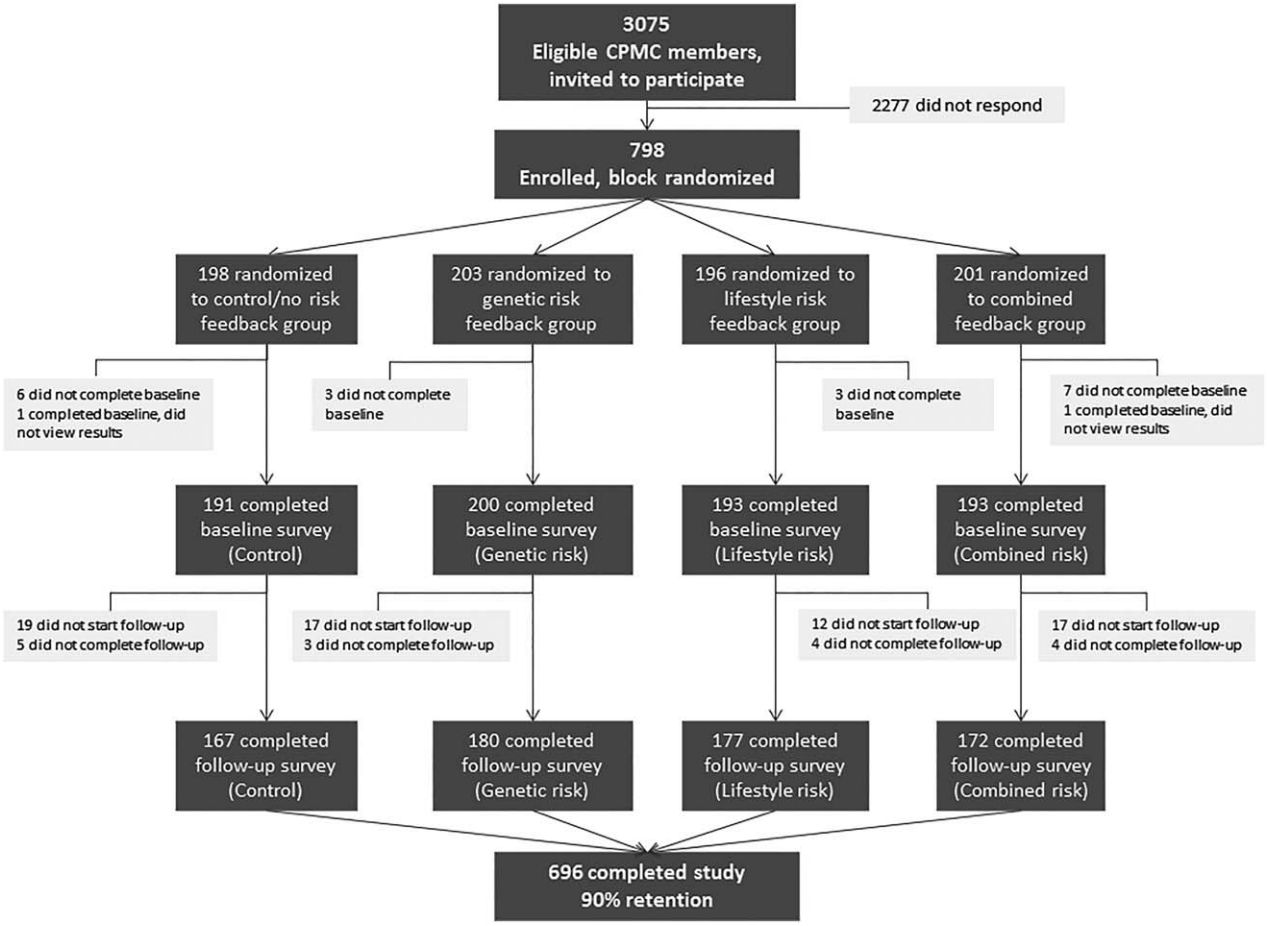

Figure 1 Study CONSORT diagram.

based on limited evidence. Research based on opinion surveys or vignette-based studies have suggested that genetic information would be beneficial and increase motivation to adopt healthy weight management behaviors (12-15). Yet concerns have been raised about the possibility of increasing fatalistic or deterministic reactions in response to higher risk status, or false reassurance due to lower risk status, thereby discouraging individuals from engaging in healthy lifestyle behaviors (15,16). Pilot studies among overweight adults, however, have found that confidence in ability to lose weight is not undermined by receiving elevated genetic risk results for obesity (17) and that some are more motivated to overcome their genetic predisposition (18). Only one other randomized trial has examined the effects of obesity genetic risk feedback. This study targeted first-year undergraduate students in the UK during a transition period where the likelihood of weight gain is increased (19,20) and found that *FTO* test feedback, provided alongside a leaflet offering tips to control weight, resulted in greater readiness to control weight at 1 month follow-up compared with controls who received the leaflet only. Moreover, those who were at higher risk based on their *FTO* variant status had greater readiness to change compared with controls.

It is unclear whether genetic risk is perceived any differently from other risk factors for obesity (i.e., source of risk assessment). Prior research has noted that genetic risk has a greater influence on risk perceptions and decision making compared with nongenetic risk when presented separately, suggesting an inherent value in receiving risk information derived from genetic testing (21,22). Efforts are needed to understand the impact of conveying risk when it is based on genetic versus nongenetic factors (23) and also to determine whether genetic risk information adds value when combined with lifestyle risk intervention efforts (24).

