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Genetic predictors of depressive symptoms in the Look AHEAD Trial

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Abstract

Objective—Numerous studies find elevated depressive symptoms among individuals with type 2 diabetes, yet the mechanisms remain unclear. We examined whether genetic loci previously associated with depressive symptoms predict depressive symptoms among overweight/obese individuals with type 2 diabetes or change in depressive symptoms during behavioral weight loss.

Methods—The *Illumina CARe iSelect* (IBC) chip and Cardiometabochip were characterized in 2,118 overweight or obese participants with type 2 diabetes from Look 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 focused on baseline Beck Depression Inventory (BDI) scores and depressive symptom change at one year.

Results—Of eight single nucleotide polymorphisms (SNPs) in six loci, three *a priori* SNPs in two loci (Chr5: rs60271; *LBR:* rs2230419, rs1011319) were associated with baseline BDI scores, but in the opposite direction of prior research. In joint analysis of 90,003 IBC and Cardiometabochip SNPs, rs1543654 in the region of *KCNE1* predicted change in BDI scores at year 1 in DSE (beta= −1.05, SE=0.21, $p=6.9 \times 10^{-7}$) at the level of chip-wide significance, while also showing a nominal association with baseline BDI (beta=0.35, SE=0.16, $p=0.026$). Adjustment for antidepressant medication and/or limiting analyses to Non-Hispanic White individuals did not meaningfully alter results.

Conclusions—Previously reported genetic associations with depressive symptoms did not replicate in this cohort of overweight/obese individuals with type 2 diabetes. We identified *KCNE1* as a potential novel locus associated with depressive symptoms.

Keywords

genetics; depression; diabetes; weight loss; obesity

Introduction

Numerous studies have documented a disproportionately high prevalence of depression among patients with type 2 diabetes (1–3). Elevated depressive symptoms predict difficulty with adherence to diabetes regimens (4), diabetes complications (5, 6) and mortality (7, 8). Several mechanisms have been suggested to account for the greater prevalence of depression, including poor health behaviors, the stress of managing a chronic disease, altered autonomic and neuroendocrine function, systemic inflammation and cerebrovascular mechanisms (9, 10). Little attention has been paid to the potential for a genetic role.

Diabetes and cardiac disease frequently co-occur, and depressive symptoms are elevated in both. Our team has examined genetic predictors of depressive symptoms in patients with established cardiac disease (11) focusing on candidate genes coding for key elements within select biological pathways thought to contribute to both depression and cardiovascular disease: inflammation, platelet aggregation, endothelial function and omega-3 and –6 fatty acid metabolism (12–14). Following correction for multiple testing, one single nucleotide polymorphism (SNP), rs216873 in intron 38 of the vonWillebrand factor (*VWF*) gene was

found to be significantly associated with depressive symptoms. Several other SNPs relevant to endothelial function and platelet aggregation showed suggestive associations with depressive symptoms, including additional markers within *VWF* and markers within the vascular cellular adhesion molecule 1 (*VCAM1*), calcium channel, voltage-dependent, L type, alpha 1C subunit (*CACNA1C*) and 5-hydroxytryptamine (serotonin) receptor 2A (*HTR2A*) genes.

A recent genome-wide association study (GWAS) confirmed the role of *CACNA1C* and the calcium channel pathway in major depression (15). Furthermore, a GWAS examining depressive symptoms identified novel candidate loci, including one in a gene desert region on chromosome 5 and one in the lamin B receptor gene (*LBR*) (16).

Intensive lifestyle intervention, involving calorie and physical activity goals designed to produce weight loss, may also impact depressive symptoms. Physical activity is well known to produces a moderate reduction in depressive symptoms that is of similar magnitude to behavioral and pharmacologic treatments for depression (17). Additional research suggests that behavioral weight loss, combining diet and physical activity, reduces depressive symptoms (18).

The Action for Health in Diabetes (Look AHEAD) study is a multi-center trial that randomly assigned participants with type 2 diabetes who were overweight or obese to an Intensive Lifestyle Intervention (ILI), with the goal of producing ≥7% weight loss through calorie restriction and physical activity, or to Diabetes Support and Education (DSE) which provided diabetes education but no weight loss treatment per se. After the first year, compared with DSE, participants in the ILI arm lost significantly more weight and showed greater improvement in fitness, waist circumference and indices of diabetes control including metabolic syndrome, diabetes medication use, hemoglobin A1c and fasting glucose (19). Depressive symptoms, as measured by the Beck Depression Inventory (BDI) (20), were not elevated on average at baseline in Look AHEAD (mean=5.5, SD=5.0, range 0–35); nonetheless, participants randomized to ILI exhibited a larger improvement in depressive symptoms at year 1 relative to DSE (ILI= −1.4±4.7, DSE= −0.4±4.5; $p<0.001$) (21).

