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The Association between Post-traumatic Stress Disorder and Insulin Resistance

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Master of Public Health

Epidemiology

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The Association between Post-traumatic Stress Disorder and Insulin Resistance

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Bachelor of Science
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An abstract of
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2015

Abstract

Introduction: Previous studies has linked posttraumatic stress disorder (PTSD) with insulin resistance (IR), however, most of these studies are cross-sectional and did not capturing familial and early environmental factors.

Methods: We examined whether PTSD associates with future IR before and after controlling for shared genetics and childhood environment in a prospective study of middle-aged male twins from the Vietnam Era Twin Registry. PTSD was diagnosed at enrollment in 1992 with Diagnostic Interview Schedule (DIS) for psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders-Third Edition-Revised (DSM-III-R). IR was measured by insulin and glucose levels as determined by the homeostatic model assessment (HOMA). A total of 475 twins were included in the analysis of PTSD and IR. Of these, 59 were new cases of diabetes diagnosed during follow-up. Mixed-effects regression models were used to examine individual, between-pair and within-pair associations.

Results: Approximately, 23% of participants met the criteria for lifetime PTSD at enrollment. When evaluating twins brothers as a family unit, PTSD was associate with 1.32 mmol/L higher HOMA-IR (95% Confidence Interval: 1.01, 1.73) adjusted for social demographic factors. However, the association became insignificant after controlling for obesity. We found no significant association when evaluating PTSD within discordant twin pairs, however.

Conclusion: Among Vietnam War-era veterans, familial PTSD is positively associated with future insulin resistance, but the effect is mostly mediated by obesity.

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Background

Posttraumatic stress disorder (PTSD) is a maladaptive response to psychological trauma that is a common cause of morbidity and mortality. People with PTSD may feel frightened even when they are out of danger, experience sleep disturbance, feel detached, or have prolonged, intense distress [1,2]. According to the National Comorbidity Survey Replication, the prevalence of lifetime PTSD among adults Americans is 6.8%, and women are twice as likely as men to have PTSD [3]. In particular, the prevalence of PTSD among Vietnam-era veterans is approximately 12%-16%.

Insulin resistance, which is defined as a state of reduced responsiveness to normal functions of exogenous or endogenous insulin [4], is a syndrome responsible for diseases such as obesity, hypertension, type 2 diabetes, and chronic liver disease [5]. IR, even in non-diabetics, plays an importance role in the development of different diseases such as coronary heart disease [5] and fatty liver.

Though the relationship between PTSD and diabetes has been recognized [6], few studies have studied insulin resistance and PTSD in the larger population of non-diabetics as well. In addition, it remains unclear whether the increased insulin resistance is the result of PTSD or other confounding factors. Familial factors, such as low birth weight, associates with both IR and adulthood mental disorders [7 8], but are typically not measured directly. Genetic factors may also confound the relationship between PTSD and insulin resistance [9-13].

In order to overcome the limitations of previous studies, we propose an analysis using twins. The advantage is that twins have matched genetics (50%-100%) and early

family environment (e.g. diet, family social economic status, parental factors). By comparing within twin pairs discordant for PTSD, we can adjust for these unmeasured effects. In this study, we examine a sample of Vietnam-era veteran twins and examined the association of PTSD with IR and diabetes. We also examine whether the association remains after adjusting for potential confounder and mediators, including genetic and familial.

Methods

Study Population

We conducted an analysis in the Emory Twin Study (ETS) which combines samples from the Twin Heart Study (THS) and the SAVEIT (Stress and Vascular Evaluation in Twins) [13]. This includes 562 (281 pairs) middle-aged male twins who were originally enrolled in the Vietnam Era Twin (VET) Registry [14]. All twins were born between 1946 and 1956. Twin pairs that were discordant for depression and PTSD were oversampled as part of the original study design.