The Obesity Risk Communication Study is a randomized controlled trial designed to examine the short-term impact of providing personalized obesity risk information, using a 2 × 2 factorial design (25). Obesity risk was ascertained from two sources: (I) genetic risk based on *FTO* genotype (6), and (II) lifestyle risk based on hours spent sitting and watching television (26). In this report, we present the main results of the trial, focused on weight-related intentions and outcomes. There were two research aims specified for the trial (25):

- Aim 1: To examine the effects of providing genetic risk information, alone or in combination with lifestyle risk information, on participants' intentions to lose weight and self-reported weight.

- Aim 2: To determine the extent to which the effects of risk information vary as a function of risk status (elevated vs. non-elevated).

Methods

Study population

This study was conducted as an ancillary study within the Coriell Personalized Medicine Collaborative (CPMC), an ongoing longitudinal study designed to determine the utility of using genome information in clinical decision making. Described elsewhere (27), the CPMC has recruited people to different research cohorts, performed genetic analysis, and provided genetic risk feedback via an online patient portal for over 20 common complex conditions, as well as drug metabolism. Ethics approval was obtained from Boston University and Coriell.

Study intervention

The Internet-based obesity intervention consisted of a risk report containing information on obesity risk factors and personalized risk as specified within experimental arm (see Online Supporting Information). All participants were provided with background including definitions of obesity and BMI, and obesity prevalence rates in the United States. Those randomized to receive genetic risk information were presented with relative risk estimates based on their *FTO* genotype (RR = 1.0, TT; RR = 1.1, AT; RR = 1.3, AA) (6). Participants randomized to receive lifestyle risk information were presented with relative risk estimates based on self-reported time spent sitting while watching television (RR = 1.0, no more than 1 h/week; RR = 1.2, 2–5 h/week; RR = 1.4, 6–20 h/week; RR = 1.7, 7–40 h/week; RR = 1.9, greater than 40 h/week) (26).

Procedures

All active CPMC enrollees were eligible to participate in the obesity study 90 days after they received their initial CPMC risk results for other conditions. Eligible participants were notified of the obesity study via a series of emails and could link to the CPMC Web portal for further study details, review study consent document, and provide consent online. Once enrolled, participants were stratified by CPMC cohort and *FTO* genotype and randomized to one of four study arms: (1) no risk information (control), (2) genetic risk only, (3) lifestyle risk only, or (4) combined genetic/lifestyle risks (see Figure 1). Participants received personalized risk information online via the CPMC patient portal. Surveys were administered at baseline and 3-month follow-up. Additional study details are presented elsewhere (25).

Measures

Demographics. Demographic information collected from study participants included age, gender, education, race/ethnicity, and self-reported weight and height.

Intention to lose weight. A single item asked participants "I intend to lose 10 pounds or more in the next 6 months." Responses were based on a 5-point Likert ranging from strongly disagree to strongly agree.

Self-reported weight. A single item asked participants to indicate their weight in pounds. Change in weight was derived based on the difference in self-reported weight from baseline to 3-month follow-up.

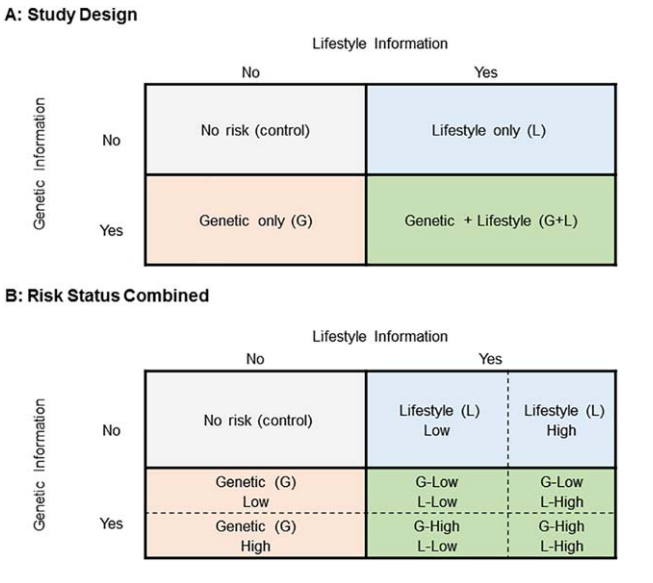

Figure 2 (**A**) Study design (2 × 2 factorial) and (**B**) risk status combinations (nine groups). [Color figure can be viewed at wileyonlinelibrary.com.]

Data analyses

Descriptive statistics included means, standard deviations, and counts with percentages. Randomization effectiveness was examined by comparing and testing distributions of baseline variables by intervention arm using cross-tabulation with chi-square or Fisher's exact tests as appropriate. Any lack of balance on these variables between the arms was addressed by the inclusion of these variables as covariates in multivariable analyses.

Genetic risk was dichotomized as non-elevated (no risk variant) and elevated (one or two risk variants) for the purposes of multivariable analyses. Lifestyle risk was dichotomized by comparing those who watched 5 h or less of television a week versus those who watched more than 5 h a week. For ease of communication in this report, we use descriptors of low and high to label our risk categories, acknowledging that actual risk quantification as "high" is relative.