The objective of the present study was to examine whether genetic loci previously associated with depressive symptoms would predict BDI scores at baseline and/or change in BDI scores at one year after randomization to ILI or DSE. We further examined whether any SNPs represented on either the Cardiometabochip (22), a genotyping platform of over 200,000 SNPs designed to capture genetic regions associated with cardiovascular and/or diabetes risk traits, or the IBC chip (23), a gene-centric chip including roughly 50,000 SNPs in biologic candidates for cardiovascular disease risk traits, predicted baseline BDI scores or change in BDI scores with weight loss.

Material and Methods

Study cohort

The Look AHEAD study enrolled 5,145 ethnically-diverse overweight/obese subjects with type 2 diabetes (and aged 45 to 76 years) from 16 clinical centers. Of these, 3,905 contributed genetic data on the IBC chip that passed genotyping quality control procedures, while 4,047 did so for the Metabochip. Overall, 3,676 subjects provided genotypes on both the IBC and Metabochip platforms. However, only 8 out of 16 study sites collected consent for genetic analyses sufficiently broad to permit analyses of depressive symptoms. This left 2,120 individuals whose genotypes could be analyzed in the present study. Two of these individuals lacked phenotypic data related to depression, leaving 2,118 subjects with genotyping data from the IBC chip and Metabochip as our final analytic sample.

The design and methods of the Look AHEAD trial have been reported elsewhere (24), as have the baseline characteristics of the randomized cohort (25). Briefly, both the ILI and DSE groups were provided one session of education on diabetes and cardiovascular risk factors. In addition, ILI participants received an intensive lifestyle program, combining diet modification and increased physical activity, designed to produce a loss ≥7% of initial weight and maintain this weight loss. 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. ILI sessions focused on behavioral weight loss strategies, such as self-monitoring, goal setting and stimulus control, as well as gradually increasing physical activity (primarily walking) to ≥175 minutes per week. 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. The assessments reported herein occurred between June 2001 and December 2005. The Look AHEAD trial, including genetic analyses, was approved by local Institutional Review Boards.

Anthropometric Measures

Participants wore light clothing or a hospital gown and removed their shoes. Weight was measured to the nearest 0.1 kilogram in duplicate at baseline and year 1 using a digital scale. Height was measured in centimeters at baseline using a standard wall-mounted stadiometer. Where discrepant, averages of the duplicate measures were used.

Depressive symptoms

Symptoms of depression were assessed at baseline and year 1 using the Beck Depression Inventory (BDI) (26), a 21-item questionnaire that assesses mood over the previous 2 weeks. This instrument is an effective screening tool for major depression in diabetic patients (27). Total scores range from 0–63, with higher values indicating greater symptoms of depression. In the present study, however, item # 19, which assesses recent weight loss, was excluded from analysis because participants were overweight/obese, were required to be weight stable at entry and half were randomized to weight loss intervention. Thus, our use of the inventory yielded scores of 0–60. Continuous BDI scores were used as the primary outcome.

Genotyping

Genotyping was carried out using the IBC chip (23) and Metabochip (22). On both platforms, we excluded study participants with failed genotyping, gender inconsistency, or familial relatedness (kinship coefficient > 0.025). SNPs with genotyping call rate <95% in any ethnic group were also excluded. After quality control procedures, the mean genotyping success rate per SNP was >99.9%. SNPs derived from the prior literature on depressive symptoms in cardiac patients (11) or genome-wide association studies of depressive symptoms (16) were selected *a priori*. Where possible, SNPs previously associated with depressive symptoms, but not directly represented on either the IBC chip or the Metabochip, were replaced by proxies ($r^2 \geq 0.97$) using phased genotype data from the 1000 Genomes Project and the SNP Annotation and Proxy Search tool (28) based on individuals of European ancestry (CEU) and Yoruba people of Ibadan (YRI). We also examined all SNPs represented on the IBC chip or Metabochip for association with baseline or year 1 change in depressive symptoms.

Observed genotype frequencies were compared with those expected under Hardy Weinberg Equilibrium (HWE) using stratified χ^2 tests within the two largest racial/ethnic groups (non-Hispanic White and African-American). As the sample was selected for overweight and diabetes, we did not exclude SNPs *a priori* based on deviation from HWE on a chip-wide basis. However, we reviewed individual SNP results to ensure SNPs showing significant associations did not deviate from HWE. All markers highlighted in the analyses herein showed no deviation from HWE in either racial stratum at the $p<0.05$ significance level.

Statistical Analysis

For candidate gene analyses, nominal *p*-values are reported, as all 8 SNPs under consideration have shown prior associations with depressive symptoms, and our study represents an attempt at replication. For novel marker discovery using chip-wide analyses, we calculated the effective number of independent hypothesis tests among the 90,003 distinct SNPs on the autosomal chromosomes across both genotyping platforms that were relatively common (minor allele frequency (MAF) >0.05). After accounting for linkage disequilibrium (LD) as pooled across ethnicities, we estimated the effective number of uncorrelated SNPs to be 63,444 (29), resulting in a chip-wide significance threshold of $p=8.085 \times 10^{-7}$. We used a false discovery rate (FDR) approach to guide our reporting of suggestive (FDR $q<10\%$) associations, operationalized via a rank ordering of the genetic markers according to their *q*-values. FDR controls the expected proportion of false negative results among those deemed significant. Q-values are marker-specific quantities that recalibrate the rank ordering of *p*-values by the probability that they represent a false discovery; they were calculated using the *Q-value* package (30).

