Genetics of Food Intake Self-Regulation in Childhood: Literature Review and Research Opportunities

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Key Words

Pediatric obesity · Food intake self-regulation · Eating in the absence of hunger · Eating rate · Caloric compensation · Food responsiveness

Abstract

Pediatric obesity results from a daily energy imbalance between intake and expenditure, an imbalance potentially as slight as ~30–50 kcal/day (e.g., a few extra sips of cola or bites of a cookie). That an ‘energy gap’ so small may be so powerful suggests the importance of understanding mechanisms of food intake self-regulation (FISR). This review focuses on 4 behavioral indices of FISR in childhood: (1) eating in the absence of hunger; (2) eating rate; (3) caloric compensation and satiety responsiveness, and (4) food responsiveness. Evidence from pediatric samples around the world indicates that these traits are associated with body mass index, are heritable, and are linked to polymorphisms in the FTO gene. We review these data, also discussing their relevance to practical issues of parental feeding styles, portion sizes, and health literacy and numeracy. Research gaps and opportunities for future investigation are discussed. Multidisciplinary approaches and study designs that can address gene-environment interactions are needed to advance the science of FISR and stimulate new avenues for childhood obesity prevention.

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Introduction

Childhood obesity results from an energy imbalance, that is, total energy intake exceeding total expenditure. What is less obvious, if not surprising, to many health professionals is that the daily ‘energy gap’ leading to childhood obesity onset can be strikingly small. In early childhood (~2–5 years of age), a sustained positive energy balance as slight as ~30–50 kcal/day may promote obesity [1, 2]. This theoretically could be achieved with only a few extra sips of cola or bites of a cookie. Although other research [3] estimates a higher energy gap (i.e., 110–165 kcal/day), daily binges and ‘voracious’ overeating do not appear to drive obesity onset for most young children. That the daily energy gap is so subtle underscores the importance of understanding how children self-regulate

food intake. This question is significant given the prevalence of pediatric obesity in the United States [4] as well as around the world [5–7].

The aim of this paper is to present evidence for genetic influences on food intake self-regulation (FISR) in childhood. We focus on 4 behavioral indices of FISR: (1) eating in the absence of hunger (EAH); (2) eating rate; (3) caloric compensation and satiety responsiveness, and (4) food responsiveness. As described below, these traits have been reliably linked to childhood obesity and/or obesity risk. This paper is organized into four parts. First, we define each FISR behavior and review evidence for genetic influence. Specifically, we summarize evidence for (i) phenotypic associations between that behavior and child weight status, (ii) familial correlations for and heritability of the behavior, and (iii) genetic associations. Such a cascade of evidence, when present, supports the notion of genetic influences on eating behavior [8, 9]. Although this is an emerging scientific field, we conclude that existing evidence generally supports genetic influences on these traits. The magnitude of genetic influence, though, may depend on measurement issues and other study or sample characteristics (e.g., age and development) that should be examined in future research. Second, we summarize parental feeding practices that might disrupt FISR, including provision of large portion sizes. Then, we tie the present discussion to the broader issue of health literacy and numeracy, in particular, the public's knowledge of genetics concepts and why this is important. In the final section, we highlight a number of exciting research opportunities in this domain.

With respect to molecular genetics findings, we focus primarily on evidence relating to common variants of the fat mass and obesity-associated (FTO) gene, for which there is most evidence for a role in FISR in children, as well as on the melanocortin-4 receptor (MC4R) gene, for which there are also a number of studies. FTO was the first gene to be associated with body mass index (BMI) in large genome-wide association studies (GWAS) [10, 11]; its high-risk allele has been estimated to be present in 42% of individuals, with each additional risk allele accompanied by a 0.39 increase in BMI [12]. Weight-associated variants of MC4R were revealed in subsequent GWAS [12]. Studies of children and adults have since revealed that FTO and MC4R are associated with differences in weight status [13]. Although little is known about the specific mechanisms by which these genetic variants affect weight, expression is high in the brain [14] and particularly in the hypothalamus [15–17]. This is consistent with the fact that these genes are playing a role in appetite and food intake.

We do not focus on other specific obesity genes in this review. Also, we do not address the genetics of food and taste preferences, which are different phenotypes from FISR, even though there is important genetics research being conducted on these topics with children [18–20].