We ran three linear regression models to examine the effect of experimental arm (aim 1) on intentions to lose weight, self-reported weight at follow-up, and change in weight from baseline to follow-up. Models adjusted for age, gender, BMI or weight, and length of time between survey completions (follow-up time). As an additional precaution, we examined whether the study arms were balanced by genetic risk for other related health conditions included in the CPMC parent study (i.e., coronary artery disease [CAD] and type 2 diabetes [T2D]). Genetic risk for CAD did vary significantly across study arms and thus was adjusted for in the models.

The study design generated nine possible obesity risk status combinations (Figure 2). To examine the effect of obesity risk status (aim 2), we ran four linear models for each dependent variable. First, we

TABLE 1 Participant demographics

	No risk (control), *N* = 167, *N* (%)	Genetic only, *N* = 180, *N* (%)	Lifestyle only, *N* = 177, *N* (%)	Genetic + lifestyle, *N* = 172, *N* (%)	Total *N* = 696, *N* (%)
Age, Demographic (*M*)	51	51	51	48	50
21–30	20 (12)	19 (11)	17 (10)	27 (16)	83 (12)
31–45	31 (19)	36 (20)	42 (24)	47 (27)	156 (22)
46–64	92 (55)	96 (53)	93 (52)	72 (42)	353 (51)
65+	24 (14)	29 (16)	25 (14)	26 (15)	104 (15)
Gender					
Male	56 (34)	59 (33)	59 (33)	50 (29)	224 (32)
Female	111 (66)	121 (67)	118 (67)	122 (71)	472 (68)
Education					
<HS/HS grad/GED	9 (5)	5 (3)	8 (5)	5 (3)	27 (4)
Some college	17 (10)	19 (11)	23 (13)	14 (8)	73 (11)
Associate's degree	11 (7)	19 (11)	12 (7)	16 (9)	58 (8)
Bachelor's degree	59 (35)	58 (32)	65 (37)	65 (38)	247 (35)
Graduate degree	71 (43)	79 (44)	69 (39)	72 (42)	291 (42)
Race/ethnicity					
White, non-Hispanic	155 (93)	166 (92)	161 (91)	154 (90)	636 (91)
Hispanic/Latino	2 (1)	3 (2)	7 (4)	3 (2)	15 (2)
African American	2 (1)	4 (2)	2 (1)	4 (2)	12 (2)
Asian	5 (3)	1 (1)	1 (1)	6 (3)	13 (2)
Multiracial	1 (1)	5 (3)	6 (3)	5 (3)	17 (2)
Unknown	2 (1)	1 (1)	–	–	3 (<1)
BMI					
Underweight (<18.5)	2 (1)	2 (1)	–	4 (2)	8 (1)
Normal (18.5-24.9)	67 (40)	67 (37)	70 (40)	63 (37)	267 (38)
Overweight (25.0–29.9)	50 (30)	70 (39)	56 (32)	56 (33)	232 (33)
Obesity (≥30.0)	47 (28)	40 (23)	51 (29)	48 (28)	186 (27)
Missing	1 (<1)	1 (<1)	–	1 (<1)	3 (<1)
FTO genotype (# risk variant copies)					
TT (no copies)	60 (36)	69 (38)	68 (38)	63 (37)	260 (37)
AT (one copy)	82 (49)	83 (46)	85 (48)	82 (48)	332 (48)
AA (two copies)	25 (15)	28 (16)	24 (14)	27 (16)	104 (15)
Lifestyle risk (hours of TV per week)					
0–1	8 (5)	20 (11)	12 (7)	14 (8)	54 (8)
2-5	36 (22)	39 (22)	42 (24)	39 (23)	156 (22)
6-20	99 (59)	90 (50)	101 (57)	94 (55)	384 (55)
21–40	21 (12)	28 (15)	18 (10)	23 (13)	90 (13)
>40	3 (2)	3 (2)	4 (2)	2 (1)	12 (2)
CAD genotype (# risk variant copies)[a]					
GG (no copies)	48 (29)	40 (22)	44 (25)	67 (39)	199 (29)
GC (one copy) or CC (two copies)	119 (71)	140 (78)	133 (75)	105 (61)	497 (71)

[a]From parent CPMC study. χ^2 *P* value = 0.0031.

examined the impact of risk among those in groups that received risk information from a single risk factor (i.e., genetic or lifestyle) compared with controls. Next, we examined the effect of risk status among participants in the combined feedback arm compared with controls. Finally, we ran two linear models to explore the added value of risk information that was derived from a different source. Thus, to examine the added value of lifestyle information, controls were compared with those receiving high genetic risk, high genetic/low lifestyle risk, or high on both genetic and lifestyle risk. Similarly, the added value of genetic information was examined by comparing controls to those receiving high lifestyle risk, high lifestyle/low genetic risk, or high on both lifestyle and genetic risk.