After excluding SNPs in LD ($r^2>0.30$), EIGENSTRAT was used to compute principal components (PCs) from available SNPs to use as covariates to control for population stratification (31). All four primary racial/ethnic groups were adequately captured by the first three PCs: Non-Hispanic White, African American, Hispanic, and Asian.

BDI scores exhibited considerable skewness at both baseline and follow-up, due to the significant number of subjects reporting minimal symptoms of depression. Since regression coefficients are easier to interpret in the original scale, we avoided transfoming the data prior to analysis. Instead, we modeled baseline and year 1 BDI measurements jointly, as bivariate normal variables with an unstructured covariance matrix. However, we subsequently corrected the model-based standard errors using Generalized Estimating Equation (GEE) methodology (32), as implemented in Splus 8.2 (33).

We considered a second outcome in which we adjusted BDI scores for antidepressant medication use. Following the methods used by Hek and colleagues to adjust for antidepressant use (16), previously employed for correcting blood pressure outcomes for antihypertensive medication use (34), we assumed that the BDI score of a person using antidepressants is a right-censored value, i.e., lower than the untreated value would be. Our nonparametric imputation procedure consisted of starting with the highest treated BDI score and replacing it with the mean BDI score of all untreated persons of the same gender that reported the same or higher BDI score. We proceeded in this fashion until all treated values had been replaced by imputed values of the corresponding untreated BDI scores. Regression of the imputed on the observed scores showed that the medication benefit for subjects taking antidepressants could be well characterized over the 0–25 range of treated BDI scores by a linear regression relationship in both men (Intercept=3.82, Slope=0.97) and women (Intercept=4.84, Slope=0.87), with R^2 values in excess of 99%. Findings suggested an approximately constant antidepressant medication benefit of 3.82 BDI points for men and a maximum benefit of 4.84 BDI points for women that decreased with depression severity.

Three-way interaction models of individual SNP markers (0, 1 or 2 copies of the minor allele; additive model) with measurement time (baseline vs. year 1) and study arm (ILI vs. DSE) were estimated using GEE procedures. Three distinct types of SNP effects (beta coefficients) are presented in the paper, which can be interpreted as the effect of one additional copy of the corresponding minor allele on a) depression levels within each of the two treatment arms (ILI and DSE); b) depression levels combined across treatment arms; and c) ILI vs. DSE differences in depression levels. When evaluated on baseline BDI scores, type (c) coefficients serve as a check of randomization imbalances across genotypic groups at baseline; when applied to year 1 change in BDI scores, they allow us to test SNP * time * treatment interactions. Longitudinal regression models adjusted all of these genetic effects for age at interview, gender, genetic ancestry (PC1, PC2, PC3), and clinic site. In addition, due to marked differences in allele frequency across major racial and ethnic groups in Look AHEAD for *a priori* SNPs (Supplemental Table 2), we conducted analyses limited to participants reporting Non-Hispanic White descent to guard against results solely attributable to residual population stratification not captured by PCA adjustment.

Results

Descriptive statistics

Participant characteristics of the genetic sub-cohort of Look AHEAD used in these analyses are shown in Table 1, with the characteristics for the Non-Hispanic White subset presented in Supplemental Table 1. In both subsets, individuals were evenly distributed between the

ILI and DSE intervention arms and had comparable age, gender and ethnicity across arms. No baseline differences in weight, clinical characteristics or depressive symptoms across ILI and DSE were observed. Similar to the parent study (19), participants in the genetic substudies that were assigned to ILI lost more weight at year 1 than those assigned to DSE, and showed larger improvements in depressive symptoms (Table 1; Supplemental Table 1). Characteristics for markers chosen for the candidate gene study are presented in Supplemental Table 2.

Candidate SNPs from prior GWAS of depressive symptoms

Two of the five loci with the strongest associations with depressive symptoms in GWAS meta-analysis (16) could be captured by proxies on either the Cardiometabochip or the IBC chip (Chr5 rs161645: proxy rs60271, r^2=1.0 in CEU, LD data not available in YRI; LBR rs4653635: proxy rs2230419, r^2=1.0 in CEU, r^2=0.77 in YRI; LBR rs4653635: proxy rs1011319, r^2=1.0 in YRI; r^2=0.89 in CEU). Associations of these loci with BDI scores before and after adjustment for antidepressant medication are presented in Table 2.

