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A Gender Analysis of the Study of the Pharmacotherapy of Psychotic Depression (STOP-PD): gender and age as predictors of response and treatment-associated changes in body mass index and metabolic measures

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Abstract

Background: Gender differences exist in psychiatric disorders; however gender has not been well studied in psychotic depression. This analysis of the largest clinical trial in psychotic depression examined the effects of age and gender on clinical characteristics and predictors of treatment outcome and treatment-associated changes in body mass index (BMI) and metabolic measures.

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Gender differences have been found for several psychiatric disorders; however the impact of gender has not been well studied in psychotic depression. This analysis by Deligiannidis, et. al is the largest study in psychotic depression to investigate the impact of gender on sociodemographic and clinical characteristics and the first to investigate the impact of gender and age on treatment response and treatment-associated change in BMI. Analyses were performed on data from adult subjects in “STOP-PD”, a double-blind randomized controlled trial of olanzapine plus sertraline vs. olanzapine plus placebo for the acute treatment of psychotic depression. This analysis found evidence of both gender differences and similarities in sociodemographic and clinical characteristics in psychotic depression and compares them to those found in other mood and psychotic disorders. The findings that a greater percentage of females than males have all types of hallucinations and delusions with disorganization suggest that females experience psychotic depression differently than males. In addition, the finding that females have higher cholesterol measures should be taken into consideration when monitoring metabolic adverse effects of psychotropic medications. Larger studies are needed to confirm and extend the present analysis of gender differences in psychotic depression with a focus on hypothesized differences in treatment outcomes and adverse effect burden among men and pre-, peri- and postmenopausal women.

Methods: Analyses were performed on data from 259 subjects aged 18-93 in the double-blind randomized controlled trial of olanzapine plus sertraline (OLZ/SERT) vs. olanzapine plus placebo (OLZ/PBO) for psychotic depression (STOP-PD). Sociodemographic factors, clinical characteristics, treatment outcome and treatment-associated changes in BMI and metabolic measures were analyzed by gender and age.

Results: Female gender was associated with divorced (χ^2=5.3, d.f.=1, p=0.03) or widowed (χ^2=8.1, d.f.=1, p=<0.01) marital status. Co-morbid anxiety disorders were more common in females than males (χ^2=4.9, d.f.=1, p=0.03). Hallucinations(χ^2=7.8, d.f.=1, p=0.005) and delusions with disorganization (t-test= −2.10, d.f. =257, p=0.04) were significantly associated with female gender as were higher cholesterol measures(χ^2=7.15, d.f.=1, p=0.008).There were no significant interactions between treatment and gender in terms of change in BMI. Gender was not associated with treatment response.

Discussion: This is the first analysis of gender and age as predictors of treatment outcome and treatment-associated changes in BMI and metabolic adverse effects in psychotic depression. Gender differences exist in patients with psychotic depression, most notably the presence of hallucinations. Female gender was associated with metabolic measures. Future studies with larger sample sizes may detect small gender differences in treatment outcome and treatment-associated changes in BMI and metabolic measures in psychotic depression.

Keywords

psychotic depression; clinical trial, gender differences; clinical characteristics; body mass index; metabolic measures

INTRODUCTION

Major depression with psychotic features, or “psychotic depression” (MDpsy), is a serious illness characterized by the presence of delusions or hallucinations during a major depressive episode[1]. Compared to major depression without psychotic features, MDpsy is associated with increased rates of relapses and recurrences[2-4], mortality from medical causes[5], suicide attempts and completed suicide[6-8]. Effective treatments for MDpsy are available[9-15], but misdiagnosis is common[16] and many patients do not receive adequate pharmacotherapy[17]. Evidence supports that a combination of an antipsychotic and an antidepressant is the most effective pharmacotherapy for MDpsy [9,10,12-14] but not all patients respond and some experience adverse effects which can lead to early treatment discontinuation. Identification of predictors of response and treatment-associated adverse effects in this population would help clinicians detect likely treatment-responders and may help identify patients at risk for adverse effects, especially metabolic effects associated with antipsychotic use. To date, predictors of response and adverse effects in this population are ill-defined.

