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The Relation of Light-to-Moderate Alcohol Consumption to Glucose Metabolism and Insulin Resistance in Nondiabetic Adults: the Moderating Effects of Depressive Symptom Severity, Adiposity, and Sex

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Abstract

Purpose—We examined the relation of alcohol consumption to glucose metabolism and insulin resistance (IR) as a function of depressive symptoms, adiposity, and sex.

Method—Healthy adults (aged 18–65 years) provided fasting blood samples and information on lifestyle factors. Alcohol intake was categorized as never, infrequent (1–3 drinks/month), occasional (1–7 drinks/week), and regular (≥ 2 drinks/day) drinkers. The Beck Depression Inventory (BDI) was used to assess symptom severity. Primary out-comes were fasting insulin, glucose, and IR assessed by the homeostasis model assessment (HOMA).

Results—In univariate analysis, alcohol consumption was negatively associated with HOMA-IR ($p = 0.03$), insulin ($p = 0.007$), and body mass index (BMI) ($p = 0.04$), but not with glucose or BDI. Adjusting for potential confounders including BMI, alcohol consumption was associated with HOMA-IR ($p = 0.01$) and insulin ($p = 0.009$) as a function of BDI and sex. For women with

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Conflict of Interest All authors declare that they have no conflict of interests.

Human and animal rights All procedures performed in this study were conducted in accordance with the ethical standards of the Duke University Health System Institutional Review Board (IRB) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent All participants gave written consent prior to study participation and data collection. The Duke University Health System Institutional Review Board (IRB) approved the consent process. We thank those who kindly volunteered to participate in this study.

²For women, we also examined whether the BDI total score was positively associated with log (HOMA-IR) and insulin within each alcohol group. Previous studies have suggested that increases in BDI are associated with increases in insulin resistance and, to a lesser extent, increases in fasting insulin in nondiabetic adults [34, 58]. Results of analysis revealed that increasing log(HOMA-IR) was significantly associated with increasing BDI ($b = 0.30$, $t = 2.56$, $p = 0.02$) for nondrinkers, but not for infrequent ($b = -0.70$, $t = -0.99$, ns) and regular/occasional ($b = 0.14$, $t = 1.38$, ns) drinkers. Similarly, insulin values were significantly associated with total BDI score ($b = 5.20$, $t = 2.46$, $p = 0.02$) for nondrinkers, but not for infrequent ($b = -0.15$, $t = -0.19$, ns) or regular/occasional ($b = 0.92$, $t = 0.86$, ns) drinkers. Lastly, when alcohol group was used as a covariate, results of multivariate linear regression revealed positive associations between log(HOMA-IR) and BDI ($b = 0.12$, $t = 1.93$, $p = 0.057$) and between insulin and BDI ($b = 1.85$, $t = 2.19$, $p = 0.03$) for never drinkers. In drinkers, no associations between BDI and either log(HOMA-IR) or fasting insulin were observed. Combined, these findings suggest that higher levels of depressive symptom severity are associated with greater IR and fasting insulin and that these associations are significant only in women who abstain from alcohol. While we do not recommend that woman with elevated symptoms of depression begin drinking alcohol, the findings underscore the complex nature of the relationship among sex, alcohol consumption, glucose metabolism, IR, and depressive symptom severity.

minimal depressive symptoms, light-to-moderate alcohol consumption was associated with lower HOMA-IR and insulin. Alcohol consumption was not associated with metabolic markers in women with higher depressive symptoms and in men. In analysis using BMI as a continuous moderator, alcohol consumption was only associated with insulin ($p = 0.004$). Post-hoc comparisons between BMI groups (<25 vs ≥ 25 kg/m²) revealed that light-to-moderate alcohol consumption was associated with lower insulin but only in subjects with BMI ≥ 25 kg/m².

Conclusions—The benefits of light-to-moderate alcohol consumption on fasting insulin and IR are sex dimorphic and appear to be independently moderated by adiposity and depressive symptom severity.