TABLE 2 Impact of experimental arm on intent to lose weight and weight outcomes (aim 1)

	Intention to lose weight ($N = 693$)		Weight (lbs) at follow-up ($N = 691$)		Change in weight (lbs) ($N = 691$)	
Predictor variable	β (SE)	P	β (SE)	P	β (SE)	P
Intercept	−0.0114 (0.2086)		5.0280 (1.4553)		4.1092 (1.3634)	
Age	−0.0000 (0.0023)	0.9991	−0.0019 (0.0150)	0.8988	0.0010 (0.0151)	0.9496
Gender						
Female	0.0735 (0.0694)	0.2899	−0.5855 (0.4797)	0.2226	0.0399 (0.4481)	0.9292
Male (ref)						
BMI	0.0369 (0.0064)	<0.0001	–		−0.1127 (0.0347)	0.0012
Baseline measure of outcome	0.6299 (0.0299)	<0.0001	0.9798 (0.0054)	<0.0001	–	
Follow-up time	−0.0005 (0.0006)	0.4356	−0.0043 (0.0039)	0.2746	−0.0043 (0.0040)	0.2790
CAD genotype						
One or two copies	−0.0057 (0.0717)	0.9361	−1.2787 (0.4666)	0.0063	−1.2913 (0.4677)	0.0059
0 Copies (ref)						
Experimental arm						
Genetic	0.3130 (0.0910)	0.0158	0.3165 (0.5923)	0.9353	0.2776 (0.5939)	0.9473
Lifestyle	0.2055 (0.0910)	0.4525	−0.0947 (0.5924)	0.3690	−0.1729 (0.5929)	0.3147
Genetic × lifestyle	−0.3142 (0.1288)	0.0150	−0.5648 (0.8398)	0.5015	−0.4996 (0.8414)	0.5529
R^2	0.5765		0.9823		0.0290	

Results

Participant demographics

A total of 696 of 777 participants completed both baseline and follow-up surveys, resulting in a retention rate of 90%. The average age of participants was 50 years, 68% were female, 93% were White, and 60% had a BMI of 25 or greater at baseline (Table 1). Distribution of *FTO* genotype was similar to overall population distribution patterns (6). Demographics did not differ significantly across study arms, with the exception of CAD genotype (P = 0.0031).

Effect of experimental arm (aim 1)

Intention to lose weight. A significant interaction effect between genetic feedback and lifestyle feedback was found for intention to lose 10 pounds or more in the next 6 months (P = 0.0150; Table 2). *Post hoc* analyses revealed that those who received genetic only information had greater intentions to lose weight at follow-up (M = 3.37, 95% CI: 2.24–3.50), compared with those who received no risk information/controls (M = 3.06; 95% CI: 2.92–3.19, P = 0.0034). Those who received lifestyle only information did not differ in intentions compared with any of the other groups (M = 3.26, 95% CI: 3.13–3.39). Providing both genetic and lifestyle risks combined did not result in greater intentions (M = 3.26, 95% CI: 3.13–3.39). Additional analyses stratifying by BMI revealed that the interaction effect observed between genetic feedback and lifestyle feedback was significant among participants who were normal weight (P = 0.0222) but not those with overweight/obesity (P = 0.1682; Supporting Information Table S1).

Self-reported weight. Analyses for self-reported weight at follow-up and change in weight over time did not reveal any significant effects by study arm (Table 2). Notably, genetic risk for CAD, which served as a covariate in the models, was associated with weight outcomes. Those who were at elevated CAD risk based on genotype weighed less at follow-up (P = 0.0063) and had greater reductions in weight over time (P = 0.0059), compared with those at non-elevated CAD risk.

Effect of obesity risk status (aim 2)

Intention to lose weight. Table 3 presents the results examining the impact of risk status on intentions. Model 1 examining the impact of a single risk showed a significant effect of risk status (P = 0.0102). *Post hoc* analyses demonstrated that those receiving a high genetic risk had greater intentions compared with controls (P = 0.0365; Figure 3). No other pairwise comparisons were significant. Model 2 examining the impact of combined risks did not reveal a statistically significant effect of risk status (P = 0.0718). *Post hoc* analyses comparing controls versus those who received elevated risk for both genetic and lifestyle was also modest (P = 0.0622).

Models 3 and 4 examined the added value of either lifestyle or genetic risk. The results showed similar patterns to models 1 and 2. Model 3 showed a significant effect of risk status (P = 0.0096); those receiving high genetic risk only had greater intentions to lose weight compared with controls (P = 0.0135; see Figure 4). Receiving a combined high genetic but low lifestyle risk did not result in differences compared with controls (P = 0.7116). Receiving high risk for both genetic and lifestyle showed a borderline difference compared with controls (P = 0.0656). Model 4 showed a modest effect of risk status (P = 0.0625), but also saw a significant difference in intentions between controls and those receiving a combined high lifestyle and high genetic risk difference (P = 0.0474).

Self-reported weight. Although there are no significant differences by study arm for self-reported weight outcomes, we ran the models

TABLE 3 Impact of obesity risk status on intent to lose 10 lbs or more in the next 6 months (aim 2)