Food Intake Self-Regulation Indexes

Eating in the Absence of Hunger

Definition and Measurement

EAH refers to children's tendency to eat in the presence of palatable snack foods despite being satiated [21, 22]. The behavior is assessed in the laboratory using a 'free-access procedure', during which children have access to a variety of snack foods that they can eat ad libitum; however, this occurs ~15 min after children have consumed a standardized lunch or dinner to satiety [21, 23]. Foods typically provided during the EAH protocol include chocolate bars, popcorn, pretzels, and other items that are generally low in nutrient density and higher in energy density. These foods are presented as part of a 'play session', in which children are also given the opportunity to read books, play with toys, or engage in other age-appropriate activities. Children can eat as much or little as they desire, with EAH operationalized as total snack intake [typically expressed as calories (kcal) or grams consumed]. Additional details on the assessment of EAH can be found elsewhere [21–23]. A child-report questionnaire measure of EAH has been developed for children [24]. However, the laboratory protocol remains the gold standard.

Phenotypic Association between EAH and Child Weight Status

Children who consume more food in the absence of hunger have a higher BMI and are more likely to be overweight/obese [25]. For example, Fisher and Birch [21] found that girls who showed increased EAH at ages 5 and 7 years were 4.6 times more likely to be obese at both ages compared to girls who showed less EAH at both ages. 'High' versus 'low' scores were based on median splits at each age, specifically, 49 kcal (age 5 years) and 76 kcal (age 7 years) [21]. EAH was associated with a greater BMI z-score and overweight/obesity status (i.e., not overweight/obese vs. overweight/obese) among adolescents, even when the ad libitum lunch meal preceding the free-access procedure provided multiple food options comprising more than 10,000 kcal [26]. A recent study of 5- to 9-year-old children that invoked an anticipatory laboratory

stressor (i.e., instructing children to deliver a speech and solve math problems) found that children consumed on average 250 kcal in the absence of hunger, with intakes ranging as high as 700 kcal [27]. Among 8- to 9-year-olds in this study, greater cortisol secretion during the stress induction procedure was associated with greater EAH and higher child BMI. Finally, in two community-based samples of children (7- to 9-year-olds and 9- to 12-year-olds), EAH showed a significant linear association with BMI z-scores in boys but not girls [28]. The authors speculate that this null finding may have been due to social desirability effects inhibiting girls' behavior during the free-access procedure at school. We return to this point below.

Obesity Risk and EAH

Faith and colleagues [29] compared EAH in two groups of 5-year-old boys and girls, of whom 28 were born at 'high risk' for obesity and 25 at 'low risk'. Children were participants in a prospective birth cohort, the University of Pennsylvania's Infant Growth Study [30], that classified obesity risk based on the maternal pre-pregnancy BMI [31]. In this study, high-risk compared to low-risk boys consumed twice as much energy in the absence of hunger. There was no risk group difference among girls, for whom greater EAH was marginally associated with greater limitations on snack foods at home. Interestingly, in a follow-up of this same cohort at age 13 years, the risk group difference in EAH initially seen among boys was no longer present [32]. Moreover, EAH was significantly greater among low-risk girls compared to high-risk girls, a finding that may have been due to developmental factors such as dieting or social desirability that were not assessed but could have inhibited the snack intake of obese-prone girls.

Family Correlations for and Heritability of EAH

In a sample of 47 same-sex sibling pairs aged 5–12 years, Kral et al. [33] reported a familial association for EAH that was significant among full siblings [intraclass correlation coefficient (ICC) = 0.37, $p < 0.05$] but not half-siblings (ICC = 0.16, $p > 0.05$). These results are consistent with genetic influences on the phenotype, although heritability was not formally estimated. Fisher et al. [34] studied 801 children from 300 Hispanic families enrolled in the Viva la Familia Study [35], a study of genetic and environmental influences on behavioral and metabolic phenotypes contributing to childhood obesity onset. EAH was assessed following a laboratory dinner meal that provided more than 50% of children's estimat-

ed daily caloric needs. The results indicated that overweight children consumed 14% more energy in the absence of hunger compared to nonobese peers. The heritability of EAH was estimated to be 51%.

