FTO predicts weight regain in the Look AHEAD Clinical Trial

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Abstract

Background—Genome-wide association studies have provided new insights into the genetic factors that contribute to the development of obesity. We hypothesized that these genetic markers would also predict magnitude of weight loss and weight regain after initial weight loss.

Methods—Established obesity risk alleles available on the Illumina CARe iSelect (IBC) chip were characterized in 3,899 overweight or obese participants with type 2 diabetes from the Look AHEAD study.
AHEAD (Action for Health in Diabetes), a randomized trial to determine the effects of intensive lifestyle intervention (ILI) and Diabetes Support and Education (DSE) on cardiovascular morbidity and mortality. Primary analyses examined the interaction between 13 obesity-risk polymorphisms in 8 genes and randomized treatment arm in predicting weight change at year 1, and weight regain at year 4 among individuals who lost 3% or more of their baseline weight by year 1.

**Results**—No SNPs were significantly associated with magnitude of weight loss or interacted with treatment arm at year 1. However, *FTO* rs3751812 predicted weight regain within DSE (1.56 kg per risk allele, p = 0.005), but not ILI (p = 0.761), resulting in SNP×treatment arm interaction (p = 0.009). In a partial replication of prior research, the obesity risk (G) allele at *BDNF* rs6265 was associated with greater weight regain across treatment arms (0.773 kg per risk allele), although results were of borderline statistical significance (p=0.051).

**Conclusions**—Variations in the *FTO* and *BDNF* loci may contribute risk of weight regain after weight loss.

**Keywords**
type 2 diabetes; obesity; weight loss; diet; genetics

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**Introduction**

Obesity is a major public health problem associated with increased risk of a number of diseases, including cardiovascular disease (CVD), type 2 diabetes and certain cancers. Behavioral weight loss is the treatment of choice for mild to moderate obesity1 as weight losses of 10% have repeatedly been documented to improve diabetes2 and cardiovascular disease risk factors3,4. At the same time, the long-term maintenance of these losses remains a critical issue in obesity treatment.

Obesity susceptibility loci identified through genome-wide association studies (GWAS) and replicated in multiple independent cohorts have provided new insights into the genetic factors that contribute to the development of obesity. The fat mass and obesity associated gene (*FTO*) was one of the first genes to be identified by this approach and it has emerged as an important gene associated with obesity and body mass in numerous cohorts 5–7. With increasing samples sizes in GWAS studies, the number of confirmed loci continues to increase 5–7.

The treatment implications of these obesity susceptibility loci remain unclear. In particular, it is not known whether obesity-risk genetic markers predict success with weight loss or weight loss maintenance. Previously, in the Diabetes Prevention Program, *FTO* rs9939609 predicted a greater increase in subcutaneous adipose tissue in the placebo group compared to lifestyle intervention at year 1, but no significant genotype×treatment interaction was observed for overall weight loss8. The obesity risk allele at rs6265 in *BDNF* was also associated with greater weight regain at two year follow-up among those who lost 3% or more of their initial weight at six-months9.
The goal of the present study was to define the effects of obesity genetic risk markers available on the Illumina CARe iSelect IBC chip10 (within or in the region of FTO, SH2B1, MC4R, BDNF, TNNT3K, MTIF3, QPCTL/GIPR, and TFAP2B) on weight loss at 1 year in response to gold standard behavioral weight loss intervention, and weight regain from year 1 to 4 among those who lost 3% or more of their initial weight at year 1. The Look AHEAD trial, a randomized controlled trial designed to determine the effects of intensive lifestyle intervention, including diet and physical activity, on cardiovascular morbidity and mortality among overweight individuals with type 2 diabetes, provides a unique opportunity to conduct such analyses.

Material and Methods

Study cohort

The Look AHEAD study enrolled 5,145 ethnically diverse overweight and obese subjects with type 2 diabetes and aged 45 to 76 years. Of these, 1,038 did not provide genetic consent to be included in a genetic ancillary study, including all participants from three Southwest American Indian sites, 10 withdrew consent for genotyping and 60 were identified to have no or a low concentration of DNA. This left 4,037 individuals, of which 3,899 contributed genetic data on at least one of the 13 markers of interest that passed genotyping quality control procedures. These subjects form the basis for the present analyses. Overall, relative to those who provided genetic consent, those who did not were more frequently African-American, Hispanic, female, more highly educated and not dyslipidemic. Consent rates did not differ by BMI11.

The design and methods of the Look AHEAD trial have been reported elsewhere, as have the baseline characteristics of the randomized cohort12. Briefly, at baseline participants were randomized to either an Intensive Lifestyle Intervention (ILI) or a Diabetes Support and Education (DSE) arm. Both the ILI and DSE groups were provided one session of education on diabetes and cardiovascular risk factors. In addition, ILI patients received an intensive lifestyle program, combining diet modification and increased physical activity, designed to produce an average of 7% weight loss and maintain these weight losses. The ILI included one individual and three group meetings per month for six months, followed by one individual and two group meetings per month through one year. From years 2–4, participants were seen individually at least once a month, contacted another time each month by telephone or email, and offered a variety of ancillary classes. These sessions focused on behavioral weight loss strategies, such as self-monitoring, goal setting and stimulus control, to achieve and maintain weight loss. The DSE group received the option of attending three sessions per year on nutrition, physical activity and social support with no explicit weight loss goals. In the full trial3,4, maximal difference in average weight loss across intervention arm occurred at 1 year follow-up (8.6% in ILI vs. 0.7% in DSE, p < 0.001), with an average weight loss of 4.7% in ILI and 1.1% in DSE at year 4 follow-up.

The Look AHEAD trial was approved by local Institutional Review Boards, including genetic analyses.
Anthropometric Measures

Weight was measured in duplicate at baseline and year 1 and 4 follow-ups using a digital scale and height was measured at baseline and year 4 using a standard wall-mounted stadiometer. Weight regain was defined as weight change from year 1 – year 4 among individuals initially losing at least some weight (>=3%) at year 1 following methods used in the Diabetes Prevention Program. As can be seen in Table 1a, among those who lost 3% or more weight at year 1, women regained 3.7±8.2 and men regained 4.8±7.8 from year 1 – 4 on average. It is important to note, however, that only 72.5% of women and 78.5% of men in this subgroup regained weight, as defined by a weight at year 4 greater than their weight at year 1, while the remaining individuals either maintained or continued to lose weight.