Keywords

Depressive symptom severity; Adiposity; Insulin resistance; Alcohol consumption

Introduction

Evidence suggests a dose-response relationship between alcohol consumption and risk of type 2 diabetes [1,2] and cardio-vascular diseases [3]. Compared to heavy drinkers (≥ 5 drinks/day) and never drinkers, 1–2 drinks/day have been linked with a 10 to 50% reduction in the risk of cardiometabolic conditions [4–7]. More recent evidence, however, has suggested that the risk benefits of light-to-moderate alcohol consumption may be more pronounced in women than in men [5,8,9]. For example, moderate alcohol consumption has been associated with a greater reduction in risk of type 2 diabetes in women than in men (40 vs 13%, respectively) [1]. Similarly, light consumption of alcohol has been associated with a reduced risk of hypertension, but only in females and not males [9]. At this time, it is not well understood what mechanisms underlie reported sex difference in the relation of alcohol consumption to cardiometabolic risk. One possibility is that light-to-moderate alcohol consumption is associated with metabolic function in a sex-specific manner. Results of a meta-analysis have suggested that moderate alcohol consumption is associated with lower fasting insulin level and greater insulin sensitivity in women, but not in men [10], a result also reported in a separate meta-analysis by Koppes et al. [7]. Thus, sex differences in the relation of alcohol consumption to early risk markers of cardiometabolic diseases may, in part, account for sex differences in the risk benefits of light-to-moderate alcohol intake.

In addition to sex, evidence suggests that adiposity moderates the relation of moderate alcohol consumption to risk of type 2 diabetes [11, 12]. Relative to nondrinkers, moderate alcohol consumption has been associated with a lower risk of type 2 diabetes but only in normal and overweight adults [11]. In obese individuals, however, no protective effects of alcohol consumption were reported [11]. Although null findings have been reported [13], evidence has also suggested that, in combination with sex, adiposity moderates the relation of alcohol consumption to metabolic factors. For example, adiposity, as measured by BMI, moderated the relation of alcohol consumption to IR and fasting insulin with moderate alcohol consumption associated with lower IR and fasting insulin in men with normal BMIs (<25 kg/m²), but not those with BMIs greater than or equal to 25 kg/m² [14]. In women, however, a different pattern has been observed. Moderate alcohol consumption was associated with lower insulin, but only among women who were overweight and obese (BMI

25 kg/m²) [15]. For women with BMI less than 25 kg/m², alcohol consumption was not related to metabolic markers. Thus, it is not well established if light-to-moderate alcohol consumption is associated with metabolic benefits as a function of adiposity alone or in combination with sex

Aside from sex and adiposity, we have speculated that psychological factors may also have a moderating effect on the relationship between alcohol consumption and glucose metabolism. While evidence for metabolic makers is lacking, recent evidence from our laboratory has suggested that the relation of alcohol consumption to inflammation is moderated by both depressive symptom severity and sex [16]. Specifically, we found that relative to abstainers, light-to-moderate alcohol consumption was associated with lower high-sensitivity C-reactive protein (hsCRP), but only in men with low levels of depressive symptoms. For men with high levels of depressive symptoms, alcohol consumption was not associated with hsCRP. Regardless of the level of depressive symptom severity, alcohol consumption was not associated with hsCRP in women. Given our previous observations, the current study examined whether depressive symptom severity, alone or in conjunction with sex, also moderated the relation of alcohol consumption to HOMA-IR, fasting insulin, and glucose in nondiabetic men and women. We also examined whether adiposity, as indexed by BMI, moderated the relation of alcohol consumption to metabolic markers and whether this association differed between men and women.

Research Design and Methods

The study sample was composed of 213 nonsmoking healthy men and women aged 18 to 65 years. Characteristics of the sample and study procedures have been presented in greater detail elsewhere [17]. Briefly, subjects were recruited from the general community for a study on the relation of stress to health outcomes. Potential subjects were screened using a self-report health questionnaire and face-to-face interview. Subjects were enrolled if they reported being in good health defined as no acute medical symptoms or physical injury, no history or current diagnosis of psychiatric and medical conditions including liver diseases, and no use of tobacco. Women who reported use of oral contraceptives and hormone replacement therapy and men undergoing testosterone replacement were excluded. Pregnant women and women who were breast feeding were excluded.

For the 2 weeks preceding the laboratory visit, subjects were asked to refrain from the use prescription medications and over-the-counter preparations, including low-dose aspirin. For premenopausal women, laboratory visits were conducted during the follicular phase (days 6–10 of the menstrual cycle) so as to minimize the influence of menstrual cycle phase on fasting insulin and HOMA-IR [18]. On the day of the laboratory visit, staff interviewed participants to ascertain that they were free of acute infections and recent injuries, had not undergone any medical/dental procedures, and had not taken any medications, whether over-the-counter or prescribed, during the prior 2 weeks. Each participant's oral temperature was recorded. All participants gave written consent, and the Duke University Health System Institutional Review Board (IRB) approved the study.