All twins were examined in pairs at the Emory University General Clinical Research Center between 2002 and 2010 [13]. All the data were collected within 24-hour admission under controlled conditions. A comprehensive panel of risk markers, including data on sociodemographics, medical history, and physical examination, were assessed. Zygosity information of all pairs were determined by means of DNA typing. All physical examination measurements were conducted with research staff blind to PTSD status.

Consents were obtained from both Emory Institutional Review Board and all study subjects.

Measurement of Insulin Resistance

Insulin and glucose levels were used to measure insulin resistance (IR) as determined by the homeostatic model assessment (HOMA), which calculates IR based on the formula glucose times insulin, divided by 22.5. Venous blood samples were collected after an overnight fast, and glucose level was measured using Bechman CX7 chemistry auto-analyzer. Both labs were measured by the Emory Hospital labs. Insulin was measured using the ADVIA Centaur 2-sided sandwich immunoassay (Siemens) which has a range of 0.5 to 300 microunits/liter, and a coefficient of variation of 4%.

Assessment of PTSD

The measurement of PTSD status, collected at the Registry's inception in 1992, was based on the Diagnostic Interview Schedule (DIS) for psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders-Third Edition-Revised (DSM-III-R).

Assessment of potential confounders and mediators

Demographic characteristics (age, marriage and education), and behavioral factors (cigarette smoking, alcohol consumption, and coffee consumption) were collected via self-report. Abdominal and hip circumferences were measured to calculate the waist

to hip ratio (WHR), which has a well-characterized relationship with IR. A fasting glucose level over 126 mg/dl or current treatment with anti-diabetic medications were used to define diabetes. Hypertension was defined as having systolic blood pressure over 140 mm Hg or current treatment with anti-hypertension medications. Alcohol and coffee intake were measured using the Willett food frequency questionnaire. Cigarette smoking was classified into current, past and never smoker. Homogeneous assays (Equal Diagnostics, Exton, PA) was used to measure direct high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol in subjects.

Statistical Analysis

All analyses were conducted using SAS 9.4 for Windows (SAS Institute, Inc., Cary, North Carolina). Baseline differences between twins with PTSD and twin free of PTSD were evaluated. Mixed regression models with random intercept for each twin pair were used, taking into consideration pair-level clustering. Analysis using HOMA-IR as a continuous variable was conducted. HOMA-IR was log transformed because of its right skewed distribution. Multivariable adjusted models were conducted sequentially with confounders, and mediators. Adjusted factors include: 1) demographic factors (age, employment, marriage, education); 2) behavioral factors (smoking, alcohol, coffee); 3) obesity factors (BMI, WHR); 4) psychiatric comorbidity (depression, combat exposure). Tests of statistical significant were 2-sided, with 95% confidence interval.

We first evaluated the association between a history of PTSD and diabetes to evaluate for any general relationships between PTSD and clinical diabetes; this was then

followed by an analysis of PTSD and IR those who did not develop diabetes, since diabetes diagnosis and treatment may interfere with IR[15]. In addition, if PTSD and diabetes were significant, this increased the likelihood of skewing the non-diabetic subgroup. For each analysis, twin brothers were first considered individually. Next, we examined the relationship between PTSD and diabetes both between and within twin pairs. Twin pairs with three different levels of PTSD exposure were compared in the between-pair analyses. This includes twin pairs in which 0, 1, or 2 twin brothers had PTSD. In the within-pair analyses, twin pairs discordant for lifetime PTSD exposure were compared. The within-pair effects are controlled for shared genetic (50% for dizygotic, 100% for monozygotic), familial and early environmental influences, which are potential cofounders. To evaluate the potential effect of exposure on HOMA-IR was different among monozygotic twins and among dizygotic twins, interaction between zygosity and the within-pair association of PTSD and HOMA-IR was tested.