Genotyping

The genomic DNA extraction was based on the use of FlexiGene DNA Kit (Qiagen Inc., Valencia, CA) as described by the manufacturer and DNA quantitation was performed using the PicoGreen dsDNA Quantitation Reagent (Invitrogen, Inc., Carlsbad, CA). Genotyping was carried out at the Children’s Hospital of Philadelphia using the Illumina CARE iSelect (IBC) chip, a gene-centric 50,000 single nucleotide polymorphism (SNP) array designed to assess relevant loci across a range of cardiovascular, metabolic and inflammatory syndromes. Taqman Applied Biosystems (ABI) Assays-On-Demand were used to genotype the MC4R polymorphism rs17782313 (ABI catalogue number C_32667060_10) using an Applied Biosystems 7900HT.

Gene and SNP Selection

We performed a search of published literature and selected SNPs that had been associated with obesity by GWAS 5–7,13–19 and appeared on the IBC chip 10 or, in the case of MC4R rs17782313, had been genotyped by Taqman. References for the selection of each SNP are provided in Table 2. As multiple markers have shown the strongest association with obesity in the FTO region6,13,16,18 and two distinct loci have been identified in the BDNF region6, we retained multiple SNPs in each of these regions. FTO rs1421085, rs3751812 and rs9939609, BDNF rs6265 and rs10767664 and TFAP2B rs2272903 were assayed directly on the IBC chip. GWAS obesity SNPs not on the IBC chip were replaced by proxies where possible using the SNP Annotation and Proxy Search tool (SNAP) 20 based on haplotype maps of individuals of European ancestry (CEU) and Yoruba people of Ibadan (YRI) as follows: FTO rs9930506 was replaced by rs9922708 (distance 681 bp r2=1.00, D'=1.00 in both CEU and YRI); BDNF rs925946 was replaced by rs1401635 (distance 26,789 bp r2=0.96, D'=1.00 in CEU; no proxy was available in YRI), SH2B1 rs7498665 was replaced by rs4788099 (distance 27,514 bp r2=1.00, D'=1.00 in CEU and D'=1.00 and r2=0.94 in YRI), TNNI3K rs1514175 was replaced by rs1514176 (distance 48 bp, r2=1.00, D'=1.00 in CEU and r2=1.00, D'=1.00 in YRI), MTIF3 rs4771122 was replaced by rs7988412 (distance 19898, r2=0.83, D'=1.00 in CEU; no proxy was available in YRI), and QPCTL/GIPR rs2287019 was replaced by rs11672660 (distance 21988 bp, r2=0.83, D'=1.00 in CEU, r2=0.89, D'=1.00 in YRI).

The four FTO SNPs selected for inclusion were in strong linkage disequilibrium in non-Hispanic Whites (r2=0.78–0.97), but differed in the degree of disequilibrium among
African-Americans (rs3751812, rs1421085; r²=0.98; rs3751812, rs9922708; r²=0.70; rs1421085, rs9922708; r²=0.67; rs9939609 with other SNPs: r²<0.36). In contrast, two BDNF SNPs, rs6265 and rs10767664, were in strong linkage disequilibrium in both non-Hispanic Whites (r²=0.88) and African-Americans (r²=0.81).

Observed genotype frequencies were compared with those expected under Hardy Weinberg Equilibrium (HWE) using stratified $\chi^2$ tests within the two largest racial/ethnic groups (non-Hispanic White and African-American). All SNPs under study conformed to HWE (p > 0.001).

**Statistical Analysis**

To control for admixed study population, all IBC SNPs were examined by principal component analysis (PCA) using the EIGENSTRAT algorithm 21 as implemented in Golden Helix version 7.1 (Bozeman, Montana, USA). PCA results indicated that the majority of the variance among the Look AHEAD cohort was accounted for by the first two principal components, which agreed with self-reported ethnicity (Supplemental Figure 1). Accordingly, the first two principal components were included as covariates in our analyses to adjust for population stratification in the multi-ethnic Look AHEAD cohort.

As the primary adiposity outcome in the Look AHEAD clinical trial is weight (not body mass index), we focus on baseline weight (in kg) and change in weight (in kg) as primary outcomes. Longitudinal linear mixed models were used to model the effect of SNP on weight change by treatment arm over time. As baseline weight as well as treatment response can be associated with the SNPs, baseline was modeled as the first time point in longitudinal analyses as recommended by McArdle & Whitcomb, 200922. Within this model, differential SNP effects on year 1 weight change or by treatment arm are detected through SNP (0,1 or 2 copies of the minor allele) × time (baseline, year 1) × treatment arm (ILI, DSE) interaction. An additive genetic model was used for all markers, with genotype coded by the number of minor alleles. Therefore, all our SNP effects can be interpreted as the effect on the outcome of interest of one additional copy of the corresponding minor allele. Models were estimated in Splus 8.2 23 using restricted maximum likelihood. Longitudinal outcomes were additionally adjusted for age, gender, study site, and the first two ancestry informative marker principal components.

Next, we examined the extent to which the genetic markers predicted weight regain at year 4. As weight regain implies initial weight loss, we limited analyses to those who lost 3% or more of their initial weight at year 1, consistent with prior analyses focusing on weight regain in the Diabetes Prevention Program9. Interest centered on whether SNP effects, if present, could be averaged across treatment arms or should be presented in a treatment-specific fashion (SNP × treatment arm interaction). The same covariates were employed as above, with the addition of year 1 weight.

To adjust for multiple comparisons, we calculated the effective number of independent genetic loci using principal component analysis as recommended by Li and Ji24. Principal component analysis of the genotypic correlation matrix of the 13 markers of interest identified 10 independent loci in the full and non-Hispanic White samples. Therefore, one
can maintain the family-wise error rate at 0.05 via Sidak’s adjustment for multiplicity by declaring as significant only those markers with a nominal significance level of 0.05/10=0.005. However, as the markers were selected \textit{a priori}, we also discuss results with p values less than 0.05 not adjusted for multiple testing. All analyses were performed at Brown University.