	Model 1 (N = 522), single risk		Model 2 (N = 337), combined risk		Model 3 (N = 385), added value—lifestyle		Model 4 (N = 407), added value—genetic	
Predictor variable	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P
Intercept	−0.0459 (0.2421)		−0.1348 (0.2639)		−0.2544 (0.2715)		−0.0506 (0.2367)	
Age	−0.0014 (0.0028)	0.6233	0.0033 (0.0030)	0.2716	0.0040 (0.0031)	0.1944	0.0006 (0.0027)	0.8234
Gender								
Female	0.0781 (0.0808)	0.3341	0.0293 (0.0939)	0.7551	0.1425 (0.0933)	0.1276	0.0661 (0.0833)	0.4279
Male (ref)								
BMI	0.0391 (0.0072)	<0.0001	0.0379 (0.0092)	<0.0001	0.0403 (0.0091)	<0.0001	0.0333 (0.0072)	<0.0001
Baseline intent to lose weight	0.6306 (0.0350)	<0.0001	0.6661 (0.0397)	<0.0001	0.6457 (0.0391)	<0.0001	0.6902 (0.0362)	<0.0001
Follow-up time	−0.0004 (0.0007)	0.5615	−0.0010 (0.0008)	0.2148	−0.0016 (0.0009)	0.0697	−0.0008 (0.0008)	0.3599
CAD genotype (one or two copies)	0.0347 (0.0871)	0.6903	−0.1517 (0.0912)	0.0972	−0.0497 (0.0956)	0.6033	−0.0793 (0.0835)	0.3431
Risk feedback group		0.0102						
No risk (control)	Ref							
Gene low	0.3278 (0.1234)							
Gene high	0.3008 (0.1055)							
Life low	0.3327 (0.1344)							
Life high	0.1451 (0.1023)							
				0.0718				
No risk (control)			Ref					
Gene low/life low			0.2888 (0.1085)					
Gene low/life high			0.0336 (0.1362)					
Gene high/life low			0.1538 (0.1489)					
Gene high/life high			0.3059 (0.1086)					
						0.0096		
No risk (control)					Ref			
Gene high					0.3107 (0.1022)			
Gene high/life low					0.1702 (0.1599)			
Gene high/life high					0.2884 (0.1165)			
								0.0625
No risk (control)							Ref	
Life high							0.1418 (0.0904)	
Life high/gene low							0.0589 (0.1331)	
Life high/gene high							0.2759 (0.1061)	
R^2	0.5721		0.6590		0.6119		0.6567	

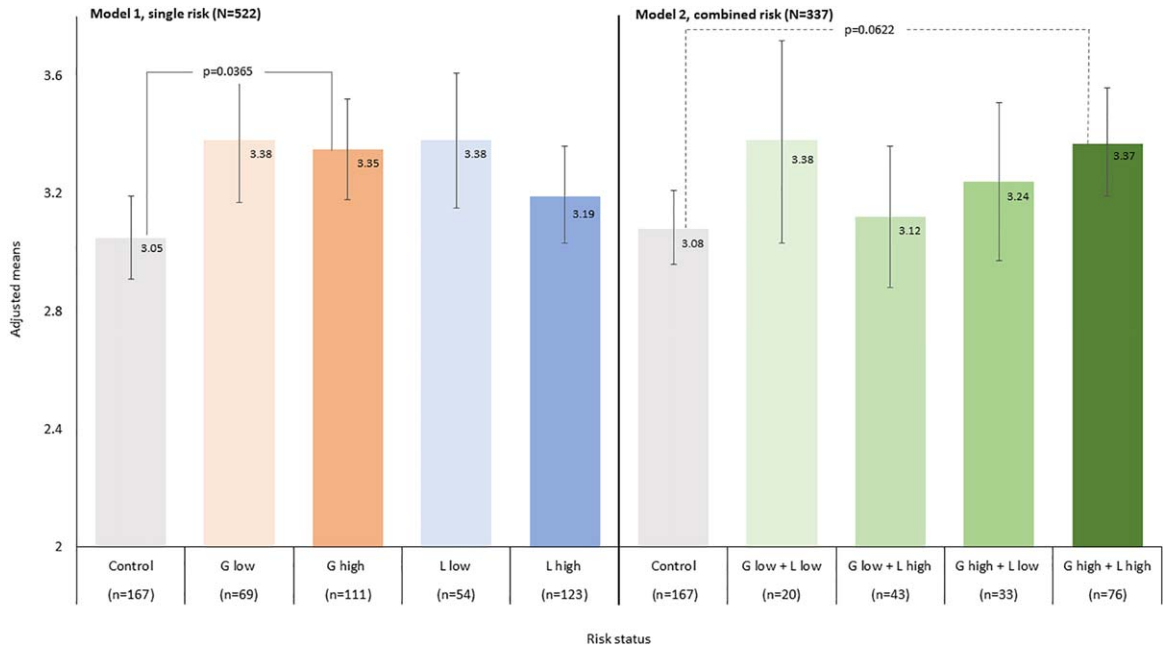

Figure 3 Aim 2, Impact of risk status on intention to lose 10 pounds or more in the next 6 months. [Color figure can be viewed at wileyonlinelibrary.com.]