Results

Of the original 562 twins enrolled in the Emory Twins Study, we excluded 6 subjects who were diabetic at baseline (1992), 19 subjects with missing PTSD baseline status, and 1 with missing diabetes data at follow-up, yielding a study sample of 536. In the second group of analyses examining IR in the subgroup without diabetes at follow-up, we excluded the 59 subjects who developed diabetes upon enrollment in the ETS. HOMA-IR was not available in 2 subjects, yielding a final sample size of 475.

Of the 475 twins included in the final analysis, 110 had PTSD. This included 217 pairs complete twin pairs and 41 singletons. There were 87 twin pairs discordant for PTSD and 18 pairs in which both had PTSD. There were no significant differences in average age, hypertension, education and physical indexes between twins with a history of lifetime PTSD and those without PTSD (Table 1). Twins with lifetime PTSD were more likely to be unemployed. Twins with PTSD were significantly more likely to be smokers, consume alcohol, abuse drugs, and have a history of depression.

PTSD and Diabetes

Among the 536 twins who were free of diabetes in 1992, 59 (11 %) new diabetes cases were diagnosed in second examination at the Emory University General Clinical Research Center. The prevalence of diabetes were similar among subjects diagnosed with lifetime PTSD in 1992 to those free of PTSD in 1992 (10.95% vs. 11.20%). No statistical significant association between PTSD and diabetes was found in analyses (Table 2).

PTSD and HOMA-IR

Of the 475 twins, the overall mean of HOMA-IR was 1.94 (SD=1.59) mmol/L, and 38.32% (n=182) had elevated HOMA-IR using 1.85 mmol/L as the cut point for non-diabetes [16]. In the analyses in which twins were treated individually, there was no statistically significant association found between PTSD and HOMA-IR in the unadjusted (change=-0.2%; 95% CI: -12%, 14%; P=0.97) model. The association remained statistically

insignificant after adjusting for potential confounders and mediators sequentially (Table 3.).

When evaluating the association of PTSD and IR within and between pairs, a significant unadjusted association between pairs was found (p=0.0056), indicating an increase of 46% in HOMA-IR for each incremental twin with PTSD in the pair. The association diminished by 30% after adjusted for demographic factors (change=32%; 95% CI: 1%, 73%; P=0.0432). Additional adjustments for alcohol drinking and smoking status resulted in little change (Table 3.). However, the association lost statistical significance when adjusting for obesity related factors (BMI, WHR) at enrollment in 1992 (change=25%; 95% CI: -3%, 60%; p=0.08) and obesity related factors collected at follow-up (change=6%; 95% CI: -0.16-15%, 34%; p=0.59). In the model with all covariates combined, HOMA-IR pair average was 11% larger for each incremental twin with PTSD in the twin pair, although this effect was not statistically significant (change=12%; 95% CI: -11%, 39%; P=0.35).No statistically significant association between lifetime PTSD and HOMA-IR was found in within pairs discordant for PTSD (Table 3.). There was no statistically significant interaction between zygosity and within-pair association of PTSD and HOMA-IR (p=0.11). Adjustment for depression resulted in little change in the association by 0.8%, and no interaction found between PTSD and depression (p=0.35).

Discussion

In this prospective study of middle-aged Vietnam-era Veterans, familial PTSD was positively associated with the development of future insulin resistance, although when

adjusting for obesity, no associations were found. This suggests the effects were mediated by increased obesity in PTSD families. Diabetes was not statistically significant associates with PTSD in our study, but likely underpowered due to small sample size, as a larger study of the cohort showed a familial association with diabetes as well. There is no statistically significant interaction between PTSD and depression, suggesting that these effects were not due to increased depression in PTSD families.

To our knowledge, the present study is the first study examining the association between familial PTSD and HOMA-IR in twin pairs without diabetes. Although there is a study that reported an association between PTSD and IR among non-diabetics [17], the study did not investigate familial factors and was cross-sectional.