Results

Descriptive statistics

Participant characteristics of the sub-cohort of Look AHEAD used in these analyses are shown in Table 1. Individuals were evenly distributed between the ILI and DSE intervention arms, and had comparable age, gender and ethnicity as in the entire cohort (data not shown). No baseline differences in demographic or clinical characteristics across ILI and DSE were observed. Similar to the larger Look AHEAD trial\textsuperscript{3}, participants assigned to ILI lost significantly more weight at year 1 and 4 than those assigned to DSE. SNP characteristics, including the obesity risk allele identified in the prior literature, are presented in Table 2.

Genetic associations with baseline weight

Genetic associations of SNP markers with baseline weight are listed in Table 3. Obesity risk alleles in \textit{FTO}, \textit{SH2B1} and \textit{QPCTL/GIPR} regions predicted baseline weight in directions consistent with prior research. Risk alleles for the markers in these 3 genes were associated with elevated baseline weight of 1.01–1.29 kg per copy. Similar associations were found for baseline BMI (Table 3), with BMI effects per risk allele in the 0.38–0.46 range.

Genetic associations with weight loss at year 1

Genetic associations of the full set of SNP markers with year 1 weight change in ILI and DSE are listed in Supplemental Table 1. No SNPs were significantly associated with the magnitude of weight change in either ILI or DSE or interacted with treatment arm in predicting the degree of weight change

Weight regain

Participant characteristics for those who lost 3% or more at year 1 of their weight at baseline are presented in Table 1a. Genetic associations of the full set of SNP markers with weight at year 4 in this subgroup is presented in Table 4. The obesity risk (A) allele at \textit{FTO} rs3751812 was significantly associated with weight regain in DSE (1.559 kg per risk allele, p = 0.005), but not ILI (-0.092 kg per risk allele, p = 0.761), resulting in SNPxtreatment arm interaction (p = 0.009). Similar effects were seen for \textit{FTO} rs1421085 and rs9922708.

A regional plot of the association of \textit{FTO} with differential change in weight regain across ILI and DSE is depicted in Supplemental Figure 2. Of interest, rs3751812 and SNPs in linkage disequilibrium do not show the strongest association with differential weight change across ILI and DSE. One SNP, rs8061397, in a distinct linkage disequilibrium block is associated with differential change in weight across ILI and DSE (p = 6.4 ×10⁻5), suggesting a possible additional signal in the region.

\textit{Int J Obes (Lond).} Author manuscript; available in PMC 2014 June 01.
In a possible replication of prior research, the obesity risk (G) allele at \( BDNF \) rs6265 was associated with greater weight regain across treatment arms (0.773 kg per risk allele), although results were of borderline statistical significance (\( p=0.051 \)). When combined, the \( FTO \) and \( BDNF \) SNPs accounted for \( R^2 = 1.43\% \) of year 4 weight across treatment arms.

**Discussion**

This paper presents the results of the largest study to date examining whether SNPs previously associated with obesity predict weight loss in response to behavioral treatment or weight regain after successful weight loss treatment. We found no significant SNP associations with magnitude of weight loss at year 1 or SNP \( \times \) treatment arm interactions in predicting year 1 weight change, suggesting behavioral factors, such as adherence to weight loss recommendations, may predominate in predicting initial weight loss. However, the obesity risk region within \( FTO \) was significantly associated with weight regain in the control group, but not in the lifestyle intervention group, resulting in SNP \( \times \) treatment arm interaction. Further, variation within \( BDNF \) was associated with weight regain across treatment arms in replication of prior results in the Diabetes Prevention Program\(^9\). Overall, these results suggest that the obesity risk alleles do not appear to be strongly predictive of the magnitude of weight loss in response to behavioral intervention but may instead be associated with weight regain after weight loss.

\( FTO \) was the first gene to show replicated association with obesity in GWAS\(^{13,16,18,25}\) and continues to show the strongest association with obesity and body mass index across a variety of populations\(^5\). This region also shows strong evidence for gene\( \times \)behavior interaction as the interaction of obesity-risk alleles at \( FTO \) with physical activity in predicting body weight has been confirmed by replication and meta-analysis in epidemiologic studies\(^{26}\). In the context of randomized, controlled trials, \( FTO \) rs9939609 predicted a greater increase in subcutaneous adipose tissue in the placebo group compared to lifestyle intervention at year 1, but no significant genotype \( \times \) treatment interaction was observed for overall weight loss in the Diabetes Prevention Program\(^8\). In the POUNDS LOST trial\(^{27}\), the minor allele at \( FTO \) rs1558902 predicted greater free fatty mass in response to a low-protein diet but less free fatty mass in response to a high fat diet at two year follow-up, again with no effect on weight change. The present results extend this gene \( \times \) behavior interaction to the context of a combined caloric restriction and physical activity intervention arm in a longitudinal randomized, controlled clinical trial with four year follow-up. Taken together, these results indicate that behavioral strategies may blunt \( FTO \) effects on weight gain and weight regain after weight loss. However, the detection of effects of the \( FTO \) region on weight loss may require detailed measurements of body fat, such as with dual energy X-ray absorptiometry scan.

Previously in the DPP, the obesity risk allele at rs6265 in \( BDNF \) was associated with greater weight regain over 2 years among those who had initially lost 3% at or more at six months. The effect occurred across all three treatment arms: a lifestyle intervention promoting weight loss and physical activity, 850 mg metformin twice daily, and placebo\(^9\). In Look AHEAD, we provide some evidence, albeit of marginal significance (\( p = 0.051 \)), for association of the obesity risk allele at rs6265 with weight regain at four-year follow-up.
among those who had lost 3% at one-year follow-up across two treatment arms. BDNF and its primary receptor TrkB are widely expressed in the brain, including key regions of the hypothalamus and dorsal vagal complex related to body weight and energy homeostasis. In these regions, infusion of BDNF produces appetite suppression and weight loss. Conversely, targeted disruption of BDNF in transgenic models results in hyperphagia and obesity. In a prior Look AHEAD study, BDNF rs6265 was associated with greater total caloric intake and more servings from the dairy and the meat, eggs, nuts and beans food groups. At least one case study also links rare mutations in BDNF to severe obesity in an 8-year-old girl.