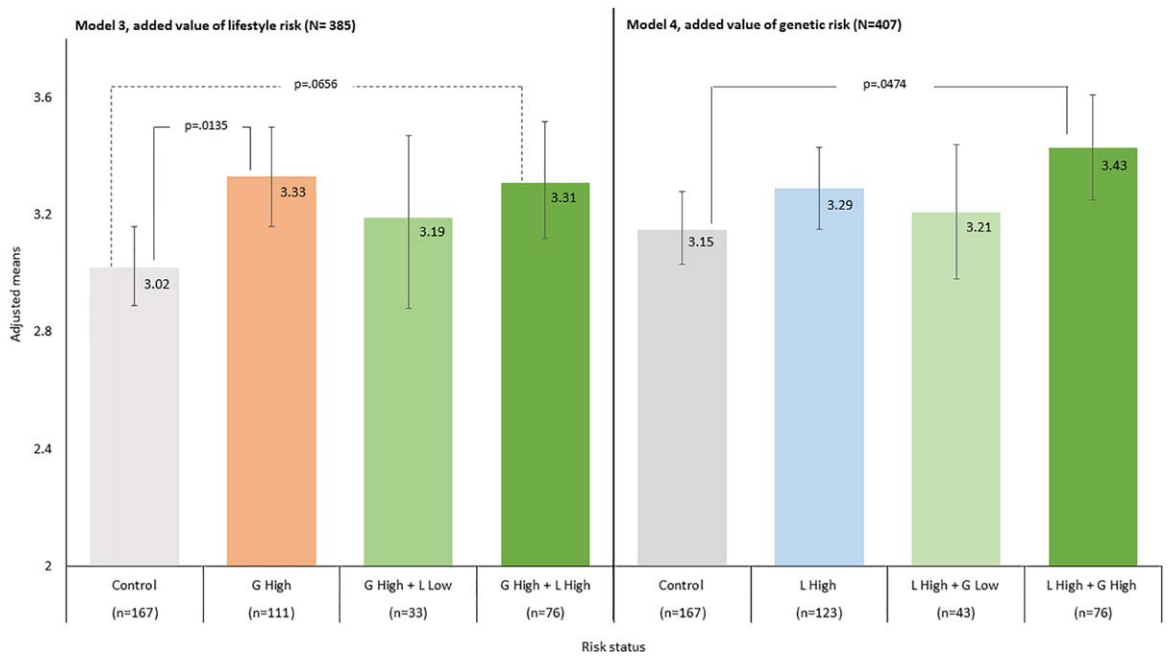

Figure 4 Aim 2, Impact of risk status on intention to lose 10 pounds or more in the next 6 months—added value models. [Color figure can be viewed at wileyonlinelibrary.com.]

to examine the effects of obesity risk status on weight outcomes. No significant differences by risk status were observed (data not shown).

Discussion

The impact of obesity genetic risk information depends on the context in which it is presented. Analyses by study arm revealed that the provision of genetic information was more effective at influencing weight loss intentions, particularly when presented alone and not in combination with lifestyle risk. Two inferences can be made from these results. First, irrespective of actual level of genetic risk conveyed, those in the genetic arm expressed greater intention to lose weight. Unlike prior vignette studies (14,15), weight loss intentions in this study did not significantly differ between those in the genetic only arm who received elevated versus non-elevated genetic risk. Rather, the only significant difference was between those receiving elevated genetic risk compared with control participants. It is possible that individuals may not be distinguishing between genetic risk values presented. We did not follow up with participants, however, to determine the extent to which they differentiated between the risk categories.

Second, providing risk estimates from different sources may result in worse outcomes due to the mixed messages participants are receiving when estimates are discordant. The risk status groups compared in the added-value analyses (model 3) closely mimic how vignette studies have previously been designed, with an increased genetic risk scenario (13). The findings clearly showed that any benefit of presenting elevated genetic risk is offset when discordant, non-elevated lifestyle risk is also presented. Conversely, model 4 suggests that genetic risk information may add value to lifestyle risk information, but only when disease risks are concordant "high."

Study findings are in contrast to prior research that has shown no discernable impact of personalized genetic risk information (for diabetes) on weight loss motives or intentions (28). The lack of benefit of genetic information in prior studies may be partly attributed to their focus on overweight individuals. A strength of this study is its inclusion of both healthy-weight and overweight individuals. Analyses stratified by BMI showed that the interaction effect observed for experimental arm on intentions remained significant among those who were underweight or normal weight but was not significant for those with overweight or obesity (Supporting Information Figure S1). In this study, 57% of those in the underweight/normal-weight group had one (45%) or two (12%) copies of the risk variant placing them at greater risk for obesity, representing a sizable portion of this subgroup receiving elevated genetic risk feedback. Genetic risk information may be more salient for those who are not yet overweight and viewed as a reason to take action to reduce the likelihood of weight gain. Interestingly, the only other *FTO* feedback trial found that the impact of genetic risk on readiness to prevent weight gain was greater for those who were overweight, compared with normal weight (20). However, that study focused on undergraduate university students, the majority (89%) of whom were not (yet) overweight and might not see the relevance of the information unless they had already experienced weight-related struggles. Future studies are needed to clarify potential differences in the effects of genetic risk information across age and BMI spectrums to determine whether there are optimal time points at which this type of information might generate greater motivating responses.

Our study findings only partially supported our original hypotheses for trial outcomes, pertaining to weight loss intentions. We did not observe any significant differences by study arm for self-reported weight loss or for other behavioral intentions and lifestyle behaviors examined (Supporting Information Tables S2 and S3). Our lack of significant findings for weight outcomes is consistent with other studies looking at implications of genetic risk information for diabetes (28-30) and obesity (20). Our trial used a simple manipulation in terms of the risk information presented and was not designed around an existing, well-validated intervention previously demonstrated to change behaviors. Nonetheless, findings suggest that there may be a motivational benefit of providing genetic information, particularly among healthy-weight individuals. If paired with known strategies to facilitate changes in lifestyle behaviors, genetic risk communication efforts may enhance the success rate of those interventions and provide additional motivation (and added value) to help individuals plan for healthy weight maintenance (11,24).