The minor allele “A” at Chr5 rs60271 (MAF = 0.28) was associated with lower baseline depressive symptoms, reaching nominal significance for BDI scores adjusted for antidepressant use (full cohort: beta=−0.39, SE=0.19, p=0.035; Non-Hispanic Whites: beta=−0.42, SE=0.20, p=0.032). Results were slightly deflated for models prior to adjustment for antidepressant use (full cohort: beta=−0.32, SE=0.17, p=0.064; Non-Hispanic Whites: beta=−0.33, SE=0.18, p=0.064). In either case, however, the direction of association was opposite from the prior report. Minor alleles of the index SNP, rs161645, conferred an increase in depressive symptoms (16) but here we find that minor alleles at the proxy, rs60271 - which is perfectly correlated with the index SNP in the largest racial or ethnic subgroup of Look AHEAD, Non-Hispanic Whites - show a negative association. The minor allele at rs60271 was also associated with year 1 increases in depressive symptoms as averaged across treatment arms. In this case, statistical significance was attained for models without adjustment for antidepressant use (full cohort: beta=0.39, SE=0.17, p=0.025; Non-Hispanic White subsample: beta=0.35, SE=0.17, p=0.044), with slightly deflated results with medication adjustment (full cohort: beta=0.31, SE=0.17, p=0.071; Non-Hispanic Whites: beta=0.33, SE=0.18, p=0.077).

SNP rs2230419 in the *LBR* region was also associated with baseline depressive symptoms, but, again, in the opposite direction of prior research. Previously, minor alleles in this region were associated with lesser depressive symptoms across studies. However, we found each copy of the minor “G” allele (MAF = 0.20) to be associated with higher depressive symptoms on the BDI scale at baseline in both the full cohort (BDI: beta=0.45, SE=0.19, p=0.018) as well as Non-Hispanic Whites (beta=0.63, SE=0.22, p=0.004) prior to adjustment for antidepressant use. Results were also significant in models after adjustment for antidepressant use (full cohort: beta=0.57, SE=0.21, p=0.007; Non-Hispanic Whites: beta=0.74, SE=0.24, p=0.002). Consistent effects were seen for SNP rs1011319, which was in high linkage disequilibrium with rs2230419, but a better proxy among individuals with African ancestry (r^2=0.89 in CEU; r^2=1.0 in YRI).

Candidate SNPs with prior association with depressive symptoms among cardiac patients

Five out of seven SNPs previously reported to be associated with depressive symptoms in cardiac patients (11) were either directly represented (*HTR2A* rs3125; *VWF* rs216873) or could be captured by proxy SNPs on one of the two genotyping platforms (*VCAM1* rs3917010: proxy rs3176861, r^2=1.0 in CEU, LD data not available in YRI; *CACNA1C* rs2239106: proxy rs2239110, r^2=1.0 in CEU, r^2=0.664 in YRI; *VWF* rs216856: proxy rs216865, r^2=1.0 in CEU; r^2 = 1.0 in YRI). None of these SNPs were associated with depressive symptoms at baseline or year 1 follow-up, within or in interaction with treatment arm, with or without adjustment for antidepressant medications, in the full genetic cohort or the genetic cohort limited to Non-Hispanic White individuals (data not shown).

Chipwide analyses across the IBC and Metabochip platforms

Baseline outcomes—No SNPs achieved chip-wide significant associations with depressive symptoms at baseline. Marker prioritization using a false-discovery approach also failed to identify any promising associations with baseline BDI scores, whether or not adjusted for antidepressant medication, in the full genetic cohort and the Non-Hispanic White subset of the genetic cohort (all FDR *q*-values >0.10). The strongest associations (FDR *q*-values >0.30) are presented in Supplemental Table 3.

One-year change—Manhattan plots for change in depressive symptoms in ILI and DSE separately, as averaged across ILI and DSE arms, and as ILI vs. DSE differences (SNP x treatment arm interactions), for the full genetic cohort are presented in Figure 1.

A SNP in the region of *KCNE1*, rs1543654, was seen to be significantly associated with change in depressive symptoms from baseline to year 1 in DSE alone, prior to antidepressant medication adjustment. The C allele (MAF=0.35) was associated with fewer depressive symptoms at year 1 in DSE (Full cohort: beta= −1.05, SE=0.21, $p=6.9 \times 10^{-7}$; Table 2). No effect was observed in ILI (beta= −0.12, SE=0.21, *p*=0.565), resulting in a nominally significant SNP x treatment arm interaction (beta= −0.92, SE=0.30, p=0.002). The minor allele at rs1543654 was also nominally associated with increased depressive symptoms at baseline (beta=0.35, SE=0.16, *p*=0.026). Similar, although slightly attenuated, results were observed for antidepressant-adjusted BDI scores in the full genetic cohort, and for BDI scores within and without medication adjustment in the Non-Hispanic White subsample (Table 2).

No other SNPs were associated with change in depressive symptoms at year 1 in ILI, DSE or in interaction with treatment arm at the level of chip-wide significance.