The effect of gender and age on clinical characteristics, treatment response and treatment-associated adverse effects has been reported for several psychiatric illnesses. Gender differences in the clinical characteristics of major depression[18,19], delusional disorder[20], bipolar psychosis[21,22] and schizophrenia[23-26] have been reported. Limited studies into gender differences in MDpsy [27-30] suggest that females may experience more fatigue, psychomotor agitation, mood-incongruent delusions[29] and somatic symptoms[28] but less suicidality[27] than males. Small gender differences exist in antidepressant and antipsychotic treatment response of psychiatric disorders and they may be associated with age. Younger females generally respond to SSRIs[31,32] including sertraline[33,34] better than males. This gender effect is lost in older females whose treatment response rates are similar to those of males. Furthermore, in schizophrenia, females respond better than males to olanzapine

treatment and younger females respond better than older females. These gender effects may be due in part to the effects of estrogen on dopamine and serotonin neurotransmission[35-38].

Although females may respond better to antipsychotics than males, clinically significant weight gain during antipsychotic treatment, including olanzapine, is associated with female gender and younger age[13,38-41]. Similarly, females with depression treated with a combination of an atypical antipsychotic and an antidepressant are at greater risk for weight gain than males[42]. Thus younger females may respond better to antidepressant and antipsychotic treatment than older females or males but they may experience greater treatment-associated increases in body mass index (BMI) or changes in metabolic measures such cholesterol and blood glucose. To our knowledge, no study has yet investigated the potential role of female gender and age on treatment-associated metabolic measures in MDpsy.

Thus, gender differences in clinical characteristics and treatment outcomes are likely due to a complex interaction of psychosocial factors, neurochemical and anatomic factors, hormonal factors, and genetic factors. Across several psychiatric disorders, gender differences are striking and encompass a range of issues from demography, premorbid functioning, onset, clinical characteristics to long-term outcome. Understanding the differences is the first step to ultimately be able to provide more personalized, gender-specific treatment.

The Study of the Pharmacotherapy of Psychotic Depression (STOP-PD) reported higher remission rates after 12 weeks of treatment with olanzapine/sertraline (OLZ/SERT) than olanzapine/placebo (OLZ/PLB)[13]. The aims of this analysis were to determine: (1) if gender differences existed in the sociodemographic and clinical characteristics of patients with MDpsy; (2) if gender and age were predictors of treatment response; and (3) if gender and age were a predictor of treatment-associated changes in BMI and metabolic measures. Based on the above cited literature in non-psychotic depression and psychotic disorders, we hypothesized that (1) female gender would be associated with the presence of co-morbid anxiety disorders; (2) younger females would have higher response and remission rates than older females; (3) younger females would experience greater increases in BMI, cholesterol and blood glucose as metabolic adverse effects.

METHOD

Study Sample

Analyses were performed on data from 259 subjects aged 18-93 in the STOP-PD study, a double-blind randomized controlled study of olanzapine plus sertraline (OLZ/SERT) vs. olanzapine plus placebo (OLZ/PBO) for MDpsy. The CONSORT diagram for this analysis was previously reported[13]. 117 subjects 18-59 years old and 142 subjects 60-93 years old were enrolled from the inpatient and outpatient services of the 4 participating academic sites from December 2002 to June 2007. Using an age group of 18-59 years to characterize younger females and age ≥60 years for older females, 75 females were designated as younger and 91 females as older. The cut-off of age 60 was used to maintain consistency with other STOP-PD reports. Sixteen females received hormone replacement therapy, of whom 6 were ≤ 59 years old and 10 were ≥ 60 years old; they were all included in the main gender analyses. Diagnosis of MDpsy, based on DSM-IV TR[1] criteria, was assessed with the Structured Interview for Clinical Diagnosis[43]. Additionally, subjects with MDpsy were required to have a delusional belief, a score of 2 or higher on one of the conviction items of the Delusional Assessment Scale (DAS)[44], and a score of 3 or higher on the Schedule of Affective Disorders and Schizophrenia (SADS) [45] delusion severity rating item. Subjects received a daily mean olanzapine dose of 14.3 mg/day (SD=5.3 mg) and a mean sertraline

dose 168.9 mg/day (SD=44.1mg)[13]; there was no statistically significant differences in dose of either sertraline or olanzapine based on gender (data not shown). They underwent repeated assessments with the Hamilton Depression Scale (HAM-D)[46], DAS, SADS, Brief Psychiatric Rating Scale (BPRS)[47], Scale for the Assessment of Positive Symptoms (SAPS)[48], Clinical Global Impressions, Severity of Illness Scale (CGI-S)[49], Mini Mental Status Exam (MMSE)[50] and other instruments as outlined elsewhere[13]. Study assessments were completed weekly for the first 6 weeks and then every other week until week 12 or termination. Analysis was completed on data collected at weeks 0, 4, 8 and 12, when metabolic measures were also collected. The local institutional review boards of the participating academic medical centers and a data safety monitoring board at the National Institute of Mental Health approved the study and written informed consent was obtained from all subjects or their substitute decision makers.