This study has several strengths, including a randomized clinical trial design, a highly effective behavioral weight loss intervention and inclusion of multiple genetic markers previously associated with obesity. The sample size of the study is both a strength and limitation. While this is the largest study to examine genetic predictors of weight loss and weight maintenance, it is smaller in size than samples used to discover the obesity risk SNPs under consideration. It is plausible that the inclusion of more obesity risk polymorphisms would have identified additional associations with weight loss or regain. However, we did include markers reflecting several of the strongest associations with obesity, including those within FTO, MC4R and BDNF. Although we sought to define the role of obesity risk SNPs in weight loss and weight regain, it is possible that genetic factors associated with weight loss and regain may derive from different pathways than those influencing obesity per se. An agnostic approach, such as GWAS or exome sequencing, may be required to identify such pathways. Finally, this cohort was selected for type 2 diabetes and overweight and the generalization of these results to other populations remains to be determined.

Overall, our findings advance existing knowledge on the treatment implications of obesity susceptibility loci derived from GWAS. No significant SNP associations with magnitude of weight loss at year 1 or SNP×treatment arm interactions in predicting year 1 weight change were observed. However, we identify FTO and BDNF as possible predictors of weight regain after weight loss.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

We acknowledge the Look AHEAD sites that participated in this ancillary study.

Johns Hopkins Medical Institutions Frederick L. Brancati, MD, MHS1; Jeff Honas, MS2; Lawrence Cheskin, MD3; Jeanne M. Clark, MD, MPH3; Kerry Stewart, EdD3; Richard Rubin, PhD3; Jeanne Charleston, RN; Kathy Horak, RD

Pennington Biomedical Research Center George A. Bray, MD1; Kristi Rau2; Allison Strate, RN2; Brandi Armand, LPN2; Frank L. Greenway, MD3; Donna H. Ryan, MD3; Donald Williamson, PhD3; Amy Bachand; Michelle Begnaud; Betsy Berhard; Elizabeth Caderette; Barbara Cerniauskas; David Creel; Diane Crow; Helen Guay; Nancy Kora; Kelly LaFleur; Kim Landry; Missy Lingle; Jennifer Perault; Mandy Shipp, RD; Marisa Smith; Elizabeth Tucker

University of Alabama at Birmingham Cora E. Lewis, MD, MSPH1; Sheikilya Thomas MPH2; Monika Safford, MD3; Vicki DiLillo, PhD; Charlotte Bragg, MS, RD, LD; Amy Dobelstein; Stacey Gilbert, MPH; Stephen Glasser,
Harvard Center

Massachusetts General Hospital: David M. Nathan, MD1; Heather Turgeon, RN, BS, CDE2; Kristina Schumann, BA2; Enrico Cagliero, MD3; Linda Delahanty, MS, RD3; Kathryn Hayward, MD3; Ellen Anderson, MS, RD3; Laurie Bissett, MS, RD; Richard Ginsburg, PhD; Valerie Goldman, MS, RD; Virginia Harlan, MSW; Charles McKirrick, RN, BSN, CDE; Alan McNamara, BS; Theresa Michel, DPT, DSc CCS; Alexi Poulos, BA; Barbara Steiner, EdM; Jocelyn Tosch, BA

Joslin Diabetes Center: Edward S. Horton, MD1; Sharon D. Jackson, MS, RD, CDE2; Osama Hamdy, MD, PhD3; A. Enrique Caballero, MD3; Sarah Bain, BS; Elizabeth Bovaird, BSN, RN; Ann Goebel-Fabbri, PhD; Lori Lambert, MS, RD; Sarah Ledbury, MEd, RD; Maureen Malloy, BS; Kerry Ovalle, MS, RCEP, CDE

Beth Israel Deaconess Medical Center: George Blackburn, MD, PhD1; Christos Mantzoros, MD, DSc3; Kristinia Day, RD; Ann McNamara, RN

University of Colorado Health Sciences Center James O. Hill, PhD1; Marsha Miller, MS, RD, RD; JoAnn Philipp, MS2; Robert Schwartz, MD3; Brent Van Dorsten, PhD3; Judith Regensteiner, PhD3; Salma Benchekroun MS; Ligia Coelho, BS;

Paulette Cohrs, RN, BSN; Elizabeth Daeninck, MS, RD, Amy Fields, MPH; Susan Green; April Hamilton, BS, CCRC; Jere Hamilton, BA; Eugene Leschinskyi; Michael McDermott, MD; Lindsey Munkwitz, BS; Loretta Rome, TRS; Kristin Wallace, MPH; Terra Worley, BA

Baylor College of Medicine John P. Foreyt, PhD1; Rebecca S. Reeves, DrPH, RD2; Henry Pownall, PhD3; Ashok Balasubramanyam, MBBS3; Peter Jones, MD3; Michele Burtting, RD; Chu-Huang Chen, MD, PhD; Allyson Clark, RD; Molly Gee, MEd, RD; Sharon Griggs; Michelle Hamilton; Veronica Holley; Jayne Joseph, RD; Patricia Pace, RD; Juliesta Palencia, RN, Olga Satterwhite, RD;

Jennifer Schmidt; Devin Volding, LMSW; Carolyn White

University of Tennessee Health Science Center

University of Tennessee East. Karen C. Johnson, MD, MPH; Carolyn Gresham, RN; Stephanie Connelly, MD, MPH; Amy Brewer, RD, MS; Mace Coday, PhD; Lisa Jones, RN; Lynne Lichterman, RN, BSN; Shirley Vosburg, RD, MPH; and J. Lee Taylor, MEd, MBA

University of Tennessee Downtown. Abbas E. Kitabchi, PhD, MD; Helen Lambeth, RN, BSN; Debra Clark, LPN; Andrea Cristler, MT; Gracie Cunningham; Donna Green, RN; Debra Force, MS, RD, LDN; Robert Kores, PhD; Renate Rosenthal PhD; Elizabeth Smith, MS, RD, LDN; and Maria Sun, MS, RD, LDN; and Judith Soberman, MD3

University of Minnesota Robert W. Jeffery, PhD1; Carolyn Thorson, CCRP2; John P. Bantle, MD3; J. Bruce Redmon, MD3; Richard S. Crow, MD3; Scott Crow, MD3; Susan K Raatz, PhD, RD3; Kerrin Brelje, MPH, RD; Caroyline Campbell;