Discussion

One of the most vexing issues in identifying genetic associations with depressive symptoms is replication. In this paper, we attempted to replicate results from two previous papers on the genetics of depressive symptoms. The first paper employed a candidate gene strategy targeting key pathways thought to contribute to both depressive symptoms and risk for cardiovascular disease and identified one locus in *VWF* reaching experiment-wide significance and several other promising loci as associated with depressive symptoms

among 977 cardiac patients of French-Canadian descent (11). The second paper employed a more agnostic GWAS approach in 51,258 middle-aged to older adults in the general population and identified one SNP reaching genome-wide significance upon replication and several additional promising leads (16). Of the eight SNPs in six loci that we were able to represent using either the IBC or Cardiometabochip in this sample of individuals who are overweight or obese and have type 2 diabetes, we found three nominal associations in two loci (Chr5, rs60271, *LBR* rs2230419, rs1011319) with baseline depressive symptoms, but in a direction inconsistent with prior research.

This report contributes to an expanding literature finding difficulty identifying and replicating genetic associations with major depression and depressive symptoms (35). Although a number of explanations have been proposed, one of the most compelling is that depression is a heterogeneous disorder with subgroups of individuals having depression attributable to distinct causes, be they genetic, environmental or a combination of both. In this study, we note that the mean of depressive symptoms was low (Mean=5.5; SD=4.9), and variation in depressive symptoms may have reflected a number of causes, including the psychological or physiological impact of having diabetes, long-standing temperament as well as subsets of individuals with liability to major depressive disorder. It is further possible that depressive symptoms may be genetically heterogeneous, with genetic vulnerability related to one set of genes in one individual and a second set of genes in a second. This heterogeneity may be resolved by continuing to increase sample sizes of GWAS to the extent that a signal can be detected despite the noise. Alternatively, intermediate phenotypes, such as neuroimaging, may identify heterogeneity. If the depression phenotype is heterogeneous genetically, it remains plausible that genetic discoveries in very large sample sizes may retain clinical relevance due to their specificity to a subgroup.

It is also plausible that the lack of replication reflects meaningful differences across studies. One prominent difference is the diverse racial and ethnic composition of Look AHEAD compared to the homogeneity of the samples used in the prior GWAS (European-descent) and candidate gene studies (French-Canadian descent) of depressive symptoms. Differences in allele frequency and patterns of co-inheritance between marker and causal variants (linkage disequilibrium) are likely to contribute to difficulty with replication particularly when causal variants are unknown. Here, we noted that the allele frequency of some of the *a priori* SNPs differed markedly across the major racial and ethnic populations in Look AHEAD (Supplemental Table 2) suggesting the potential of differences in association within the prominent racial and ethnic groups within Look AHEAD. This led us to confirm associations in the Non-Hispanic White subset to ensure that our lack of replication was not solely attributable to differences in racial and ethnic composition. Although our results were largely consistent across the full sample and the Non-Hispanic White subset, it remains plausible that associations observed in prior studies may not generalize to individuals of African, Hispanic or Native American descent.

Additionally, the prior GWAS of depressive symptoms focused primarily on the Center for Epidemiological Studies – Depression Scale (36) to index depressive symptoms, whereas we collected depressive symptoms based on the Beck Depression Inventory. Prior research

nonetheless indicates strong correlation between the two measures (e.g., r=0.86 (37)). Another key difference was inclusion/exclusion criteria, with Look AHEAD notably being comprised of overweight individuals with type 2 diabetes. As depressive symptoms were, on average, low, it is plausible that individuals could score in this range on the basis of elevated responses to one or two items (e.g., pain or fatigue).

In chip-wide analyses, one of the first conducted in relation to BDI scores, we identified a novel region associated with change in depressive symptoms from baseline to year 1 in the control arm (DSE). The SNP reaching experiment-wide significance is located within 20 kb of *KCNE1*, or potassium voltage-gated channel, Isk-related family, member 1, a primary regulator of cellular electrophysiology and function. For example, variation in this gene has previously been associated with cardiac disease, including long QT interval syndrome (38) and atrial fibrillation (39). *KCNE1* also regulates neuronal potassium channels and resting membrane electrical potential (40), although no prior associations with depressive symptoms have been reported to our knowledge. It is of note that calcium channel genes (*CACNA1C; CACANB2*), also primary regulators of voltage-based neuronal activity, were recently associated with risk across multiple psychiatric phenotypes, including schizophrenia, bipolar disorder, autism spectrum disorder, attention deficit-hyperactivity disorder and major depressive disorder (15), although association with major depressive disorder was not seen in the most recent GWAS (35). Nonetheless, given that this is the first report of association with depressive symptoms, and the association with baseline BDI scores was relatively small, it is important to consider that the result may reflect a false positive and seek replication prior to placing too much emphasis on its potential role.