We also examined the impact of receiving non-elevated genetic risk for obesity. Concerns have previously been raised about the potential negative implications (i.e., false reassurance) of "low" genetic risk feedback in this context (15,16). Our results support the findings from other obesity studies indicating no such adverse outcomes (20,31).

There were several limitations to our study. First, all study measures were based on self-reports. Study participants were predominately White and had high educational backgrounds, thus limiting the generalizability of these findings to certain populations. Due to the nature of the study design, the resulting nine different risk status combinations presented challenges in terms of uneven participant numbers for some cells and noted in the width of confidence intervals for the smaller cells. Power to detect significant effects for risk status (aim 2) was modest and varied from 57% to 81% depending on the model. For example, with sample size of 407 in model 4, we had 57% power to detect the difference among control, L high, L high + G low, and L high + G high groups with adjusted means (SD) 3.15 (0.81), 3.29 (0.81), 3.21 (0.77), and 3.43 (0.79), respectively. The power differences by model likely underlie the borderline trend differences observed.

All participants were participants in a parent CPMC study and thus were already interested in genetic information by nature of cohort participation. Prior to entering our trial, participants also received other genetic information for common diseases including CAD and T2D. Adjusting for CAD genotype, we noted a significant association with self-reported weight outcomes in the anticipated direction wherein greater risk corresponded to greater weight loss. It is possible that CAD genotype may have attenuated our obesity risk results for weight loss. Prior research has shown that heart attack is the most feared condition out of 23 conditions tested for via direct-to-consumer genetic testing, endorsed by 19.1% of participants, compared with 8.7% who endorsed obesity (32). It is conceivable that CAD genotype may have greater influence on weight outcomes due to differences in concerns about the disease, relative to obesity. We conducted additional analyses that included T2D genotype and did not find a significant association with weight outcomes, while CAD

remained significant in the model. A composite genotype score for CAD and T2D (i.e., elevated risk for 0, 1, or 2 conditions) reflecting a "dose" measure of genotype was also not associated with weight outcomes (data not shown).

Study findings have implications for future research examining the clinical utility of genetic results. First, there is a need to reframe the primary question of clinical utility from "Does genetic information motivate?" to ones that ask "How might genetic information motivate? Or for whom?" Almost every trial examining the clinical utility of genetic information for weight management has focused on an overweight target population (28-30,33). The results of our study may have been markedly different had only overweight individuals been included. Efforts to examine possible subgroup differences in responses are very much needed.

Second, research is needed to better understand how genetic risk for various conditions is processed by individuals and influences the outcomes of interest. Are there certain conditions that are more salient and attenuate the effects of others? Is there a dose effect or even a threshold effect, such that elevated genetic risk information only has an effect if a greater number or a specific number of diseases is indicated? These questions apply especially to ongoing studies examining the impact of direct-to-consumer genetic results or newer efforts to provide risk information based on whole-exome or whole-genome sequencing wherein risks for multiple conditions are presented to individuals. There is evidence to suggest that not all genetic information is equally motivating (34) and that combining information from different conditions can improve behavioral outcomes (35).

Third, studies that present multiple sources of risk for a single condition (e.g., demographics, family history, biomarkers, genetics) will need to be mindful of the possibility of conveying mixed messages, which may offset any benefit of genetic information due to discordant risk results (28,33) and consider these issues in the design of studies moving forward.

Finally, studies should strive to power on analyses needed to detect differences by risk status, which has been an ongoing challenge (11,29,36). Although our study team made every attempt to maximize study recruitment and retention (25), we were still underpowered to detect some of the effects we were hypothesizing.

Conclusion

Findings from the present study suggest that genetic risk for obesity can add value to other nongenetic risk information in terms of motivation to lose weight, but its impact will depend on the context in which the risk is presented. Future studies examining how genetic information is motivating or *for whom* may help to advance our understanding of its clinical utility.O