Jeanne Carls, MEd; Tara Carman-Mihm, BA; Emily Finch, MA; Anna Fox, MA; Elizabeth Hoelscher, MPH, RD, CHES; La Donna James; Vicki A. Maddy, BS, RD; Therese Ockenden, RN; Birgitta I. Rice, MS, RPh CHES; Tricia Skarpohl, BS; Ann D. Tucker, MA; Mary Susan Voeller, BA; Cara Walcheck, BS, RD

St. Luke’s Roosevelt Hospital Center Xavier Pi-Sunyer, MD1; Jennifer Patricio, MS2; Stanley Heshka, PhD3; Carmen Pal, MD3; Lynn Allen, MD; Diane Hirsch, RNC, MS, CDE; Mary Anne Holowaty, MS, CN

University of Pennsylvania Thomas A. Wadden, PhD1; Barbara J. Maschak-Carey, MSN, CDE2; Stanley Schwartz, MD3; Gary D. Foster, PhD3; Robert I. Berkowitz, MD3; Henry Glick, PhD3; Shiriki K. Kumanyika, PhD, RD, MPH3; Johanna Brock; Helen Chomentowski; Vicki Clark; Canice Crerand, PhD; Renee Davenport; Andrea Diamond, MS, RD; Anthony Fabricatore, PhD; Louise Hessom, MSN, Stephanie Krauthamer-Ewing, MPH; Robert Kuehnel, PhD; Patricia Lipschutz, MSN; Monica Mullen, MS, RD; Leslie Wombolt, PhD, MS; Nayyar Iqbal, MD

University of Pittsburgh David E. Kelley, MD1; Jacqueline Wesche-Thobaben, RN, BSN, CDE2; Lewis Kuller, MD, DrPH3; Andrea Krisa, PhD3; Janet Bonk, RN, MPH; Rebecca Danchenko, BS; Daniel Edmundowicz, MD3;
Mary L. Klem, PhD, MLIS; Monica E. Yamamoto, DrPH, RD, FADA; Barb Elmyczewy, MA; George A. Grove, MS; Pat Harper, MS, RD; LDN; Janet Krulia, RN, BSN, CDE; Juliet Mancino, MS, RD, CDE, LDN; Anne Mathews, MS, RD, LDN; Tracey Y. Murray, BS; Joan R. Richea; Jennifer Rush, MPH; Karen Vujevich, RN-BC, MSN, CRNP; Donna Wolf, MS

Miriam Hospital/Brown Medical School Rena R. Wing, PhD; Renee Bright, MS; Vincent Pera, MD; John Jakicic, PhD; Deborah Tate, PhD; Amy Gorin, PhD; Kara Gallagher, PhD; Amy Bach, PhD; Barbara Bancroft, RN, MS; Anna Bertorelli, MBA, RD; Richard Carey, BS; Tatum Charron, BS; Heather Chenot, MS; Kimberley Chula-Maguire, MS; Pamela Coward, MS, RD; Lisa Cronkite, BS; Julie Currin, MD; Maureen Daly, RN; Caitlin Egan, MS; Erica Ferguson, BS, RD; Linda Foss, MPH; Jennifer Gauvin, BS; Don Kiefier, PhD; Lauren Lessard, BS; Deborah Maier, Me, JI, Massaro, BS; Tammy Monk, MS; Rob Nicholson, PhD; Erin Patterson, BS; Suzanne Phelan, PhD; Hollie Raynor, PhD, RD; Douglas Raynor, Phd; Natalie Robinson, MS, RD; Deborah Robles; Jane Tavares, BS

University of Texas Health Science Center at San Antonio Steven M. Haffner, MD; Maria G. Montez, RN, MSHP, CDE; Robert Knopp, MD; Edward Lipkin, MD; Matthew L. Maciejewski, PhD; Dace Trence, MD; Terry Barrett, BS; Joli Bartell, BA; Diane Greenberg, PhD; Anne Murillo, BS; Betty Ann Richmond, MEd; April Thomas, MPH, RD

Coordinating Center, Wake Forest University Mark A. Espeland, PhD; Judy L. Bahnson, BA; Lynne Wagenknecht, DrPH; David Reboussin, PhD; W. Jack Rejeski, PhD; Alain Bertoni, MD, MPH; Wei Lang, DrPH; Gary Miller, PhD; David Lefkowitz, MD; Patrick S. Reynolds, MD; Paul Ribisl, PhD; Mara Vitolins, DrPH; Michael Booth, MBA; Kathy M. Dotson, BA; Amelia Hodges, BS; Carrie C. Williams, BS; Jerry M. Barnes, MA; Patricia A. Feeney, MS; Jason Griffin, BS; Lea Harvin, BS; William Herman, MD, MPH; Patricia Hogan, MS; Sarah Jaramillo, MS, Mark King, BS; Kathy Lane, BS; Rebecca Neiberg, MS; Andrea Ruggiero, MS; Christian Speas, BS; Michael P. Walkup, MS; Karen Wall, AAS; Michelle Ward; Delia S. West, PhD; Terri Windham

Central Laboratory, Northwest Lipid Research Laboratories Santica M. Marcovina, PhD, ScD; Greg Stylerwicz, MS

Federal Sponsors

National Institute of Diabetes and Digestive and Kidney Diseases: Barbara Harrison, MS; Van S. Hubbard, MD PhD; Susan Z. Yanovski, MD

National Heart, Lung, and Blood Institute: Lawton S. Cooper, MD, MPH; Jeffrey Cutler, MD, MPH; Eva Obarzanek, PhD, MPH, RD

Centers for Disease Control and Prevention: Edward W. Gregg, PhD; David F. Williamson, PhD; Ping Zhang, PhD

Funding and Support

This study is supported by the Department of Health and Human Services through the following cooperative agreements from the National Institutes of Health: DK57136, DK57149, DK56990, DK57177, DK57161, DK57151, DK57151, DK57182, DK57131, DK57002, DK57078, DK57154, DK57178, DK57219, DK57008, DK57135, and DK56992. The following federal agencies have contributed support: National Institute of Diabetes and Digestive and Kidney Diseases; National Heart, Lung, and Blood Institute; National Institute of Nursing Research; National Center on Minority Health and Health Disparities; Office of Research on Women’s Health; and the Centers for Disease Control and Prevention.