Although this is the largest genetic association study of depressive symptoms among overweight or obese individuals with type 2 diabetes, it is important to note limitations. First, we leveraged existing genotype data available in Look AHEAD, including the IBC chip and Cardiometabochip. These platforms provide complementary approaches with the IBC chip providing candidate gene coverage and the Cardiometabochip covering GWAS loci related to cardiovascular or type 2 diabetes and their risk factors; however, these chips do not provide genome-wide coverage of common variation. As such, we could not test all previously reported associations. Furthermore, although SNPs from several candidate genes often considered in the depressive symptom literature, such as those within serotonin (e.g., *SLC6A4* (*SERT*), *HTR1A*, *HTR2A*, *TPH1*, *TPH2*), dopamine (e.g., *DBH*, *DRD1*, *DRD2*, *DRD4* and *COMT*) and monoamine oxydase (*MAOA*, *MAOB*) pathways, were represented on the IBC chip, no data were available on insertion/deletion or copy number variants.

Overall, this study attempted to replicate prior SNP associations with depressive symptoms in a novel cohort of individuals who were overweight or obese and had type 2 diabetes. We further examined whether any common SNPs represented on the IBC chip or Cardiometabochip were associated with depressive symptoms at baseline or year 1 follow-up after randomization to behavioral weight loss intervention or a minimal contact control condition. No direct replications were found. In chip-wide analyses, a novel locus in close proximity to *KCNE1*, a key regulator of potassium channels, was associated with change in depressive symptoms over one year, a finding that awaits replication.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding sources: Please see appendix

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Abbreviations

Look AHEAD	The Action in Health and Diabetes trial
BMI	body mass index
GWAS	genome-wide association study
MAF	minor allele frequency
SNP	single nucleotide polymorphism
SE	standard error
LD	linkage disequilibrium
FDR	false discovery rate
Chr	chromosome
ILI	Look AHEAD intensive lifestyle intervention treatment arm
DSE	Look AHEAD diabetes support and education treatment arm
BDI	Beck Depression Inventory
HWE	Hardy-Weinberg Equilibrium

CEU	Hapmap samples from U.S. residents with northern and western European ancestry from the Centre d'Etude du Polymorphisme Humain
YRI	Hapmap samples from Yoruba people of Ibadan
VWF	vonWillebrand factor gene
VCAM1	vascular cellular adhesion molecule 1 gene
CACNA1C	calcium channel, voltage-dependent, L type, alpha 1C subunit gene
HTR2A	5-hydroxytryptamine (serotonin) receptor 2A gene
LBR	lamin B receptor gene
RAB9BP1	RAB9B, member RAS oncogene family pseudogene 1
KCNE1	potassium voltage-gated channel, Isk-related family, member 1

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Appendix: Look AHEAD Research Group at Year 1

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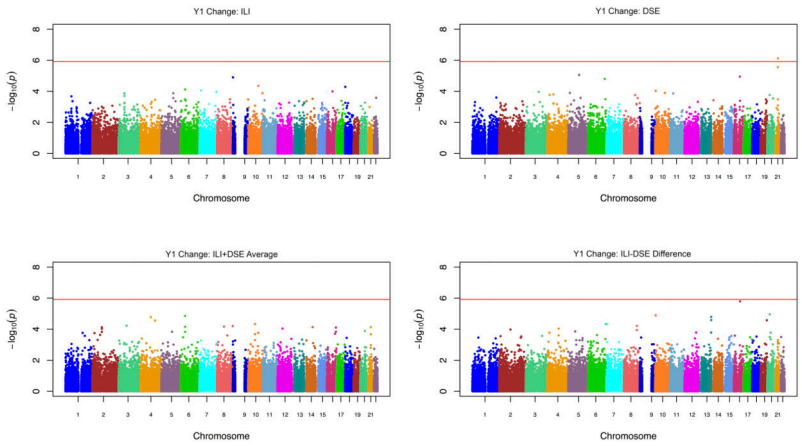

Figure 1.

Manhattan plots of combined IBC and Cardiometabochip results for year 1 depressive symptoms without antidepressant adjustment in ILI, DSE, averaged across intervention arms and difference across intervention arm.