Statistical analyses

Subjects' baseline sociodemographic and clinical characteristics were compared according to gender, age, and treatment using χ^2 tests for categorical variables and t-tests for continuous variables (with Satterthwaite's adjustment for unequal variances, as appropriate). Because of the potential for small cell sizes with categorical variables, we report the p-value for the likelihood ratio chi-square test statistic throughout this paper. For cross-sectional data, we used a t-test for comparison of means and, a χ^2 test for comparison of proportions. We analyzed the longitudinal BMI, HAM-D and metabolic measures using generalized estimating equation (GEE) methods. This approach allowed us to analyze all available data across the study for each patient while controlling for the inherent correlation among the data collected at weeks 0, 4, 8, and 12. Both main and interaction effects (i.e., age group*gender, age group*visit, gender*visit, gender*treatment group, age group*treatment group in relation to BMI and HAM-D-17; gender*age group in relation to metabolic measures; time*treatment group in relation to BMI) were investigated. Reported p-values are for either a test that a single regression coefficient was equal to 0 or, for an overall test, a Type 3 test of any difference among the levels of a factor (such as Weeks) adjusting for the other factors in the model. Because of sample size, the study had limited power to detect significant interactions. To determine if data missing at later visits was random and not related to gender or treatment, we conducted a sensitivity analysis on all subjects for BMI, each metabolic measure, and HAM-D-17. SAS Version 9.2 (SAS Institute, Cary, NC) was used for all data analysis.

We chose not to adjust the critical significance level (i.e., p=0.05) for multiple comparisons because: (1) the adjustment would be extreme, eliminating any indication of results that might be of interest for further study; and (2) the presentation of the results using the conventional critical value allows the reader to make his/her own decision on the significance (and plausible causality) of the results. In fact, the literature is undecided, ranging from Rothman[51], who advocates never adjusting for multiple comparisons, to Cook and Farewell[52], who advocate a strong adjustment. The balance is between a substantial adjustment, which, while potentially controls (in some sense) the experiment-wise Type I error rate at 0.05, also substantially increases the Type II error rate, and not making any adjustment, which will control the Type II error rate but increases the Type I error rate. In a clinical trial where lives are at risk, controlling the Type I error is certainly a priority. In this study, the answer is not so clear and, thus, we have left the decision to the reader.

RESULTS

Baseline Sociodemographic and Clinical Variables

Females comprised 64.1% of the study sample. Female gender was associated with divorced (χ^2=5.3, d.f.=1, p=0.03) or widowed marital status (χ^2=8.1, d.f.=1, p=<0.01) but there were no gender differences in race or education level achieved (Table 1). Female gender was associated with: lifetime and past month anxiety disorder (χ^2=5.5, d.f.=1, p=0.02 and χ^2=4.9, d.f.=1, p=0.03 respectively), lifetime panic disorder (χ^2=7.2, d.f.=2, p=0.03) and specific phobia in the past month (χ^2=4.7, d.f.=1, p=0.03) (Table 2). Gender effects on baseline clinical characteristics as measured by the SADS, SAPS, BPRS and DAS were examined. Female gender was associated with probable or definite presence of hallucinations on the SADS (χ^2=7.8, d.f.=1, p=0.005), as were auditory (χ^2=4.8, d.f.=1, p=0.03), somatic or tactile (χ^2=6.7, d.f.=1, p=0.01) and olfactory hallucinations (χ^2=11.9, d.f.=1, p=0.001) as measured by the SAPS.

Hallucinations were also associated with female gender on the BPRS (t-test=−2.54, d.f.=257, p=0.01). In all cases, the significant effect noted on the Breslow-Day test was caused by the low levels of hallucinations reported by males ages 60 or older. The presence of a fixed delusion with conviction was an inclusion requirement of the study. Delusion characteristics including disorganization was associated with female gender (t-test= −2.10, d.f. =257, p=0.04), while temporal pressure was associated with male gender (t-test=1.94, d.f. =257, p=0.05) on the DAS.