Genetic Association Studies of EAH

An association between the FTO genotype and EAH was reported in a British sample of 131 children aged 4–5 years participating in the Twins Early Development Study [36, 37]. EAH was assessed at the participants' homes using a free-access procedure that provided three varieties of (sweet and savory) biscuit snacks to children. The results indicated that children with one or two copies of the A (risk) allele for the FTO polymorphism rs9939609 consumed significantly more biscuits in the absence of hunger compared to children with no risk allele. Specifically, EAH was significantly greater for children with the AA (mean = 39.95 g) or AT (mean = 37.93 g) genotype compared to children with the TT genotype (mean = 30.00 g).

As far as we are aware, no studies have reported associations between the MC4R genotype and EAH. However, one study [38] using 24-hour food recalls demonstrated an association with increased energy intake in children, while another [39] reported an association with greater snacking behavior in children and adolescents. These findings are both consistent with food intake occurring in the absence of deprivation and homeostatic hunger [40, 41].

Eating Rate

Definition and Measurement

The eating rate is operationally defined as total energy (typically kcal) or mouthfuls of food consumed within a given time interval during a laboratory test meal. Thus, the unit of measurement typically is kcal/min or bites/min. Although faster eating could simply result in the same amount of food being consumed in a shorter period, it tends to be associated with greater intake [42], supporting its use as an index of FISR. As noted below, some studies have used parent-report measures to assess the child's eating rate, although the laboratory methodology is considered the gold standard.

Phenotypic Association between Eating Rate and Childhood Obesity

Rapid eating has been associated with increased adiposity among young children whose eating was directly observed in preschool settings [43, 44]. Waxman and Stunkard [45] reported that obese brothers had a faster

eating rate than their nonobese siblings at dinner (65.7 vs. 31.7 kcal/min) and lunch (103.5 vs. 46.2 kcal/min). Barkeling et al. [46] used a universal eating monitor to compare the eating behaviors of 23 normal-weight and 20 obese 11-year-old children with respect to total food intake, duration of consumption, rate of eating, and the relative rate of consumption at two lunch meals. They observed that obese children ate faster ($p < 0.05$) and did not slow their eating rate towards the end of the meal ($p < 0.05$) compared to normal-weight children. Similar results were reported by Laessle et al. [47]. Lindgren et al. [48] also found a relative lack of deceleration through the meal in obese compared to normal-weight 5- to 18-year-olds. Sugimori et al. [49] studied 8,170 children in the Toyama Birth Cohort study at ages 3 and 6 years. Children were classified in terms of their eating speed, based on parent reports, at both assessment times. Compared to children who were normal-weight at both ages 3 and 6 years (prevalence = 5.7%), slightly rapid or rapid eating was significantly greater among children who were normal-weight at age 3 years but became obese at age 6 years (prevalence = 22.6%) as well as in children who were obese at both ages 3 and 6 years (prevalence = 26.8%). Berkowitz et al. [50] found that a faster eating rate at 4 years of age, expressed as mouthfuls of food/min at a single laboratory test meal, predicted a greater BMI and fat gain in children between ages 4 and 6 years.

Family Correlations for and Heritability of Eating Rate

Llewellyn et al. [51] assessed the eating rate (mouthfuls/min) of 254 pairs of twins aged 10–12 years. The children were video-recorded while eating a standard meal at home (i.e., 24 sandwich quarters on two plates plus mixed/chopped fruit salads). The results indicated that overweight/obese youth had a significantly faster eating rate (bites/min) and total food bites compared to lower normal-weight youth. Biometric analyses revealed a significant heritable component to eating rate, with 62% of the variance in the phenotype due to additive genetic factors. Interestingly, the same investigators confirmed a heritable component to infant eating rate in a British population-based twin registry, the Gemini study [52]. Gemini is a prospective cohort of 2,042 families with twins born in England and Wales between March and December 2007. The infant eating rate was assessed at 4 months of age by the parent-report Baby Eating Behavior Questionnaire (BEBQ) [53], and biometric analyses revealed that 84% of the variance in the trait was due to additive genetic factors [54].

Genetic Association Studies of Child Eating Rate

We are unaware of any studies reporting an association between specific genes and individual differences in child eating rate.