Additional support was received from The Johns Hopkins Medical Institutions Bayview General Clinical Research Center (M01RR02719); the Massachusetts General Hospital Mallinckrodt General Clinical Research Center (M01RR01066); the University of Colorado Health Sciences Center General Clinical Research Center (M01RR00051) and Clinical Nutrition Research Unit (P30 DK48520); the University of Tennessee at Memphis General Clinical Research Center (M01RR0021140); the University of Pittsburgh General Clinical Research Center (M01RR0005644) and NIH grants (DK 046204 and DK072497); and VA Puget Sound Health Care System and Department of Veterans Affairs; Frederic C. Bartter General Clinical Research Center (M01RR01346). AKH was supported by the Training Program in Cardiovascular Research (NIH, 5T32HL069770)

The following organizations have committed to make major contributions to Look AHEAD: Federal Express; Health Management Resources; Johnson & Johnson, LifeScan Inc.; Optifast-Novartis Nutrition; Roche Pharmaceuticals; Ross Product Division of Abbott Laboratories; Slim-Fast Foods Company; and Unilever.

Int J Obes (Lond). Author manuscript; available in PMC 2014 June 01.
All other Look AHEAD staffs are listed alphabetically by site.

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Table 1

| Characteristic                  | Total (N = 3,899) | DSE (N = 1,964) | ILI (N = 1,935) |
|---------------------------------|-------------------|-----------------|-----------------|
| Women (%)                       | 2,192 (56.2)      | 1,096 (55.8)    | 1,096 (56.6)    |
| Ethnicity (%)                   |                   |                 |                 |
| African American                | 618 (15.8)        | 305 (15.5)      | 313 (16.2)      |
| American Indian/Alaskan Nativea | 20 (0.5)          | 9 (0.5)         | 11 (0.6)        |
| Asian/Pacific Islander          | 41 (1.1)          | 19 (1.0)        | 22 (1.1)        |
| Hispanic/Latino                 | 307 (7.9)         | 159 (8.1)       | 148 (7.7)       |
| Non-Hispanic White              | 2,835 (72.7)      | 1,430 (72.8)    | 1,405 (72.6)    |
| Other (multiple)                | 78 (2.0)          | 42 (2.1)        | 36 (1.9)        |
| Age (years)                     | 59.1±6.8          | 59.2±6.8        | 59.0±6.9        |
| BMI (kg/m^2)                    |                   |                 |                 |
| Women                           | 36.8±6.2          | 36.9±6.1        | 36.7±6.3        |
| Men                             | 35.3±5.5          | 35.1±5.2        | 35.5±5.8        |
| Waist circumference (cm)        |                   |                 |                 |
| Women                           | 111.4±13.7        | 111.5±13.6      | 111.3±13.8      |
| Men                             | 118.8±13.4        | 118.5±12.9      | 119.2±13.9      |
| Weight at Y0 (kg)               |                   |                 |                 |
| Women                           | 96.7±17.5         | 96.6±17.4       | 96.8±17.7       |
| Men                             | 109.6±18.5        | 109.4±17.8      | 109.8±19.2      |
| Weight at Y1 (kg)               |                   |                 |                 |
| Women                           | 92.1±17.8         | 95.6±17.5       | 88.7±17.3       |
| Men                             | 104.1±18.9        | 108.7±17.9      | 99.4±18.8       |
| Weight at Y4 (kg)               |                   |                 |                 |
| Women                           | 93.3±17.8         | 94.4±17.7       | 92.3±17.9       |
| Men                             | 106.1±19.1        | 108.4±18.2      | 103.7±19.7      |
| Weight Change Y1-Y0 (kg)        |                   |                 |                 |
| Women                           | −4.6±7.1          | −0.9±5.1        | −8.1±7.1        |
| Men                             | −5.6±8.4          | −0.9±5.2        | −10.5±8.3       |
| Weight Change Y4-Y0 (kg)        |                   |                 |                 |
| Women                           | −3.3±9.0          | −2.2±9.4        | −4.5±8.5        |
| Men                             | −3.3±8.8          | −0.9±7.8        | −5.8±9.0        |

a. Population Characteristics among individuals who lost 3% or more of baseline weight at year 1
## a. Population Characteristics among individuals who lost 3% or more of baseline weight at year 1

| Characteristic          | Total (N= 2,022) | DSE (N=477) | ILI (N=1,545) |
|-------------------------|------------------|-------------|---------------|
| Ethnicity (%)           |                  |             |               |
| African American        | 300 (14.8)       | 64 (13.4)   | 236 (15.3)    |
| American Indian/Alaskan Native$^a$ | 8 (0.4)       | 2 (0.4)     | 6 (0.4)       |
| Asian/Pacific Islander  | 21 (1.0)         | 3 (0.6)     | 18 (1.2)      |
| Hispanic/Latino         | 145 (7.2)        | 39 (8.2)    | 106 (6.9)     |
| Non-Hispanic White      | 1,511 (74.7)     | 360 (75.5)  | 1151 (74.5)   |
| Other (multiple)        | 37 (1.8)         | 9 (1.9)     | 28 (1.8)      |
| Age at Y1 (years)       | 61.0±6.9         | 61.1±6.8    | 61.0±6.9      |
| BMI at Y1 (kg/m$^2$)    |                  |             |               |
| Women                   | 33.2±5.9         | 34.9±6.0    | 32.6±5.8      |
| Men                     | 31.7±5.5         | 33.2±5.0    | 31.3±5.5      |
| Waist circumference at Y1 (cm) |    |             |               |
| Women                   | 103.6±13.4       | 107.4±13.3  | 102.4±13.2    |
| Men                     | 109.3±14.0       | 114.1±12.9  | 107.9±14.1    |
| Weight at Y1 (kg)       |                  |             |               |
| Women                   | 87.4±16.5        | 91.3±17.3   | 86.1±16.0     |
| Men                     | 98.5±18.0        | 104.2±17.0  | 96.9±18.0     |
| Weight at Y4 (kg)       |                  |             |               |
| Women                   | 91.1±17.4        | 91.8±17.2   | 90.8±17.4     |
| Men                     | 103.3±19.1       | 106.6±17.6  | 102.4±19.4    |
| Weight Change Y4-Y1 (kg)|                  |             |               |
| Women                   | 3.7±8.2          | 0.5±9.1     | 4.7±7.6       |
| Men                     | 4.8±7.8          | 2.4±7.0     | 5.5±7.8       |
| Weight Regain Y4-Y1 (%)$^b$ |            |             |               |
| Women                   | 834 (72.5)       | 157 (54.7)  | 677 (78.4)    |
| Men                     | 684 (78.5)       | 123 (64.7)  | 561 (82.4)    |

$^a$The number of American Indian participants included in this study is less than that of the parent Look AHEAD trial due to limitations in genetic consent.