Depressive Symptom Severity

We assessed depressive symptom severity using the Beck Depression Inventory (BDI) [19]. The BDI is a self-rated scale used to evaluate symptoms of depression. The BDI contains 21 items with respondents asked to rate each item (e.g., “I often feel sad.”) based upon the past 2 weeks. Each BDI item is rated on a 4-point frequency scale (ranging from 0 to 3), with the total score ranging from 0 to 63. While the BDI is not designed to yield a clinical diagnosis, scores are significantly correlated with a diagnosis of major depressive disorder [19]. It has been suggested that BDI scores above 14 indicate the presence of significant depressive symptoms with scores of 17 and above suggestive of clinical depression. For analysis, BDI score was log-transformed to decrease the skewness noted in the distribution of untransformed BDI (Shapiro-Wilk’s $W = 0.80$, $p < 0.0001$).

Patterns of Alcohol Consumption

We classified patterns of alcohol consumption using the same criteria used by Albert et al. [20]: never/former (<1 drink during past 12-months), infrequent (1–3 drinks/month), occasional (1–7 drinks/week), and regular (2 or more drinks/day). In this sample, no subject reported alcohol consumption of more than 3 drinks/day. Due to low numbers of subjects who reported regular use of alcohol ($n = 16$), we combined the “occasional” and “regular” classification.¹ Combining these two categories yielded a subgroup (occasional/regular) that consisted of women who reported drinking an average of half a drink/day (median = 0.43 drinks/day, interquartile range (IQR) range 0.29–1.14) and men who consumed one drink/day (median = 1 drink/day, IQR range 0.57–1.86). In this combined category, the number of drinks/day for men and women is consistent with sex-specific reports of greatest cardiovascular benefits for alcohol consumption [21, 22].

Insulin Resistance, Insulin, and Glucose

Fasting blood specimens were drawn between the hours of 0830 and 0930. For fasting, subjects were instructed not to eat or drink anything other than water for at least 8 h prior to the laboratory visit. Plasma glucose was measured using a hexokinase-coupled reaction, and plasma insulin was measured using a solid-phase radioimmunoassay procedure. Insulin resistance was calculated using the HOMA method as described by Matthews et al. [23]. The HOMA-IR index was calculated as the product of fasting glucose (G_0) (mmol/l) and fasting insulin (I_0) (μ U/l) values divided by the constant 22.5: $HOMA = (G_0 \times I_0)/22.5$. Estimates of insulin resistance using HOMA are correlated with results from euglycemic hyperinsulinemic clamp method [24].

¹Due to the small number of regular drinkers (7.6%, $n = 16$ out of 213), we combined the occasional and regular drinking categories to form one category representative of light-to-moderate drinking. Before establishing this combined category, we examined whether the two categories, occasional and regular, differed on demographics, anthropometrics, and depressive symptom severity. As expected, occasional drinkers ($n = 70$) reported fewer drinks per week (median = 0.43, IQR 0.15–1.0) relative to regular ($n = 16$) drinkers (median = 1.43, IQR 0.86–2.14). No subject in the regular consumption group reported drinking more than 3 drinks/day; thus, heavy drinkers (> 5 drinks/day) were not represented in this sample. Comparisons between occasional and regular drinkers did not reveal significant differences in age ($F = 2.86$, ns), BMI ($F = 1.15$, ns), educational status ($F = 0.49$, ns), and BDI ($F = 0.14$, ns). In addition, the distribution of men and women did not differ by alcohol group $\chi^2(1) = 0.46$, ns. Using the same set of covariates as in the primary analysis (e.g., age, BMI, race, sex, educational status, and physical activity), we examined differences between occasional and regular drinkers on log(HOMA-IR), insulin, and glucose. Results showed no group differences for log(HOMA-IR) ($F = 0.32$, ns), insulin ($F = 0.21$, ns), and glucose ($F = 2.29$, ns).

Clinical Variables

Height and weight were measured and BMI calculated as weight in kilograms divided by height in meter squared. Participants reported race/ethnicity, their highest level of education, and physical activity. Staff verified and recorded any acute conditions (e.g., injury) or the presence of symptoms (e.g., fever, cough, runny nose) in the 2 weeks prior to laboratory visits. Subjects reporting any symptoms or injuries were rescheduled for a later time.

Analysis

Descriptive analyses were conducted to characterize the sample and sex differences with respect to the relation of alcohol intake to continuous study variables. Associations between alcohol consumption and categorical study variables were tested using χ^2 statistics for the entire sample and as a function of sex.

The primary hypothesis was tested using a multivariate model which included the interaction between logtransformed BDI, alcohol group (i.e., never, infrequent, and occasional/regular), and sex. Age, race, educational status, physical activity, and BMI were entered as covariates. As recommended by Aiken and West [25], significant interactions were decomposed using simple slope analysis with continuous covariates centered and held constant (<http://www.jeremydawson.co.uk/slopes.htm>). A simple effect is the effect of one factor on the outcome variable that is moderated by the other factor(s) that form the interaction. In the current study, we predicted that the effect of alcohol consumption on metabolic indicators would be moderated by both sex and depressive symptom severity. To explore significant interactions that included BDI, simple effect tests were performed at ± 0.5 standard deviation (SD) of BDI. In moderated regression, the simple slopes allowed for comparisons of the slope of the regression line for the outcome variables at different levels of the independent variable. In this case, patterns of alcohol consumption were compared on different levels of the moderators and severity of depressive symptoms (higher and lower BDI), independently for men and women.