Caloric Compensation and Satiety Responsiveness

Definition and Measurement

‘Caloric compensation’ and ‘satiety responsiveness’ refer to a similar construct, that is, the ability to recognize and adjust eating in response to internal feelings of fullness or satiety [55, 56]. Operationally, however, they are measured very differently. Compensation is measured by a laboratory-based preloading paradigm that assesses the children’s ability to adjust food intake following a low- versus high-calorie preload (food or beverage). The protocol is based on the assumption that children should eat less food at an ad libitum meal ~20 min following the higher- compared to the lower-energy preload, an adjustment that reflects ‘compensation’. The ability to compensate can be numerically quantified for individual children, with deviation from perfect compensation reflecting poorer self-regulatory eating [57–63]. This assessment method is considered the gold standard because it is a direct behavioral measurement obtained under controlled laboratory conditions. Satiety responsiveness, in contrast, is assessed by the parent-report Child Eating Behaviour Questionnaire (CEBQ) [64], with the attendant disadvantage of potential reporting bias by parents. The benefit of this measure, though, is the possibility to characterize the eating behavior of children across a range of situations, rather than behavior in the laboratory on a small number of occasions, which could be vulnerable to situational influences. This questionnaire instructs parents to respond to situations such as ‘My child gets full up easily’ and ‘My child gets full before his/her meal is finished’.

Phenotypic Association between Caloric

Compensation, Satiety Responsiveness, and Obesity

Several laboratory-based studies have demonstrated poorer compensation in heavier children. Johnson and Birch [65], for example, reported a significant negative association ($r = -0.37$) between compensation ability and adiposity in 3- to 5-year-olds, but among girls only, while Birch and Fisher [66] found that compensation predicted the 24-hour energy intake, which in turn predicted the relative weight, in a sample of 4- to 6-year-old girls. A study of 9- to 14-year-old boys also reported poorer compensation in obese than normal-weight children [67]. We found in two independent samples that poorer compen-

sation was associated with greater total percent body fat measured by dual energy X-ray absorptiometry, although, interestingly, not with child BMI [68, 69].

A number of studies using the CEBQ to assess satiety responsiveness have found that children with a higher BMI or who were overweight/obese had, according to their parents, poorer satiety responsiveness than normal-weight children [65, 70–74].

Family Correlations for and Heritability of Compensation and Satiety Responsiveness

Carnell et al. [75] studied 5,435 twin pairs aged 8–11 years whose satiety responsiveness was assessed by the CEBQ [64]. Their results indicated that 63% of the variance in satiety responsiveness was due to additive genetic factors, with the remaining variance accounted for by environmental factors. In Gemini, the study of infant twins, the heritability of satiety responsiveness was estimated to be even higher (72%) [54]. Surprisingly, a different conclusion was reached by Faith et al. [68], who assessed compensation using a laboratory-based pre-loading paradigm [59, 65]. They studied a sample of 69 same-sex twins aged 4–7 years recruited from the New York metropolitan area. In this investigation, the heritability was estimated to be 0% (i.e., no genetic influence). The inconsistent findings between this study and others may be due to measurement issues (e.g., parent report vs. laboratory observation), age differences (e.g., 8 years and older and infants vs. 4–7 years), and/or sample size differences (e.g., hundreds of child participants vs. less than 70). We return to this point in the Conclusions section.

In a sample of weight-discordant siblings aged 5–12 years, Kral et al. [33] reported a familial association for %COMPX that was significant among full siblings (ICC = 0.36, $p < 0.05$) but not half-siblings (ICC = 0.02, $p > 0.05$). Again, these results are consistent with genetic influences on the %COMPX phenotype, although heritability was not formally estimated.

Genetic Association Studies of Compensation and Satiety Responsiveness

An association between the FTO genotype and child satiety responsiveness, as assessed by the CEBQ, was reported in a study of 3,337 children aged 8–11 years [76]. Specifically, responsiveness to internal fullness cues was significantly poorer for children with the AA genotype (mean = 2.55) compared to the AT (mean = 2.65) and TT genotypes (mean = 2.67) ($p = 0.008$). Moreover, mediator analyses confirmed that satiety responsiveness par-

tially mediated the association between the FTO genotype and child BMI z-score. A more recent study [77] using the CEBQ additionally reported an association between the MC4R genotype and this CEBQ scale, such that the risk variant was associated with lower satiety responsiveness scores in a community sample of obese children. Similarly, Cecil et al. [78] found that total energy intake at a school lunch test meal was significantly greater among 4- to 10-year-old children carrying the A (risk) allele compared to children not carrying the A allele.