A recent study based on the same VET twin registry showed PTSD associated with a 40% increased risk of new-onset diabetes in a larger sample size [18], and suggested familial level effect of PTSD predicts diabetes through influencing metabolic and behavioral risk factors of IR. However, this study did not look at the association of PTSD and IR among non-diabetics, who may be unaware of their possibly 40% increased risk due to IR. Our study confirms a family-level effect and demonstrates the importance of obesity as a mediator [19].

The results of our twin study suggests that familial factors shared by the twins play an important role in the association of PTSD and future IR through increased obesity. PTSD may be a marker for exposures related to both obesity and IR. For example, people of low birth weight or exposed to low soceioeconomic status in childhood are at higher risks of suffering from PTSD and becoming IR later in life [7,8,20-22]. Tobacco and alcohol

consumption are common behaviors among PTSD patients, which also associate with IR [23-25]. Gestational age influences the risk of IR, and children who had been born prematurely were reported to have reduced insulin sensitivity [26]. Negative parental lifestyles and parental history of diseases also increase their offspring's vulnerability to IR and PTSD. Offspring with parental diabetes or parental high-fat diet have significantly higher level of HOMA-IR compared with those without such histories [27,28]. Figure 1 summarizes the pathways by which familial factors for PTSD may lead to increased insulin resistance.

Insulin resistance is a syndrome responsible for many diseases, including type 2 diabetes, obesity, hypertension, and cardiovascular disease [5]. In return, insulin resistance might be the consequence of obesity (mediator) based on our study. It has been reported that PTSD is a risk factor of coronary heart disease (CHD) [29]. It is possible that IR mediate the association of PTSD and CHD. Due to the high prevalence of IR, interventions should be taken to reduce not only the incidence of IR but also potential downstream toxicities. According to our findings, weight-loss interventions such as physical exercise and energy restriction would be efficient ways to prevent development of IR among PTSD families. Also, early therapies on childhood obesity will help decrease the risk of IR.

This study has a number of limitations. Despite of the advantages of using prospective study design to investigate the possible causality and capturing familial and early environmental factors, the sample size in this study is limited, which restricted the power of our analysis to detect smaller differences. In addition, the findings of this study is cannot be generalized to women or to people of different ages, because the study

population is restricted to middle-aged male veterans. Furthermore, there might be many other factors other than PTSD that triggered the onset of unhealthy lifestyles responsible for obesity, in this case, the inferences we made were limited. On the other hand, we relied on interviews and questionnaires to collect covariates data such as alcohol and coffee consumption, which reduces the veracity of our results because of the subjectivity of responders. Finally, it is possible that there is additional confounding due to unmeasured factors.

In conclusion, in this cohort of middle-aged non-diabetic veteran male twins, familial PTSD was associated with future IR, primarily due to obesity. This complements previous research that shows a relationship between familial PTSD and diabetes by showing a similar effect in non-diabetics who may not be aware of their increased risk. Further researches should focus on elucidating the specific familial and early environmental factors that involved in IR/diabetes and PTSD base on a larger and more generalized study population.

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Tables and Figures

Table 1. Twin Demographics Classified by History of PTSD at 1992 Interview, Emory Twin Study

	Characteristic	No PTSD (N=365)		Lifetime PTSD (N=110)	
		%	Mean (SD)	%	Mean (SD)
Enrollment (1992)	BMI [a]		25.5 (3.0)		25.6 (3.2)
	Current smoker	41		60	
	Past smoker	87		92	
	Never smoker	7		3	
	Depression history	20		39	
	Additive combat Index		3.3 (3.2)		5.4 (3.5)
Follow-up	***Demographic factors***				
	Age		55.2 (3.1)		56.0 (3.2)
	Education [b]		14.2 (2.2)		13.8 (2.2)
	Married	1		3	
	Employed	79		66	
	Physical factors				
	BMI [a]		29.3 (4.9)		29.3 (4.9)
	Waist-hip Ratio		0.9 (0.1)		1.0 (0.1)
	LDL Cholesterol		125.0 (34.2)		119.1 (33.5)
	HDL Cholesterol		39.5 (10.5)		39.1 (11.2)
	Behavioral factors				
	Smoking status				
	Current smoker	22		35	
	Past smoker	43		45	
	Never smoker	36		20	
	No. of alcoholic beverages per day		5.0 (8.7)		6.6 (13.2)
	Alcohol abuse history	4		5	
	No. of coffee cups per day		2.8 (3.6)		3.2 (3.0)
	Drug Abuse History	21		39	
	Psychiatric comorbidity				
	Depression history	21		42	
	Combat exposure scale [c]		3.8 (6.2)		8.5 (8.4)
	Hypertension	48		55	