There were no gender differences in baseline HAM-D17, HAM-D psychotic or somatic anxiety subscale, CGI or MMSE total score and both genders were equally randomized to either OLZ/SERT or OLZ/PBO. There was no gender difference in the number of antidepressant trials, antipsychotic trials, combination of antidepressant and antipsychotic trials, or use of electroconvulsive therapy prior to entering the study.

Treatment Response

There was no difference in change in HAM-D scores by gender either overall (Overall Type 3 Chi-square p=0.73, d.f.=1) or by visit by gender (Overall Type 3 Chi-square p=0.15, d.f.=3).There was no difference in change in HAM-D scores in females by age group, either overall (Overall Type 3 Chi-square p=0.0.93, d.f.=1) or by visit (Overall Type 3 Chi-square p=0.70, d.f.=3). Using age groupings based on published gender analyses[31,33,34,53] which differed from that used in STOP-PD did not change the results (data not shown). Similarly, there were no significant interactions between treatment and age (Overall Type 3 Chi-square p=0.22, d.f.=1) or gender (Overall Type 3 Chi-square p=0.31, d.f.=1), indicating that the treatment effect on HAM-D was consistent across age groups and for both genders.

Treatment-Associated Change in Body Mass Index (BMI) and Metabolic Measures

Compared to baseline, subjects experienced a significant overall mean increase in BMI (BMI: weight (kg)/ height (m) ^{2}) across all study visits (χ^2=96.14, d.f. =3, p<0.0001).Compared to subjects age 60 or older, subjects age 59 or younger had a BMI 3.6 (0.8) units greater with significant increase in BMI across visits (χ^2=18.9, d.f. =1, p=<. 0001).There was no gender difference in BMI overall or across visits or between treatment groups and there was no gender-by-treatment interaction or time-by-treatment interaction with BMI. On average, across visits, younger subjects had significantly lower glucose than older subjects (mean=−7.3 mg/dl, S.E.=3.3 mg/dl,χ^2=5.32 ,d.f.=1, p=0.02); however, there were no significant differences in glucose as a function of an age by gender interaction (p=0.18).There were significant gender differences in total cholesterol, HDL and LDL. Males overall had lower total cholesterol than females (mean=−16.4 mg/dl, S.E.=6.0 mg/dl,

χ^2=7.15,d.f.=1, p=0.008), with males in the younger age group having higher cholesterol (mean=35.2 mg/dl, S.E.=11.7 mg/dl, χ^2= 8.4,d.f.=1, p-value=0.004) than the other subjects: there was no difference in total cholesterol as a function of age group. There was a significant difference in total cholesterol, LDL and triglycerides across visits, but it was not consistent, with increases at Weeks 4 and 8, but decrease at Week 12. Male subjects had HDL and LDL levels that were −10.4 mg/dl (S.E.=2.1 mg/dl, χ^2=23.6,d.f.=1, p=<0.0001) and −13.3 mg/dl (S.E. =5.2 mg/dl, χ^2= 6.5,d.f.=1, p=0.01) lower than female subjects, respectively). For glucose, total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol, there were no significant differences by treatment (Table 3). Results of the sensitivity analysis showed no relationship between missing data and treatment or gender, implying that any missing data was missing-at-random.

Hormone Replacement Therapy (HRT)

Of 159 females with baseline data on HRT use, 16 (10.1%) received hormone replacement therapy (HRT). Due to the small number of females on HRT, there was not enough statistical power to analyze potential interactions between HRT status and BMI, change in HAM-D or other outcome measures.

DISCUSSION

To our knowledge, this analysis of the STOP-PD data is the largest analysis of gender differences in subjects with in MDpsy. The female gender prevalence (64.1%) found in the STOP-PD study is strikingly similar to that reported for the STAR*D study (63.8%)[18] and other depression studies[19]. Females and males had a similar severity of illness entering the study as measured by the HAM-D17. Although males and females were of a similar age, females were more often divorced or widowed, but equally likely to have achieved the same level of education and to be currently employed, as males. This is similar to that reported in a study of chronic major or double depression without psychotic features[19], even though the average age of females in that study was approximately 15 years younger than that in STOP-PD. Our finding is in contrast to the mixed reports of gender differences in bipolar disorder studies in which females were equally[54] or more likely[55] to be married and had attained a similar[54] or lower education level than males[55], but males were more often employed[54,55]. In comparison, females with schizophrenia have been found to be married more often than males[56,57], have either more[58] or a similar amount of education[56] and better work history than males[56,57]. In STOP-PD, there were no gender differences in enrollment setting status or race.