Food Responsiveness

Definition and Measurement

Food responsiveness refers to the tendency to eat in response to food cues [56, 71]. That is, certain children are more responsive than others to the presence (e.g., sight and smell) of foods in the environment. This construct is based on classical experiments by Schachter and colleagues [79–81] and subsequent work by Wardle and colleagues [55, 56, 71, 73, 82–84]. Child food responsiveness has been assessed by the CEBQ [64] as well as with the external eating scale of the Dutch Eating Behaviour Questionnaire (DEBQ [85]), which is available in both a child-report (DEBQ-C [86]) and parent-report form (DEBQ-P [87]).

Phenotypic Association between Food Responsiveness and Obesity

In a report of 572 children aged 3–5 years recruited from a British community sample, greater food responsiveness assessed by the CEBQ was associated with a higher BMI z-score ($r = 0.18$, $p < 0.001$) [71]. In a sample of 294 Chilean children aged 6–12 years, food responsiveness was significantly greater among obese compared to normal-weight boys and girls [88]. In another cross-sectional investigation of 6- to 7-year-old youth residing in the Netherlands, greater food responsiveness was associated with higher BMI z-scores in multiple regression models that adjusted for child sex and age, parental education, and parental employment status [89]. Evidence using the DEBQ is more mixed, with some evidence suggesting higher scores in obese children [87], but other evidence suggesting a negative association [90, 91] or no relationship [92]. This variance in results is likely because the CEBQ aims to capture the normal range of eating styles, while the DEBQ is designed to assess disordered eating behavior.

Familial Associations for and Heritability of Food Responsiveness

Carnell et al. [75] reported that 72% of the variance in a measure of food cue responsiveness (CEBQ enjoyment of food scale) was due to additive genetic factors in a sample of several thousand twin pairs assessed at 8–11 years of age, while analyses of the Gemini cohort reported 59% heritability in BEBQ food responsiveness scores for infants, suggesting that this particular measure of FISR may show more environmental influence early in life [54].

Genetic Association Studies of Food Responsiveness

An association between food responsiveness and the FTO genotype has been recently reported in an analysis of 1,718 children of European descent enrolled in the Generation R study [93], a population-based cohort of fetal life onwards in the city of Rotterdam, the Netherlands. Velders et al. [94] found that, at age 4 years, children with the A (risk) allele at rs9939609 were significantly more likely to be high in food responsiveness as assessed by the CEBQ compared to children without the A allele. We are not aware of any reports of significant associations between the MC4R genotype and the CEBQ food responsiveness scale. However, the study by Valadares et al. [77] revealed a positive association with the CEBQ enjoyment of food scale, such that the risk variant was associated with higher scores.

Parental Feeding Styles, Food Portioning, and FISR

Parents are key ‘gate-keepers’ of the home food environment, especially for young children. They determine which foods come into the home and interact with children during meals. To this end, it is important to know whether certain parental feeding practices promote poorer FISR and/or contribute to childhood obesity by disrupting FISR. There is consistent evidence that ‘restrictive’ feeding by parents (i.e., limiting access to palatable, typically high-fat high-sugar foods) is associated with poorer compensation and greater EAH [23, 95, 96]. The association appears to be bidirectional, although experimental research supports the hypothesis that restricting access to foods leads to greater intake of those foods when children have subsequent access [96]. ‘Indulgent’ parenting practices have also been linked to childhood obesity [97]. It is conceivable that genetic influences on child FISR are moderated by (i.e., exacerbated or protected by) specific feeding styles, although data on this topic are lacking. This represents a great opportunity for research

given the current interest in epigenetic pathways leading to obesity [98].

Parents also play a role in determining the portion size of foods served to their children. This is important because portion size is a strong determinant of energy intake in adults [99–103] and children [104–108]. To date, few individual differences have been identified with respect to children’s susceptibility to overeating when served large food portions. Some evidence suggests that overweight and obese children may be more vulnerable to overeating than normal-weight children when presented with large food portions. For example, when the portion size of three fruit and vegetable side dishes was doubled at a meal, Kral et al. [109] demonstrated that overweight and obese children showed an almost three times greater increase in intake of those foods compared to normal-weight children. Similarly, data from two recent laboratory studies also indicate that obese children, in particular, may be more susceptible to overeating when served large portions of palatable energy-dense foods [110, 111]. Whether genes for FISR influence children’s responsiveness to large food portions remains to be seen.