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; PTSD, posttraumatic stress order; SD, standard deviation; BMI, body mass index;

[a] Weight (kg)/height $(m)^2$;

[b] Education years;

[c] Values ranges from 0 to 28.

Table 2. Association between PTSD and Diabetes, Emory Twin Study

	Total No.	Effect Estimates	95% CI		p-value
Individual[a]	536	0.08	-0.46	0.63	0.77
Between-pairs	522	-0.49	-1.71	0.73	0.43
Within-pairs[a]		0.12	-0.64	0.87	0.76

[a] Unadjusted model.

Table 3. Sequential Models for the Association between Lifetime Posttraumatic Stress Disorder and Insulin Resistance, Emory Twins Study

Model	Individual			Between-Pairs			Within-Pairs		
	Effect Estimates	95% CI	P [e]	Effect Estimates	95% CI	P [e]	Effect Estimates	95% CI	P [e]
Unadjusted	<-0.01	-0.13, 0.13	0.97	0.38	0.11, 0.64	0.01	-0.11	-0.26, 0.04	0.15
Adjusted for potential confounders									
Socio-demographic factors									
Age and education	-0.02	-0.15, 0.11	0.78	0.28	0.01, 0.55	0.04	-0.12	-0.27, 0.03	0.12
Marriage and employment status	-0.01	-0.14, 0.13	0.93	0.36	0.09, 0.63	0.01	-0.12	-0.27, 0.04	0.14
Combined [a]	-0.02	-0.15, 0.12	0.79	0.28	0.01, 0.55	0.04	-0.12	-0.28, 0.03	0.11
Health behavior related factors [b]									
Alcohol	<-0.01	-0.13, 0.13	0.99	0.33	0.06, 0.59	0.02	-0.10	-0.26, 0.05	0.18
Coffee	-0.02	-0.15, 0.12	0.80	0.28	0.01, 0.55	0.04	-0.12	-0.27, 0.03	0.12
Smoking	<-0.01	-0.13, 0.14	0.94	0.31	0.04, 0.58	0.02	-0.10	-0.25, 0.06	0.21
Obesity at enrollment	<-0.01	-0.12, 0.12	0.98	0.22	-0.03, 0.47	0.08	-0.08	-0.21, 0.06	0.28
Obesity at follow-up	<-0.01	-0.11, 0.11	0.98	0.06	-0.16, 0.29	0.59	-0.05	-0.18, 0.09	0.50
Combined [c]	0.02	-0.09, 0.13	0.75	0.10	-0.12, 0.33	0.36	-0.03	-0.16, 0.11	0.71
Final Model [d]	0.02	-0.09, 0.14	0.69	0.11	-0.12, 0.33	0.35	-0.02	-0.16, 0.11	0.75

[a] This combined model is adjusted for all the socio-demographic factors listed in the table.
[b] In addition to the controlled variable listed in the table, each model is controlling for age and education years.
[c] This combined model is adjusted for age and education years together with all the health behavior-related factors listed in the table.
[d] The final model is controlling for all the socio-demographic and health behavior related factors.
[e] p-value.c

Figure 1. Hypothesis pathways between PTSD and IR