A set of secondary analysis utilized general linear modeling to examine the moderating effect of adiposity as indexed by BMI. These analyses were specifically conducted to replicate previous studies reporting a relationship between alcohol consumption and metabolic factors as a function of BMI [11, 12, 26]. In the regression analysis, BMI was entered as a continuous variable with post-hoc decomposition using normal ($<25 \text{ kg/m}^2$) and overweight ($\geq 25 \text{ kg/m}^2$) groups so as to be comparable to previous studies. If the results revealed a significant moderating effect for BMI, we then explored whether the moderating effects of depressive symptom severity and BMI on the relation of alcohol consumption to metabolic markers were independent.

Results

One subject was excluded from the analysis due to missing BDI and one subject had missing values for metabolic markers; thus, results are based on the 211 subjects with complete data. Study variables descriptive characteristics for the total sample and by sex are presented in Table 1. We assessed the number of drinks in the week prior to study participation. Of those

who reported alcohol consumption (71% of the sample), the median number of drinks/week was 5 (interquartile range (IQR) 2–9). Test of chi-square did not reveal sex differences in the distribution across alcohol consumption groups ($\chi^2(2) = 1.37$, ns). For the total sample, 29% were classified as never drinkers, 31% as infrequent, and 40% as occasional/regular drinkers.

Total score for the BDI ranged from 0 to 34 (out of a possible 0 to 63), with higher scores indicating more severe depressive symptoms. Mann-Whitney U test indicated that women scored higher on the BDI than men ($U(1) = 2.96$, $p < 0.098$), although the difference between groups was only trend. Approximately 10% of the sample scored 14 or higher and 2% scored 17 or above, the latter suggestive of borderline clinical depression [19].

Relation of Alcohol Consumption to Metabolic Indicators, Demographics, Adiposity, and Depressive Symptom Severity

In line with previous findings [12,27,28], we observed a main effect for alcohol consumption for log (HOMA) ($F(2, 210) = 2.62$, $p = 0.03$) and fasting insulin ($F(2, 210) = 5.11$, $p < 0.01$), but not fasting glucose ($F(2, 210) = 0.02$, ns). Inspection of means (not normalized) revealed that never drinkers had higher HOMA-IR values ($M = 2.22$, $SD = 2.23$) than infrequent ($M = 1.43$, $SD = 0.67$) ($p < .01$) and occasional/regular drinkers ($M = 1.62$, $SD = 1.29$) ($p < .05$). Infrequent and occasional/regular drinkers did not differ on HOMA-IR. A similar pattern emerged for insulin with never drinkers exhibiting higher fasting insulin ($M = 10.0 \mu\text{IU/mL}$, $SD = 9.30$) than infrequent ($M = 6.6 \mu\text{IU/mL}$, $SD = 2.81$) ($p < .03$) and occasional/regular drinkers ($M = 7.46 \mu\text{IU/mL}$, $SD = 5.55$) ($p < .05$). Insulin levels did not differ between infrequent and occasional/regular drinkers.

Alcohol consumption was significantly associated with BMI ($F(2, 210) = 3.20$, $p = .04$). Nondrinkers had higher BMI ($M = 26.8 \text{ kg/m}^2$, $SD = 5.15$) than infrequent ($M = 24.9 \text{ kg/m}^2$, $SD = 4.48$) and occasional/regular drinkers ($M = 24.6 \text{ kg/m}^2$, $SD = 4.54$). Infrequent and occasional/regular drinkers did not differ on BMI. Age was significantly associated with alcohol consumption $F(2, 210) = 4.28$, $p = 0.02$ with nondrinkers being significantly older ($M = 31.6$ years, $SD = 11.2$) than infrequent ($M = 28.3$ years, $SD = 9.1$) and occasional/regular drinkers ($M = 27.1$ years, $SD = 8.4$). Alcohol consumption was not associated with physical activity ($\chi^2(2) = 3.76$, ns) and educational attainment ($\chi^2(16) = 21.8$, ns). Alcohol consumption was not associated with BDI ($F(2, 208) = 0.32$, ns) in the total sample or as a function of sex (alcohol group $\times$ sex, $F(2, 205) = 0.66$, ns). In addition, sex did not moderate any of the relationships between alcohol consumption, metabolic indicators, demographics, educational status, physical activity, and BMI (all $p > .40$).