To the extent that certain parenting behaviors disrupt children’s FISR, there might be advantages to having children self-serve food portions. Indeed, Fisher et al. [112] showed that children with a tendency to ‘overconsume’ when served large food portions reduced their meal energy intake by 11% when allowed to self-serve themselves than when the portion was served to them. The beneficial effect on intake of having children self-determine their food portions, however, has not been consistent across studies [113] and may be influenced by external eating cues [114].

Health Literacy, Numeracy, and Genetics of FISR

The present review should be considered in the broader context of discussions on health literacy and numeracy, the public’s understanding of genetics, and how this broader knowledge potentially could promote healthier eating. There is a growing field of health literacy and numeracy specifically as they relate to genetics information, concepts, and the potential for motivating behavioral changes [115–118]. Data are limited but increasing [119]. Interestingly, a Cochrane literature review examined the impact of communicating DNA-based disease risk estimates on the motivation for behavioral changes [120]. The results indicated that genetics feedback had no impact on smoking or physical activity but a significant ef-

fect on self-reported diet. It is possible that providing information on genetic risk and eating regulation to some individuals, in the broader context of obesity, might promote healthier eating. Randomized controlled clinical trials [e.g., 121] are needed to answer this question.

Conclusions and Research Opportunities

The studies presented in this review, taken together and when reviewed as a ‘cascade’ of evidence [9], support the notion that genes influence children’s capacity to self-regulate food intake. The emerging picture is one of nature and nurture, with molecular genetic associations only beginning to be discovered. The 4 traits examined in this report, on balance, are associated with variations in overweight status. Moreover, evidence from the larger twin studies across the age spectrum suggests sizable heritable influences. That said, there are important caveats to this conclusion that are relevant for the design of future studies. First, FISR traits can be measured via direct observation or parent reports, and findings from these methods do not necessarily converge [75, 122]. Each approach has virtues and disadvantages and, ideally, multiple measurement strategies should be used to establish convergent findings. Second, social desirability may have an impact on the assessment of FISR, especially when directly measuring food intake. For example, older girls may be inclined suppress eating during the free-access protocol of the EAH assessment [28, 32], which may affect the internal validity of genetics studies. Future studies should be mindful of this potential drawback and should attempt to manage or minimize these influences, if possible, especially with older children. Third, there may be age-specific genetic influences on FISR traits, an issue that, to our knowledge, has not been formally tested yet. This is possible as genetic influences on BMI increase during childhood [123]. Fourth, of the few genetic association studies published to date, all have used a candidate gene strategy focusing on FTO rather than examining multiple genes or genetic profile scores. This latter approach may prove fruitful in future studies.

At present, the genetics of FISR is a relatively young research field, and many exciting questions remain to be addressed. Questions to explore include:

- To what extent are the aspects of FISR that we have discussed distinct conceptually and/or biologically? Is it scientifically helpful to separate them and probe the etiology of each, or are they all imperfect measures of the same underlying biobehavioral phenomenon?

- To what extent do gene-environment interactions exist, such that genetic influences on FISR are amplified or suppressed depending on environmental factors known to influence food intake (e.g., large vs. small portion sizes, variety)?
- To what extent do epigenetic factors during pregnancy/infancy impact FISR traits? For example, how do maternal dietary patterns during pregnancy influence infants’ food responsiveness or satiety responsiveness?
- To what extent do parenting styles (e.g., restrictive or indulgent feeding) moderate genetic influences on FISR? Do interactions between parent behaviors and specific genes exist?
- To what extent do genetic influences on FISR influence children’s general self-control and self-regulation? Are these traits correlated or orthogonal? To what extent do they share common genetic underlying pathways?
- To what extent do cultural and social norms mitigate genetic influences on FISR?
- How can the information presented in this literature be used to guide pediatric obesity treatment and prevention efforts? For example, would parents behave differently if they knew that their child had a genetic predisposition to eat in response to food cues? How else might this information guide novel interventions, if at all?

Developing and answering these questions will require multidisciplinary collaborations, careful choice of behavioral, environmental, genetic, and biological assessments as well as samples that are large and variable enough to achieve adequate power to examine gene-environment interactions. Such efforts promise not only to advance the science of FISR but to stimulate new approaches to obesity prevention and treatment.

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