$^b$Percentage of individuals who gained weight (>0 kgs) from year 1 – year 4.
Table 2
SNP characteristics in the full genetic sample and two most common racial groups: Non-Hispanic Whites and African-Americans.

| Chr | Positional candidate gene | SNP | Risk allele | Major/Minor Allele | MAF (Full Sample N = 3,899) | Major/Minor Allele | MAF (American Non-Hispanic Whites N = 2,835) | Major/Minor Allele | MAF (African American N = 618) | Reference PMID; year |
|-----|--------------------------|-----|------------|-------------------|----------------------------|-------------------|--------------------------------|-------------------|----------------------------|---------------------|
| 1   | TNNI3K                   | rs1514176 | G           | A/G               | 0.48 | A/G         | 0.43 | G/A           | 0.34 | 20935630; 2010 |
| 6   | TFAP2B                   | rs2272903 | G           | G/A               | 0.14 | G/A         | 0.11 | G/A           | 0.28 | 20935630; 2010 |
| 11  | BDNF                     | rs626S  | G           | G/A               | 0.16 | G/A         | 0.18 | G/A           | 0.05 | 19079260; 2009 |
| 11  | BDNF                     | rs1401635 | C           | G/C               | 0.29 | G/C         | 0.31 | G/C           | 0.26 | 19079260; 2009 |
| 11  | BDNF                     | rs10767664 | A           | A/T               | 0.19 | A/T         | 0.21 | A/T           | 0.07 | 19079260; 2009 |
| 13  | MTIF3                    | rs7988412 | A           | G/A               | 0.18 | G/A         | 0.17 | G/A           | 0.20 | 20935630; 2010 |
| 16  | SH2B1                    | rs4780999 | G           | A/G               | 0.37 | A/G         | 0.38 | A/G           | 0.29 | 20935630; 2010 |
| 16  | FTO                      | rs1421085 | C           | T/C               | 0.39 | T/C         | 0.46 | T/C           | 0.14 | 17496892; 2007 |
| 16  | FTO                      | rs3751812 | A           | C/A               | 0.38 | C/A         | 0.45 | C/A           | 0.13 | 19079260; 2009 |
| 16  | FTO                      | rs993609  | A           | T/A               | 0.44 | T/A         | 0.45 | T/A           | 0.49 | 17434869; 2007 |
| 16  | FTO                      | rs992708f | A           | G/A               | 0.43 | G/A         | 0.49 | G/A           | 0.24 | 17658951; 2007 |
| 18  | MC4R                     | rs17782313 | C           | T/C               | 0.25 | T/C         | 0.25 | T/C           | 0.29 | 18454148; 2008 |
| Chr | Positional candidate gene | SNP  | Risk allele | Major/Minor Allele | MAF<sup>a</sup> | Major/Minor Allele | MAF<sup>a</sup> | Major/Minor Allele | MAF<sup>a</sup> | Reference PMID; year |
|-----|--------------------------|------|-------------|---------------------|------------|---------------------|------------|---------------------|------------|-------------------|
| 19  | *QPCTL/GIPR* rs11672660<sup>g</sup> | G    | G/A         | 0.18                | G/A        | 0.21                | G/A        | 0.10                | 20935630; 2010 |

<sup>a</sup>MAF – minor allele frequency

<sup>b</sup>*TNNI3K* rs1514175 was replaced by rs1514176 (distance 48 bp, $r^2$=1.00, D’=1.00 in CEU and $r^2$=1.00, D’=1.00 in YRI).

<sup>c</sup>*BDNF* rs925946 was replaced by rs1401635 (distance 26,789 bp $r^2$=0.96, D’=1.00 in CEU; no proxy was available in YRI).

<sup>d</sup>*MTIF3* rs4771122 was replaced by rs7988412 (distance 19898, $r^2$=0.83, D’=1.00 in CEU; no proxy was available in YRI).

<sup>e</sup>*SH2B1* rs7498665 was replaced by rs4788099 (distance 27,514 bp $r^2$=1.00, D’=1.00 in CEU and D’=1.00 and $r^2$=0.94 in YRI).

<sup>f</sup>*FTO* rs9930506 was replaced by rs9922708 (distance 681 bp $r^2$=1.00, D’=1.00 in both CEU and YRI).

<sup>g</sup>*QPCTL/GIPR* rs2287019 was replaced by rs1672660 (distance 21988 bp, $r^2$=0.83, D’=1.00 in CEU, $r^2$=0.89, D’=1.00 in YRI).
Table 3

Genetic predictors of baseline weight (in kg; N = 3,899). Age, gender, ancestry principal components and study site statistically adjusted.