Given the lack of power to investigate race/ethnicity effects across all groups (e.g., Hispanic 0.5%, Asians 15%, and Other 1.9%), we examined the prevalence of alcohol consumptions (drinkers vs nondrinkers) in Whites (54.9%) vs non-Whites (45.1%) in the total group and as a function of sex. For the total sample, results indicated a significant race effect ($\chi^2(2) = 12.5$, $p < 0.001$) with non-Whites having a greater number of abstainers (nondrinkers = 40.6% vs drinkers = 59.2%) than Whites (nondrinkers = 18.8% vs drinkers = 71.2%). Stratification by sex revealed no race differences in alcohol consumption for men ($\chi^2(2) = 2.76$, ns), but a significant race effect in women ($\chi^2(2) = 13.0$, $p < 0.01$) with non-White

women were more likely to abstain from alcohol (nondrinkers = 46.8% vs drinkers = 53.2%) than White women (nondrinkers = 16.0% vs drinkers = 84.0%).

Multivariate Analysis: the Relation of Alcohol Consumption to Metabolic Markers and Tests of Sex and Depressive Symptom Severity as Moderators

Multivariate linear regression was used to test the hypothesis that depressive symptom severity and sex, independently or jointly, moderated the relation of alcohol consumption to fasting glucose, insulin, and log (HOMA-IR). In these analyses, age, BMI, educational status, race/ethnicity, and physical activity served as covariates. As predicted, we detected a significant three-way interaction between BDI, sex, and alcohol consumption for log (HOMA-IR) ($F(2, 188) = 4.69, p = 0.01$) and insulin ($F(2, 188) = 4.79, p = 0.009$), but not glucose ($F(2, 188) = 1.97, p = 0.14$). Sex-stratified analysis was performed to evaluate the two-way interaction between alcohol consumption and BDI for HOMA-IR and insulin. For men, the BDI by alcohol consumption interaction was not significant for HOMA-IR ($F(2, 98) = 1.21, ns$) and insulin ($F(2, 98) = 1.48, ns$). In addition, in a main effect only model with the same covariates, the main effect of alcohol consumption for men was not significant for either log (HOMA-IR) or insulin (p 's > 0.18).

For women, the alcohol group by BDI interaction was significant for both log (HOMA-IR) ($F(2, 81) = 3.72, p = 0.03$) and fasting insulin ($F(2, 81) = 3.94, p = 0.02$). To decompose the significant interaction, we performed simple effect on log (HOMA-IR) and insulin at ± 0.5 SD of BDI and examined slopes for increases in alcohol consumption from never to infrequent and from never to occasional/regular drinkers (see Fig. 1a, b). For women with *lower* BDI scores (BDI = 2) (see Fig. 1a), the slope of the regression for (HOMA-IR) from never to infrequent alcohol consumption was not significant ($b = -0.17, t = -0.74, ns$). Increasing alcohol consumption from never to occasional/regular in women with minimal levels of depressive symptoms, however, was associated with decreasing values of log (HOMA-IR) ($b = -0.31, t = -1.94, p = 0.057$), although the p value did not fall below the traditional level of significance ($\alpha = 0.05$).

For women with *higher* BDI scores (BDI = 7) (see Fig. 1a, b), the slope of change in log (HOMA-IR) from never to infrequent was not significant ($b = 0.22, t = 1.10, ns$). In addition, increasing alcohol consumption from never to occasional/regular drinkers was also not associated with the slope of change in log (HOMA-IR) ($b = -0.24, t = -1.51, ns$).²

Analysis of fasting insulin revealed a similar pattern as observed for log (HOMA-IR). For women who reported minimal symptoms of depression, increasing consumption of alcohol from never to infrequent was not associated with decreasing insulin ($b = -1.18, t = -0.56, p = 0.58$). Whereas increasing alcohol consumption from never to occasional/regular was significantly associated with decreasing insulin ($b = -1.95, t = -12.40, p < 0.001$). For women with elevated symptoms of depression, the slopes of change for alcohol consumption from never to infrequent ($b = 0.26, t = 1.43, ns$) and from never to occasional/regular drinkers ($b = -0.57, t = -0.22, ns$) were not significant for insulin.