Table 1

Demographic Characteristics

Characteristic	Total (N= 2,118)	DSE (N=1,044)	ILI (N=1,074)	p-value*
Women; n (%)	1189 (56.1)	589 (56.4)	600 (55.9)	0.7981
Age, years; mean (SD)	59.1 (6.9)	59.1 (7.0)	59 (6.9)	0.6243
Ethnicity; n (%)				
Non-Hispanic African American	215 (10.2)	109 (10.4)	106 (9.9)	
American Indian/Alaskan Native	8 (0.4)	5 (0.5)	3 (0.3)	
Asian/Pacific Islander	11 (0.5)	3 (0.3)	8 (0.7)	0.4438
Non-Hispanic White	1614 (76.2)	790 (75.7)	824 (76.7)	
Hispanic/Latino	230 (10.9)	113 (10.8)	117 (10.9)	
Other (multiple)	40 (1.9)	24 (2.3)	16 (1.5)	
Baseline measurements				
Diabetes Duration, years; median (IQR)	5 (2 to 10)	5 (2 to 10)	5 (2 to 10)	0.5205
HbA1c, %; mean (SD)	7.2 (1.16)	7.3 (1.19)	7.2 (1.14)	0.6882
Insulin use; n (%)	313 (14.8)	162 (15.5)	151 (14.1)	0.3446
BMI, kg/m^2; mean (SD)	36.3 (6.1)	36.3 (6.0)	36.3 (6.1)	0.8976
Smoking; n (%)				
Year 0	80 (3.8)	42 (4)	38 (3.5)	0.5524
Year 1	71 (3.5)	37 (3.8)	34 (3.3)	0.5957
Anti-depressant use; n (%)				
Year 0	396 (18.7)	189 (18.1)	207 (19.3)	0.4898
Year 1	396 (19.7)	201 (20.4)	195 (19.1)	0.5223
Weight, kg; mean (SD)				
Year 0	102.5 (19.2)	102.3 (18.8)	102.7 (19.5)	0.6139
Year 1	97.2 (19.4)	101.2 (18.8)	93.3 (19.2)	<0.0001
Absolute change from baseline	−5.28 (7.89)	−1.05 (5.34)	−9.36 (7.81)	<0.0001
BDI; mean (SD)				
Year 0	5.5 (4.9)	5.5 (4.6)	5.5 (5.2)	0.9321
Year 1	4.7 (5.2)	5.2 (5.0)	4.2 (5.2)	<0.0001
Absolute change from baseline	−0.78 (4.72)	−0.29 (4.52)	−1.26 (4.85)	<0.0001

*P-values obtained using: independent samples *t* test results for quantitative variables with reported mean (SD); Wilcoxon rank sum test results for quantitative variables with reported median (IQR); and chi-square test results for categorical variables with reported n (%).

Table 2

Association of *LBR* and *RAB9BP1* SNPs with BDI scores at baseline and year 1 in the full sample and the Non-Hispanic White subsample.

	SNP	Chr	Position (Build 137)	Nearest Gene	Alleles*	MAF	N	Time	Effect	*Unadjusted BDI*			*Adjusted BDI*		
										Beta	**SE**	**p-value**	**Beta**	**SE**	**p-value**
OVERALL SAMPLE	rs1011319	1	225597846	LBR	G/A	19.69	2118	Baseline	*Average*	0.49	0.19	**0.0109**	0.60	0.21	**0.0042**
								Year 1	*ILI*	−0.52	0.28	0.0628	−0.57	0.29	**0.0476**
									DSE	0.01	0.26	0.9647	−0.00	0.27	0.9920
									Average	−0.25	0.19	0.1814	−0.28	0.20	0.1459
									ILI-DSE Diff	−0.53	0.38	0.1627	−0.56	0.39	0.1497
	rs2230419	1	225607144	LBR	A/G	20.02	2118	Baseline	*Average*	0.45	0.19	**0.0185**	0.57	0.21	**0.0071**
								Year 1	*ILI*	−0.49	0.28	0.0811	−0.53	0.29	0.0702
									DSE	0.00	0.26	0.9923	−0.02	0.27	0.9468
									Average	−0.24	0.19	0.1987	−0.27	0.20	0.1673
									ILI-DSE Diff	−0.49	0.38	0.1943	−0.51	0.39	0.1967
	rs60271	5	104078233	RAB9BP1	C/A	27.79	2118	Baseline	*Average*	−0.32	0.17	0.0643	−0.39	0.19	**0.0350**
								Year 1	*ILI*	0.44	0.25	0.0760	0.38	0.26	0.1450
									DSE	0.34	0.25	0.1636	0.25	0.23	0.2788
									Average	0.39	0.17	**0.0251**	0.31	0.17	0.0707
									ILI-DSE Diff	0.10	0.35	0.7834	0.12	0.35	0.7197
NON-HISPANIC WHITES SAMPLE	rs1011319	1	225597846	LBR	G/A	16.33	1614	Baseline	*Average*	0.63	0.22	**0.0039**	0.74	0.24	**0.0021**
								Year 1	*ILI*	−0.63	0.33	0.0592	−0.64	0.34	0.0567
									DSE	0.06	0.31	0.8413	−0.02	0.32	0.9513
									Average	−0.28	0.23	0.2078	−0.33	0.23	0.1547
									ILI-DSE Diff	−0.69	0.45	0.1264	−0.63	0.47	0.1807
	rs2230419	1	225607144	LBR	A/G	16.33	1614	Baseline	*Average*	0.63	0.22	**0.0039**	0.74	0.24	**0.0021**
								Year 1	*ILI*	−0.63	0.33	0.0592	−0.64	0.34	0.0567
									DSE	0.06	0.31	0.8413	−0.02	0.32	0.9513
									Average	−0.28	0.23	0.2078	−0.33	0.23	0.1547
									ILI-DSE Diff	−0.69	0.45	0.1264	−0.63	0.47	0.1807
	rs60271	5	104078233	RAB9BP1	C/A	32.09	1614	Baseline	*Average*	−0.33	0.18	0.0644	−0.42	0.20	**0.0317**