| Chr. | Gene       | SNP         | Minor allele | Value | Std. Error | P Value | Value | Std. Error | P Value |
|------|------------|-------------|--------------|-------|------------|---------|-------|------------|---------|
| 1    | TNN13K     | rs1514176   | G            | −0.054| 0.398      | 0.892   | −0.016| 0.134      | 0.906   |
| 6    | TFAP2B     | rs2272903   | A            | −0.862| 0.577      | 0.135   | −0.212| 0.194      | 0.274   |
| 11   | BDNF       | rs6265      | A            | −0.739| 0.547      | 0.177   | −0.231| 0.183      | 0.207   |
| 11   | BDNF       | rs1401635   | C            | −0.173| 0.429      | 0.687   | −0.038| 0.144      | 0.794   |
| 11   | BDNF       | rs10767664  | T            | −0.642| 0.511      | 0.209   | −0.188| 0.171      | 0.272   |
| 13   | MTIF3      | rs7988412   | A            | 0.009 | 0.520      | 0.986   | −0.115| 0.175      | 0.511   |
| 16   | SH2B1      | rs4788099   | G            | 1.014 | 0.404      | 0.012   | 0.191 | 0.135      | 0.159   |
| 16   | FTO        | rs1421085   | C            | 1.263 | 0.415      | 0.002   | 0.463 | 0.139      | 0.001   |
| 16   | FTO        | rs3751812   | A            | 1.143 | 0.416      | 0.006   | 0.432 | 0.139      | 0.002   |
| 16   | FTO        | rs9939609   | A            | 1.013 | 0.394      | 0.010   | 0.381 | 0.132      | 0.004   |
| 16   | FTO        | rs9922708   | A            | 1.245 | 0.405      | 0.002   | 0.440 | 0.136      | 0.001   |
| 18   | MC4R       | rs17782313  | C            | 0.550 | 0.459      | 0.230   | 0.550 | 0.459      | 0.230   |
| 19   | QPCTLAGHR  | rs11672660  | A            | −1.282| 0.510      | 0.012   | −0.461| 0.171      | 0.007   |
Table 4
Genetic predictors of year 1–4 weight change (in kg) among those who lost 3% or greater of initial weight (Total N = 2022; ILI N = 1545; DSE N=477). Age, gender, ancestry principal components, study site and year 1 weight statistically adjusted.

| Chr | Gene   | SNP     | Minor allele | Effect     | Beta  | Std. Error | P value |
|-----|--------|---------|--------------|------------|-------|------------|---------|
| 1   | TNNI3K | rs1514176 | G            | ILI        | 0.204 | 0.292      | 0.486   |
|     |        |         |              | DSE        | 0.334 | 0.501      | 0.512   |
|     |        |         |              | Avg        | 0.269 | 0.294      | 0.360   |
|     |        |         |              | ILI-DSE    | -0.130 | 0.586   | 0.825   |
| 6   | TFAP2B | rs2272903 | A            | ILI        | 0.122 | 0.417      | 0.769   |
|     |        |         |              | DSE        | 0.095 | 0.800      | 0.906   |
|     |        |         |              | Avg        | 0.109 | 0.451      | 0.810   |
|     |        |         |              | ILI-DSE    | 0.028 | 0.902      | 0.976   |
| 11  | BDNF   | rs6265  | A            | ILI        | -0.397 | 0.399   | 0.320   |
|     |        |         |              | DSE        | -1.150 | 0.685   | 0.094   |
|     |        |         |              | Avg        | -0.773 | 0.397   | 0.051   |
|     |        |         |              | ILI-DSE    | 0.753 | 0.793      | 0.343   |
| 11  | BDNF   | rs1401635 | C            | ILI        | 0.055 | 0.316      | 0.862   |
|     |        |         |              | DSE        | -0.864 | 0.567   | 0.128   |
|     |        |         |              | Avg        | -0.405 | 0.325   | 0.213   |
|     |        |         |              | ILI-DSE    | 0.919 | 0.649      | 0.157   |
| 11  | BDNF   | rs10767664 | T            | ILI        | -0.288 | 0.377   | 0.445   |
|     |        |         |              | DSE        | -0.504 | 0.657   | 0.443   |
|     |        |         |              | Avg        | -0.396 | 0.379   | 0.296   |
|     |        |         |              | ILI-DSE    | 0.216 | 0.758   | 0.776   |
| 13  | MTIF3  | rs7988412 | A            | ILI        | 0.243 | 0.386      | 0.531   |
|     |        |         |              | DSE        | -0.916 | 0.663   | 0.167   |
|     |        |         |              | Avg        | -0.334 | 0.384   | 0.381   |
|     |        |         |              | ILI-DSE    | 1.158 | 0.768   | 0.132   |
| Chr | Gene | SNP | Minor allele | Effect | Beta | Std. Error | P value |
|-----|------|-----|--------------|--------|------|------------|---------|
| 16  | SH2B1| rs4788099 | G | ILL | 0.072 | 0.297 | 0.809 |
|     |      |       |   | DSE | -0.480 | 0.521 | 0.358 |
|     |      |       |   | Avg | -0.204 | 0.301 | 0.498 |
|     |      |       |   | ILL-DSE | 0.552 | 0.600 | 0.358 |
| 16  | FTO  | rs1421085 | C | ILL | -0.137 | 0.300 | 0.649 |
|     |      |       |   | DSE | 1.173 | 0.553 | 0.034 |
|     |      |       |   | Avg | 0.518 | 0.315 | 0.100 |
|     |      |       |   | ILL-DSE | -1.310 | 0.629 | 0.037 |
| 16  | FTO  | rs3751812 | A | ILL | 0.054 | 0.289 | 0.851 |
|     |      |       |   | DSE | 1.029 | 0.522 | 0.049 |
|     |      |       |   | Avg | 0.541 | 0.299 | 0.070 |
|     |      |       |   | ILL-DSE | -0.975 | 0.596 | 0.102 |
| 16  | FTO  | rs9939609 | A | ILL | 0.031 | 0.295 | 0.916 |
|     |      |       |   | DSE | 1.382 | 0.551 | 0.012 |
|     |      |       |   | Avg | 0.707 | 0.312 | 0.023 |
|     |      |       |   | ILL-DSE | -1.351 | 0.625 | 0.031 |
| 18  | MC4R | rs17782313 | C | ILL | -0.275 | 0.341 | 0.420 |
|     |      |       |   | DSE | 0.252 | 0.619 | 0.685 |
|     |      |       |   | Avg | -0.012 | 0.354 | 0.973 |
|     |      |       |   | ILL-DSE | -0.527 | 0.707 | 0.456 |
| 19  | QPCTL/GIPR | rs11672660 | A | ILL | 0.131 | 0.373 | 0.726 |
|     |      |       |   | DSE | -0.850 | 0.694 | 0.221 |
|     |      |       |   | Avg | -0.359 | 0.394 | 0.362 |
| Chr | Gene | SNP | Minor allele | Effect | Beta  | Std. Error | P value |
|-----|------|-----|--------------|--------|-------|------------|--------|
|     |      | Ili-Dse | 0.980 | 0.787 | 0.213 |

\(^a\) SNP effect within the intensive lifestyle intervention arm

\(^b\) SNP effect within the diabetes support and education arm

\(^c\) SNP effect averaged across treatment arms

\(^d\) SNP × treatment arm interaction