The Relation of Alcohol Consumption to Metabolic Indicators: Test of BMI and Sex as Moderators

We examined the interaction between alcohol intake and BMI (as a continuous variable) and whether this interaction was sex dependent. Results revealed that the three-way interaction between BMI, alcohol intake, and sex was not significant for log (HOMA-IR) ($F(2, 186) = 0.33$, ns), insulin ($F(2, 186) = 1.97$, ns), and glucose ($F(2, 186) = 0.85$, ns). We revised the regression model and tested the two-way interaction between BMI and alcohol intake with sex entered as a covariate along with age, race, physical activity, and educational attainment. As others have reported, we observed a significant BMI by alcohol intake interaction for insulin ($F(2, 191) = 3.89$, $p = 0.02$), but not log (HOMA-IR) ($F(2, 191) = 1.40$, ns) and glucose ($F(2, 191) = 2.12$, ns). To decompose the significant interaction, we formed two BMI groups (<25 and ≥ 25 kg/m²). Group comparisons revealed that for adults with BMI < 25 kg/m², alcohol intake was not associated with fasting insulin (see Table 2). For individuals with BMI ≥ 25 kg/m², however, never drinkers exhibited significantly higher fasting insulin compared to infrequent ($p < 0.001$) and occasional/regular drinkers ($p = 0.004$). Insulin levels did not differ between infrequent and occasional/regular drinkers ($p = 0.58$).

Is Depressive Symptom Severity Score a Proxy for BMI? Test of Independence

Previous studies have suggested an association between BDI and adiposity (e.g., [29, 30]). Given this association, we evaluated whether the BDI by alcohol group by sex interaction would remain significant in a model that included the BMI by alcohol group interaction. These analyses were conducted only for insulin as the outcome variable. Results indicated that both the three-way interaction between BDI, alcohol intake, and sex ($p = 0.029$) and the BMI by alcohol intake interaction ($p = 0.04$) remained significant suggesting that BMI and depressive symptom severity acted independently in modifying the relationship between alcohol consumption and insulin.

Conclusion

We previously reported that depressive symptom severity, as measured by the BDI, moderated the relation of alcohol use to high-sensitivity C-reactive protein in a sex-dependent manner [16]. In the present study, we examined whether depressive symptom severity also moderated the relation of alcohol consumption to glucose metabolism and IR and whether these associations were sex dependent. The major finding of this study was that, in healthy nondiabetic adults, alcohol intake was associated with metabolic indicators and that this association was moderated not only by level of depressive symptomatology but also sex. Among women with self-reported minimal symptoms of depression, light-to-moderate alcohol consumption was associated with lower HOMA-IR values and fasting insulin. For women with higher levels of depressive symptomatology, light-to-moderate alcohol consumption was not associated with either HOMA-IR or fasting insulin. In men, light-to-moderate alcohol consumption was not associated with either lower fasting insulin or insulin

resistance in regression analysis adjusted for potential confounders, results that are consistent with recent meta-analytic reports suggesting a lack of an association between alcohol consumption and metabolic indicators in men [10]. Combined, the current findings highlight the complex nature of the relation of alcohol consumption to insulin and IR and underscore the putative role of depressive symptom severity in inhibiting the metabolic benefits of light-to-moderate alcohol in women.

Although evidence has suggested that light-to-moderate alcohol consumption is associated with lower fasting insulin and improved insulin resistance [10, 27, 31], recent metaanalysis has indicated that the relation of alcohol intake to [10]. The current findings extend previous observations by suggesting that the positive effects of light-to-moderate alcohol consumption on insulin and IR in women is only observed among women who reported minimal symptoms of depression. In contrast, women with mild-to-moderate levels of depressive symptoms failed to show a metabolic benefit of light-to-moderate alcohol consumption. Although novel, the results suggest that, in addition to its relation to cardiometabolic diseases (e.g., [32, 33]) and early risk markers [30, 34], elevated levels of depressive symptoms also play a role in inhibiting the health benefits of health-promoting behaviors such as light-to-moderate alcohol consumption. Such inhibitory actions point to a new role for elevated depressive symptoms as a factor that potentially modifies the health benefits of lifestyle factors such as light-to-moderate alcohol consumption and, as reported in our previous study, leisure time physical activity [16]. Interestingly, the moderate alcohol consumption appears to be synergistic with lifestyle factors with moderate alcohol consumption associated with lower risk of type 2 diabetes among adults with 3 or 4 low-risk behaviors (e.g., BMI less than 25 kg/m², physically active, nonsmoker, and adherence to the Dietary Approaches to Stop hypertension diet) relative to the risk in persons who exhibit only 1 or none of the low-risk behaviors [35]. Similar to the moderating effect of decreasing number of low-risk behaviors on the relation of moderate alcohol consumption to risk of type 2 diabetes, the metabolic benefits of light-to-moderate alcohol consumption were attenuated with increasing severity of depressive symptoms in women.