References

1. Bulik CM, Sullivan PF, Kendler KS. Genetic and environmental contributions to obesity and binge eating. *Int J Eat Disord* 2003;33:293-298.
2. Thomsen SF, Ulrik CS, Kyvik KO, et al. Association between obesity and asthma in a twin cohort. *Allergy* 2007;62:1199-1204.
3. Fall T, Ingelsson E. Genome-wide association studies of obesity and metabolic syndrome. *Mol Cell Endocrinol* 2014;382:740-757.
4. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015;518:197-206.
5. Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 2007;316:889-894.
6. Qi L, Kang K, Zhang CL, van Dam RM, et al. Fat mass- and obesity-associated (FTO) gene variant is associated with obesity longitudinal analyses in two cohort studies and functional test. *Diabetes* 2008;57:3145-3151.
7. Mustelin L, Silventoinen K, Pietilainen K, Rissanen A, Kaprio J. Physical activity reduces the influence of genetic effects on BMI and waist circumference: a study in young adult twins. *Int J Obes* 2009;33:29-36.
8. Payne A, Cahill F, Sun G, Loredo-Osti JC, Abarin T. Effect of FTO gene and physical activity interaction on trunk fat percentage among the Newfoundland population. *Genet Epigenet* 2014; 6:21-30.
9. Waller K, Kaprio J, Kujala UM. Associations between long-term physical activity, waist circumference and weight gain: a 30-year longitudinal twin study. *Int J Obes* 2008;32:353-361.
10. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med* 2015; 372:793-795.
11. Hollands GJ, French DP, Griffin SJ, et al. The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis. *BMJ* 2016;352:i1102.
12. Grant RW, Hivert M, Pandiscio JC, Florez JC, Nathan DM, Meigs JB. The clinical application of genetic testing in type 2 diabetes: a patient and physician survey. *Diabetologia* 2009;52:2299-2305.
13. Sanderson SC, Persky S, Michie S. Psychological and behavioral responses to genetic test results indicating increased risk of obesity: does the causal pathway from gene to obesity matter? *Public Health Genomics* 2009; 13:34-42.
14. Meisel SF, Walker C, Wardle J. Psychological responses to genetic testing for weight gain: a vignette study. *Obesity* 2012;20:540-546.
15. Frosch DL, Mello P, Lerman C. Behavioral consequences of testing for obesity risk. *Cancer Epidemiol Biomarkers Prev* 2005;14:1485-1489.
16. Vassy JL, O'Brien KE, Waxler JL, et al. Impact of literacy and numeracy on motivation for behavior change after diabetes genetic risk testing. *Med Decis Making* 2012;32:606-615.
17. Harvey-Berino J, Gold EC, et al. Does genetic testing for obesity influence confidence in the ability to lose weight? A pilot investigation. *J Am Diet Assoc* 2001;101:1351-1353.
18. Meisel SF, Wardle J. Responses to FTO genetic test feedback for obesity in a sample of overweight adults: a qualitative analysis. *Genes Nutr* 2014;9:374.
19. Meisel SF, Beeken RJ, van Jaarsveld CH, Wardle J. Genetic test feedback with weight control advice: study protocol for a randomized controlled trial. *Trials* 2012; 13:235.
20. Meisel SF, Beeken RJ, van Jaarsveld CH, Wardle J. Genetic susceptibility testing and readiness to control weight: results from a randomized controlled trial. *Obesity* 2015;23:305-312.
21. LaRusse S, Roberts JS, Marteau TM, et al. Genetic susceptibility testing versus family history-based assessment: impact on perceived risk of Alzheimer disease. *Genet Med* 2005;7:48-53.
22. Brewer NT, Edwards AS, O'Neill SC, Tzeng JP, Carey LA, Rimer BK. When genomic and standard test results diverge: implications for breast cancer patients' preference for chemotherapy. *Breast Cancer Res Treat* 2009;117:25-29.
23. Senior V, Marteau TM, Weinman J. Impact of genetic testing on causal models of heart disease and arthritis: an analogue study. *Psychol Health* 2000;14:1077-1088.
24. McBride CM, Bowen D, Brody LC, et al. Future health applications of genomics: priorities for communication, behavioral and social science research. *Am J Prev Med* 2010;38:556-561.
25. Wang C, Gordon ES, Stack CB, et al. A randomized trial of the clinical utility of genetic testing for obesity: design and implementation considerations. *Clin Trials* 2014;11:102-113.
26. Hu FB, Li TY, Colditz GA, Willett WC, Manson JE. Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *JAMA* 2003;289:1785-1791.
27. Keller M, Gordon E, Stack C, et al. The Coriell Personalized Medicine Collaborative: a prospective study of personalized medicine. *Pers Med* 2010;7: 301–317.
28. Grant RW, O'Brien KE, Waxler JL, et al. Personalized genetic risk counseling to motivate diabetes prevention: a randomized trial. *Diabetes Care* 2013;36:13-19.
29. Voils CI, Coffman CJ, Grubber JM, et al. Does type 2 diabetes genetic testing and counseling reduce modifiable risk factors? A randomized controlled trial of veterans. *J Gen Intern Med* 2015;30:1591-1598.
30. Vassy JL. Can genetic information change patient behavior to reduce type 2 diabetes risk? *Per Med* 2013;10:9-12.

31. Meisel SF, Wardle J. 'Battling my biology': psychological effects of genetic testing for risk of weight gain. *J Genet Couns* 2014;23:179-186.

32. Boeldt DL, Schork NJ, Topol EJ, Bloss CS. Influence of individual differences in disease perception on consumer response to direct-to-consumer genomic testing. *Clin Genet* 2015;87:225-232.

33. Cho AH, Killeya-Jones LA, O'Daniel JM, et al. Effect of genetic testing for risk of type 2 diabetes mellitus on health behaviors and outcomes: study rationale, development and design. *BMC Health Serv Res* 2012;12:16.

34. Hendershot CS, Otto JM, Collins SE, Liang T, Wall TL. Evaluation of a brief web-based genetic feedback intervention for reducing alcohol-related health risks associated with ALDH2. *Ann Behav Med* 2010;40:77-88.

35. Christensen KD, Roberts JS, Whitehouse PJ, et al. Disclosing pleiotropic effects during genetic risk assessment for Alzheimer disease: a randomized, controlled trial. *Ann Intern Med* 2016;164:155-163.

36. Graves KD, Hay JL, O'Neill SC. The promise of using personalized genomic information to promote behavior change: is the debate over, or just beginning? *Pers Med* 2014; 11:173-185.