Epidemiologic studies have shown that females have a higher prevalence than males of comorbid depression and anxiety disorders[59-64]. Congruent with these findings and our hypothesis, in this study, females with MDpsy were more likely than males to have co-morbid anxiety disorders, including panic disorder and specific phobia. As previously reported from the STOP-PD study, females ≥60 years of age had fewer anxiety disorder diagnoses than females ≤59 years of age[65]. Some previous studies have reported female gender to be associated with a diagnosis of PTSD[66,67] while others have not[64]. In our sample this association did not reach significance, likely due to a smaller sample size than larger pooled or epidemiological studies. Subjects with substance abuse/dependence were excluded from entry, thus gender analyses were not available for co-morbid substance use disorders, where gender differences have been previously been reported in MDpsy[29].

One of the main novel findings of this analysis was that hallucinations were more common among females with MDpsy than men and that this finding was not associated with age. Auditory hallucinations were most common followed by visual, somatic or tactile, and olfactory hallucinations. Each of these types of hallucinations was more common in females

than in males except for visual hallucinations. To our knowledge this is the first report of an association between female gender and hallucinations in unipolar MDpsy. This finding is congruent with results from a study in patients with bipolar disorder: in 155 subjects with psychotic mania[22], hallucinations were more common in females than males. In that study, females with psychotic bipolar disorder more often had a lifetime history of depression than males but gender differences in psychotic symptoms in the depressed phase have not yet been reported in the literature. Participants were excluded from the STOP PD study if they had any other Axis I psychotic or mood disorder, obsessive compulsive disorder, cognitive disorder, or substance abuse during the preceding 3 months. However, it is possible that hallucinations as part of co-morbid personality disorders that were not evaluated in the STOP-PD study, contributed to the gender effect and this is a limitation of the study.

Based on the literature in non-psychotic depression and psychotic disorders, we hypothesized that females ≤59 years of age with MDpsy would have higher response and remission rates with OLZ/PLB or OLZ/SERT than females ≥60 years of age, but that younger females would experience more treatment-associated changes in BMI and metabolic side effects such as elevated cholesterol and blood glucose. Contrary to our hypotheses, we were not able to demonstrate an effect of gender or age as on treatment outcome, on treatment-associated changes in BMI or on treatment-associated metabolic measures. However, these secondary analyses were not adequately powered to detect a small to moderate effect size. Additionally, pre-episode weight was not recorded, thus it is possible that males or females lost weight prior to treatment and weight gain as measured in the study may have represented restoration of pre-morbid weight. Similarly, due to the small number of females on HRT (N=16), there was not enough power to analyze potential interactions between HRT status and BMI change or other outcome measures. We did not collect estrogen, follicle stimulating hormone or luteinizing hormone data on study females so we could not examine the potential effects of reproductive status on outcome measures. Another important limitation to the analysis is that only HRT status and not reproductive status or other factors that affect the measurement of serum lipids (e.g., diet, smoking, physical activity, age, menopausal status[68,69] and medication[70,71]) were recorded in this study.

This study in MDpsy is the largest to investigate the impact of gender on sociodemographic and clinical characteristics and the first to investigate the impact of gender and age on treatment response and treatment-associated change in BMI. This analysis gives evidence of both gender differences and similarities in sociodemographic and clinical characteristics in MDpsy and compares them to those found in other affective and psychotic illnesses. Our findings that a greater percentage of females than males with MDpsy have all types of hallucinations and delusions with disorganization, suggest that females experience the disorder differently than males through varied symptomatology across the age spectrum. Our finding that females have higher cholesterol measures should be taken into consideration when monitoring for metabolic adverse effects of psychotropic medications. Larger studies are needed to confirm and extend the present analysis of gender differences in MDpsy with a focus on hypothesized differences in treatment outcomes and side effect burden among men and pre-, peri- and postmenopausal women.

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CLINICAL POINTS

1. One of the main novel findings of this gender analysis was that hallucinations and delusions with disorganization were more common among females with MDpsy than males and that this finding was not associated with age.
2. Our analysis did not identify gender differences in treatment response but it may have been limited by sample size.