How sex and depressive symptom severity jointly modify the relation of alcohol consumption to metabolic markers is open to speculation. Evidence has suggested, however, that alcohol consumption is associated with early risk markers of cardiometabolic diseases, such as IR and fasting insulin, in a sex-specific manner [10, 36, 37]. It has been suggested that sex differences in the relationship between alcohol intake and metabolic markers are explained by adiposity [12]. In the current study, models were adjusted for BMI, age, race, educational attainment, and physical activity, although the possibility remains for residual confounding by these factors. Moreover, in a full model that included the BMI by alcohol group interaction, the interaction between alcohol group, depressive symptom severity, and sex remained significant suggesting that adiposity, as measured by BMI, did not account for our findings. The current study also excluded smokers and individuals with a current diagnosis or past history of medical and psychiatric disorder, thus reducing the likelihood that these factors accounted for our observations. Thus, given the methodological constraints imposed on the study and statistical controls in the analysis, it is likely that unmeasured factors may explain our findings and most likely factors that show sex-dependent associations with depressive symptoms, alcohol intake, and metabolic dysregulation. One

possible biological mechanism that meets these criteria is adipokines and specifically adiponectin.

Adiponectin is an adipokine secreted by adipose tissue. It is thought that adiponectin plays an important role in the development of IR [38, 39]. Higher levels of adiponectin have been associated with insulin sensitization and are purported to have antidiabetic effects with lower levels associated with insulin resistance, obesity, and cardiometabolic diseases [40]. Emerging evidence has suggested sex difference in the relationship between adiponectin and IR, with adult men showing a less robust association [41, 42] due, in part, to the effect of testosterone on adiponectin level [41]. With respect to depression and depressive symptoms, low levels of adiponectin are speculated to increase vulnerability to depression, although a recent meta-analysis reported significant heterogeneity in the relationship between adiponectin and depression due to differences in the percentage of female participants across studies [43]. Interestingly, a study of adolescents found that the T allele of adiponectin rs1501299 was associated with reduced prevalence of depression and lower BDI score following an earthquake, but only in women and not men [44]. The T allele is associated with higher mRNA levels which are associated with higher adiponectin levels [45]. Lastly, moderate alcohol consumption is also associated with higher adiponectin level [46], although this has not been reported in all studies including those with only men [47, 48]. One randomized control trial examined the effects of moderate alcohol intake on adiponectin and reported sex-specific effects with consumption of red wine associated with increases in adiponectin in women and consumption of liquor and beer increasing adiponectin in men. Given the inter-relationship among gender, alcohol consumption, depressive symptoms, and adiponectin, it may be that, for women, depressive symptom severity mitigates the relation of alcohol consumption to IR and insulin via changes in the production of adiponectin.

We also observed that the relation of alcohol consumption to metabolic markers was mediated by BMI, whereby light-to-moderate alcohol consumption was associated with lower insulin but only among adults with BMI greater than or equal to 25 kg/m. It is well recognized that overweight individuals exhibit greater IR and higher insulin levels [49]. Thus, one possibility is that the metabolic benefits associated with light-to-moderate alcohol consumption can only be detected among those whose insulin and IR levels are sufficiently high to demonstrate significant alcohol-related decreases. We also examined the moderating effects of elevated depressive symptoms on the relation of moderate alcohol consumption to metabolic biomarker in women were due, in part, to adiposity. Results showed that this was not the case, and it appeared that adiposity and depressive symptom severity independently moderated the relation of alcohol consumption to insulin.

The current study has a number of limitations. First, BMI, as a measure of adiposity, has limitations that are well documented [50]. These limitations include limited usefulness in athletes and differences in ethnic groups and specifically the determination of distribution of body fat. Thus, individuals with greater muscle mass may be classified as overweight or obese. For individuals within the normal range of BMI ($<25 \text{ kg/m}^2$), percent body fat may be higher than expected. In addition to the use of BMI, other limitations include the crosssectional research design which does not allow for assumptions of causality. Meta-analysis of interventional studies has suggested that light-to-moderate levels of alcohol have

beneficial metabolic effects in apparently healthy men and women [8]. Secondly, a single self-report item was used to assess alcohol consumption (e.g., [51]). Given very different health implications relating to the type (red wine vs beer vs liquor), grams of alcohol, and frequency of alcohol consumption (2 drinks/day vs 5 drinks on a single occasion), it is recommended that future investigations ascertain whether different attributes of alcohol consumption are more influential on metabolic and/or cardiovascular functioning. Thirdly, the potential of response bias in the use of self-report measures can also be cited as a limitation. Evidence has suggested that an underreporting of depressive symptoms on the BDI is more likely to occur than symptom over-reporting [52]. While the present study focused on depressive symptom severity, it might be helpful for future studies to utilize a structured clinical diagnostic interview for measuring depressive symptoms. Lastly, the sample did not include individuals reporting a pattern of heavy drinking (5 drinks/day or greater); a methodological shortcoming was also reported in other published studies (e.g., [12, 53–55]). While light-to-moderate alcohol consumption may have beneficial health consequences, evidence suggests that heavy drinkers are at an increased risk for a number of chronic medical conditions including type 2 diabetes [6]. Thus, interpretations of the current findings are limited to a range of alcohol consumption stemming from comparisons among nondrinkers, infrequent drinkers (1–3 drinks/month), and individuals who reported light-to-moderate alcohol consumption, for women a half drink/day and for men 1 drink/day.