	SNP	Chr	Position (Build 137)	Nearest Gene	Alleles*	MAF	N	Time	Effect	*Unadjusted BDI*			*Adjusted BDI*		
										Beta	**SE**	**p-value**	**Beta**	**SE**	**p-value**
								Year 1	*ILI*	0.30	0.27	0.2613	0.24	0.28	0.3946
									DSE	0.40	0.23	0.0735	0.42	0.24	0.0869
									Average	0.35	0.17	**0.0440**	0.33	0.18	0.0771
									ILI-DSE Diff	−0.10	0.35	0.7649	−0.18	0.37	0.6269

*Major/minor alleles

Three-way interaction models of individual SNP markers (0, 1 or 2 copies of the minor allele; additive model) with measurement time (baseline vs. year 1) and study arm (ILI vs. DSE) were estimated using Generalized Estimating Equation procedures. Beta coefficients reflect the effect of one additional copy of the corresponding minor allele on a) depression levels across ILI and DSE at baseline; b) year 1 depression levels in ILI; c) year 1 depression levels in DSE; d) year 1 depression levels combined across treatment arms; and e) ILI vs. DSE differences in depression levels, or SNP * time * treatment interactions. Longitudinal regression models adjusted all of these genetic effects for age at interview, gender, genetic ancestry, and clinic site.

Table 3

Association of *KCNE1* top SNPs with BDI scores at baseline and year 1 in the full sample and the Non-Hispanic White subsample.

	SNP*	Chr	Position (Build 137)	Nearest Gene	Alleles**	MAF	N	Time	Effect	*Unadjusted BDI*			*Adjusted BDI*		
										Beta	**SE**	**p-value**	**Beta**	**SE**	**p-value**
OVERALL SAMPLE	rs1543654	21	35799050	KCNE1	T/C	35.03	2118	Baseline	*Average*	0.35	0.16	0.0257	0.33	0.17	0.0578
								Year 1	*ILI*	−0.12	0.21	0.5487	−0.19	0.22	0.3863
									DSE	−1.05	0.21	**6.9E-07**	−1.02	0.22	**1.9E-06**
									Average	−0.59	0.15	0.0001	−0.61	0.15	0.0001
									ILI-DSE Diff	0.92	0.3	0.0019	0.83	0.31	0.0069
	rs9975215	21	35814953	KCNE1	G/C	31.42	2118	Baseline	*Average*	0.22	0.16	0.1808	0.22	0.18	0.2164
								Year 1	*ILI*	0.06	0.21	0.7923	0.08	0.23	0.7313
									DSE	−1.05	0.22	**1.5E-06**	−1.07	0.23	**2.1E-06**
									Average	−0.50	0.15	0.0012	−0.50	0.16	0.0019
									ILI-DSE Diff	1.11	0.31	0.0003	1.15	0.32	0.0003
NON-HISPANIC WHITE SAMPLE	rs1543654	21	35799050	KCNE1	T/C	37.42	1614	Baseline	*Average*	0.33	0.17	0.0467	0.34	0.18	0.068
								Year 1	*ILI*	0.13	0.22	0.5468	0.09	0.23	0.7119
									DSE	−1.10	0.23	**1.1E-06**	−1.08	0.24	**5.3E-06**
									Average	−0.48	0.16	0.0022	−0.49	0.17	0.0028
									ILI-DSE Diff	1.23	0.32	0.0001	1.16	0.33	0.0004
	rs9975215	21	35814953	KCNE1	G/C	30.89	1614	Baseline	*Average*	0.26	0.18	0.1485	0.28	0.2	0.152
								Year 1	*ILI*	0.26	0.23	0.2676	0.30	0.25	0.2205
									DSE	−1.26	0.24	**1.7E-07**	−1.29	0.26	**4.5E-07**
									Average	−0.50	0.17	0.0027	−0.49	0.18	0.0057
									ILI-DSE Diff	1.52	0.34	5.7E-06	1.59	0.36	7.6E-06

*LD between the pair: D′=0.87, R^2 =0.80 based on the full sample and D′=0.97, R^2 =0.84 based on the NHW sample.

**Major/minor alleles

Three-way interaction models of individual SNP markers (0, 1 or 2 copies of the minor allele; additive model) with measurement time (baseline vs. year 1) and study arm (ILI vs. DSE) were estimated using Generalized Estimating Equation procedures. Beta coefficients reflect the effect of one additional copy of the corresponding minor allele on a) depression levels across ILI and DSE at baseline; b) year 1 depression levels in ILI; c) year 1 depression levels in DSE; d) year 1 depression levels combined across treatment arms; and e) ILI vs. DSE differences in depression levels, or SNP * time * treatment interactions. Longitudinal regression models adjusted all of these genetic effects for age at interview, gender, genetic ancestry, and clinic site.