Table 1

Baseline Demographic and Clinical Characteristics

Characteristic	**Females (N=166) Mean (SD)**	**Males (N=93) Mean (SD)**	**P-value**	**DF, t**
Age	57.69 (17.62)	58.40 (17.99)	0.7594	257, 0.31
HAM-D17 score	29.69 (5.23)	29.89 (5.29)	0.7624	257, 0.30
	Females (%)	**Males** (%)	**P-value**[a]	**DF, X^2**
Enrollment setting status				
-Inpatient	68.07	70.97		
-Outpatient	30.12	27.96	}0.7852[b]	3, 1.07
-Nursing home	0.60	0.00		
-Partial hospitalization	1.20	1.08		
Randomization to Olanzapine/Sertraline	50.00	49.46	0.9338	1, 0.01
Race				
-White	80.72	90.32		
-Black or African-American	14.46	5.38	}0.0604[b]	2, 5.61
-Other	4.82	4.30		
Marital status				
-Never married	23.49	30.11		
-Married	37.35	47.31		
-Separated	3.01	8.60	**}0.0014[b]**	4, 17.66
-Widowed	18.67	6.45		
-Divorced	17.47	7.53		
Marital status (combined)				
-Single/Married/Separated	63.86	86.02		
-Divorced/Widowed	36.14	13.98	**}<0.0001[b]**	1, 15.59
Employment status				
-Currently employed	16.56	15.22	0.7778	1, 0.08
Education				
-Less than high school graduate	31.10	29.35		
-High school graduate	29.27	25.00		
-Some college	18.90	21.74	}0.7063[b]	4, 2.16
-College graduate	11.59	9.78		
-Graduate/professional school	9.15	14.13		

Abbreviations: DF= Degrees of Freedom; HAM-D17 = Hamilton Depression Scale, 17 question

[a] Likelihood Ratio Test

[b] "}" denotes the p-value for the entire category (e.g. enrollment setting status, race, education, etc.)

Table 2

Baseline Comorbid Psychiatric Diagnoses by Gender

Diagnosis by SCID	Female (N=166) (%)	Male (N=93) (%)	χ^2 [a]	P-value[b]	DF
Anxiety Disorder, Lifetime	24 (14.5)	5 (5.4)	5.5	**0.019***	1
Anxiety Disorder, Past Month	23 (13.9)	5 (5.4)	4.9	**0.027***	1
PTSD, Lifetime	25 (15.2)	6 (6.5)	4.8	0.09	2
Panic Disorder, Lifetime	23 (13.9)	7 (7.5)	7.2	**0.027***	2
Panic Disorder, Past Month	21 (12.7)	5 (5.4)	3.8	0.05	1
Specific Phobia, Lifetime	17 (10.2)	3 (3.2)	4.7	0.10	2
Specific Phobia, Past Month	17 (10.2)	3 (3.2)	4.7	**0.031***	1

Abbreviations: SCID = Structured Interview for Clinical Diagnosis; DF = Degrees of Freedom

[a] Between gender chi-square tests of difference:

* $p \leq 0.05$

[b] Likelihood Ratio Chi-Square Test

Table 3

End of Study Metabolic Measures Adjusted for Age, Gender and Appropriate Interactions

Measure	Gender P-value[a], X^2 (DF)	Age Group P-value[a] X^2 (DF)	Gender*Age Group P-value[a] X^2 (DF)[b]	Age Group*Treatment Group P-value[a], X^2 (DF)[c]
BMI	0.69, 0.16 (1)	**<0.0001, 18.9 (1)**	-	0.10, 2.7 (1)
Glucose	0.17, 1.9 (1)	**0.02, 5.3 (1)**	0.182, 1.8 (1)	-
Total Cholesterol	**0.008, 7.2 (1)**	0.15, 2.1 (1)	**0.004, 8.4 (1)**	-
HDL	**<0.001, 23.6 (1)**	0.07, 3.3 (1)	0.316, 1.0 (1)	-
LDL	**0.01, 6.5 (1)**	0.14, 2.2 (1)	0.14, 2.2 (1)	-
Triglycerides	0.34, 0.91 (1)	0.34, 0.92 (1)	0.94, 0.07 (1)	

Abbreviations: DF = degrees of freedom

[a] Generalized Estimating Equation (GEE) Analysis

[b] Final metabolic models include: visit, treatment group, age group, gender, gender*age group

[c] Final BMI model includes: visit, treatment group, gender, treatment group*gender, age group, treatment group*age group