A recent meta-analysis has suggested that the risk of type 2 diabetes is greatest among individuals with both elevated depressive symptoms and metabolic dysregulation relative to individuals with only depressive symptoms, a group whose risk was similar to individuals without either depressive symptoms or metabolic dysregulation [56]. Studies have reported that the presence of depression increases threefold the odds that patients will be noncompliant with medical treatment recommendations [57]. The current findings suggest that there is more to understand about the role of depressive symptoms in type 2 diabetes and specifically that depressive symptom severity may not only increase disease risk and treatment noncompliance but also hinder the beneficial biological consequences of lifestyle factors, such as light-to-moderate alcohol consumption, associated with a reduced risk of type 2 diabetes.

In conclusion, we found that in women, but not men, elevated levels of depressive symptom severity hindered the benefits of light-to-moderate alcohol use on both fasting insulin and IR. In addition, among overweight and obese individuals, the effects of light-to-moderate alcohol consumption appeared to be more pronounced than in individuals with normal (<25 kg/m²) BMIs. Taken together, the current findings underscore the complex network of psychological, anthropomorphic, and demographic factors that can potentially alter the metabolic effects of light-to-moderate alcohol consumption. The biological benefits of light-to-moderate alcohol consumption were inhibited by depressive symptom severity that suggests a novel pathway whereby depression and depressive symptoms may influence health and disease.

Compliance with Ethical Standards

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Fig. 1a, b.

Log(HOMA-IR) according to category of alcohol intake (**a** never vs infrequent; **b** never vs occasional/regular) and depressive symptom severity in women. The statistical interaction between alcohol intake and depressive symptom severity is plotted at 0.5 SD above (high) and below (low) the total mean of the sample on the Beck Depression Inventory. *Regression lines* were generated using a model that adjusted for age, BMI, race, education, and physical activity

Table 1

Descriptive characteristic of subjects and test of gender differences

	Total	Men	Women	Gender Difference
<i>N</i>	213	116	97	
Age (years, SD)	28.8 (9.6)	28.0 (9.7)	29.5 (9.5)	NS
BMI (kg/m ² , SD)	25.2 (4.8)	25.4 (4.7)	25.0 (4.9)	NS
Race/ethnicity (%)				NS
White	54.9	57.8	51.5	
Black	27.7	21.5	35.1	
Asian	15.0	17.2	12.4	
Hispanic	0.5	0.9	0.0	
Other ^a	1.9	2.6	1.0	
Education level (%)				NS
Less than high school	0.5	0.9	0	
High school graduate	5	5	5	
Some college	32	33	30	
College graduate	25	22	29	
Post-college	37	39	35	
Alcohol consumption (%)				NS
Never/former	29	27	31	
Infrequent	31	29	33	
Occasional/regular	40	44	36	
Beck depression ^b (interquartile range)	3 (1–6)	3 (1–5)	3 (1–7)	0.08
Insulin resistance ^b (unit, interquartile range)	1.39 (0.96–2.01)	1.40 (0.95–2.05)	1.38 (0.96–1.90)	NS
Fasting glucose (mg/dL, SD)	86.4 (8.8)	87.4 (9.2)	85.1 (8.2)	0.06
Fasting insulin (μIU/mL, SD)	7.9 (6.4)	7.5 (4.4)	8.5 (8.1)	NS

Data are presented as mean (SD) and percent

^aMore than 1 race/ethnicity indicated^bDenotes median (interquartile range) for data not normally distributed

Table 2

Adjusted insulin levels (means $\pm$ SEM) by category of alcohol intake and body mass index (BMI) group.
Adjusted for age, gender, educational status, physical activity, and self-reported race

Category of alcohol intake	Fasting insulin (pmol/L) BMI < 25 kg/m ²	BMI $\geq$ 25 kg/m ²
Never	6.13 (1.9)	13.81 (2.1)
Infrequent	6.24 (1.9)	7.19 (2.1)
Occasional/regular	6.84 (1.8)	8.82 (2.0)