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## Synergistic Effect of Neuroticism and Body Mass Index on Glucose Metabolism in Nondiabetic Adults

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Obesity has an important influence on glucoregulation and is among the most prominent risk factors for developing type 2 diabetes [1–3]. While more than 80% of people with type 2 diabetes are obese, most obese people never develop diabetes [4], suggesting that other factors are involved, possibly in combination with body mass index (BMI), to influence the preclinical progression to type 2 diabetes. Increasing evidence shows that psychosocial vulnerability factors, such as stress-induced catecholamine release, perceived discrimination, and work stress, moderate the effects of BMI and central adiposity on glucose metabolism [5–7].

Neuroticism is a personality trait that reflects nervousness, moodiness, and temperamental style [8] and refers to a relatively stable tendency to respond with negative emotions to threat, frustration, and loss [9, 10]. Neuroticism has been reliably linked to adverse mental health outcomes such as depression [11–13] and anxiety [14], as well as to physical health outcomes such as metabolic syndrome [15, 16], cardiovascular disease [17], diabetes [18], and mortality [19, 20].

The two specific questions addressed by the following analysis were: (1) whether neuroticism was associated with poor glucoregulation, and (2) whether it amplified the relationship between BMI and clinical indicators of glucose metabolism – fasting glucose, insulin, an index of insulin resistance (HOMA-IR), and glycosylated hemoglobin ($HbA_{1c}$). We included only nondiabetic people, allowing us to focus on preclinical pathways leading up to type 2 diabetes. We expected that the most marked signs of dysregulation, as evidenced by high glucose, insulin, HOMA-IR, and $HbA_{1c}$, would be found among people who had the highest BMI *and* highest neuroticism scores in our sample.

We used data from 952 nondiabetic participants of the biological subsample of the MIDUS II study [21, 22]. We excluded participants with likely diabetes, including those with $HbA_{1c}$ >6.5%, fasting glucose >126 mg/dl, or taking anti-diabetic medications (e.g. metformin). Hierarchical multiple regression was used and all models included neuroticism (M = 2, SD = 0.6) and BMI (M = 29, SD = 6) as predictors and a comprehensive set of relevant covariates: age (M = 56.6, SD = 11.5), race (85% white, 15% black), gender (43% male), waist-to-hip ratio (M = 0.89, SD = 0.1), current depressive symptoms (M = 8.4, SD = 8.2) [23], lifetime depression diagnosis (23% yes), and years of education (M = 15, SD = 5). The outcomes included fasting glucose (M = 95, SD = 9.6), insulin (M = 11.9, SD = 9.8), HOMA-IR (M = 2.9, SD = 2.6), and $HbA_{1c}$ (M = 5.7, SD = 3.6). All continuous predictor variables were mean-centered and outliers were top-coded. Glucose, insulin, and HOMA-IR were log-transformed to achieve normal distributions.

Bivariate correlations showed that BMI was positively associated with all markers of glucose metabolism (r values ranged from 0.17 to 0.46, $p < 0.01$). Neuroticism was not significantly associated with BMI or glucose levels, but was positively associated with insulin ($r = 0.08$, $p = 0.01$) and HOMA-IR ($r = 0.08$, $p = 0.01$) and negatively associated with $HbA_{1c}$ ($r = 0.07$, $p = 0.03$). Multivariate-adjusted moderating analyses, in turn, showed that neuroticism interacted with BMI to predict insulin ($R^2 = 0.34$, $B = 0.05$, $p < 0.05$) and HOMA-IR ($R^2 = 0.34$, $B = 0.05$, $p < 0.05$). For both interactions, the highest levels of insulin and HOMA-IR were evident among people who had both higher BMI and higher neuroticism (fig. 1). In both models, the only statistically significant associations observed among covariates and glucoregulation were positive relationship between waist-to-hip ratio ($p < 0.001$) and insulin and HOMA-IR, and negative relationships between gender and insulin and HOMA-IR ($p < 0.01$). The interaction between neuroticism and BMI was not significantly associated with glucose or $HbA_{1c}$.

High BMI is among the most prominent risk factors for type 2 diabetes, yet the variability in the association between BMI and disease suggests other factors are required to more fully understand the progression from preclinical risk to diabetes. We investigated the relationships among BMI, neuroticism, and glucoregulation in a sample of nondiabetic people and found support for the hypothesis that neuroticism acts synergistically with BMI to promote insulin resistance and higher circulating levels of insulin, which constitute the first stage of progression to diabetes [24]. Our study suggests that neuroticism is an instigating factor that works interactively with BMI to initiate the progression to disease.

While previous studies by our research group and others [5–7] have shown that the combined influences of obesity and psychosocial variables are associated with higher glucose and $HbA_{1c}$, no relationships were detected for glucose or $HbA_{1c}$ in the present study. The overall pattern of findings underscores the fact that these four clinical indicators of glucose regulation track different steps in the progression from normoglycemia to disease [24]. Future studies need to investigate the relationships among psychosocial factors, obesity, and multiple indicators of glucose regulation longitudinally to more clearly delineate the causal antecedents and mediating pathways.

Our findings extend previous work showing that other psychosocial vulnerability factors such as stress-induced catecholamine release, perceived discrimination, and work stress interact with BMI and central adiposity to predict different clinical indicators of glucose metabolism [5–7]. Taken together, these lines of inquiry suggest that overweight and obese people, who are already at a higher risk for disease due to increased production of free fatty acids and pro-inflammatory cytokines by adipose tissue [25], may be more susceptible to the effects of psychosocial vulnerabilities on clinical indicators of glucose metabolism. While the underlying mechanisms are still unclear, a primary hormone candidate is glucocorticoid activity and its daily secretion pattern of cortisol. Previous analyses have shown that the slope of the diurnal cortisol decrease

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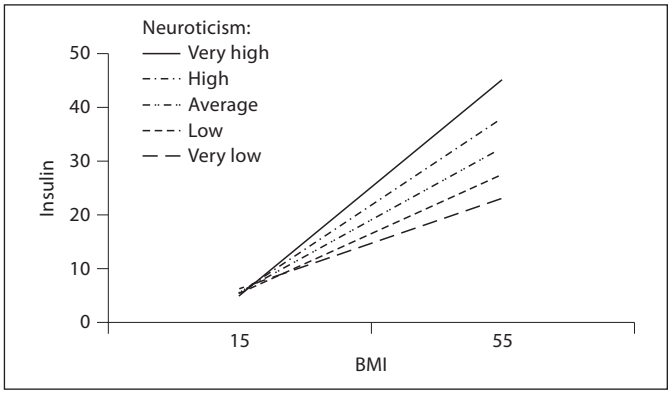


**Fig. 1.** Neuroticism amplifies the effect of BMI on insulin ($p < 0.05$). Note that high neuroticism is plotted at 1 SD above the mean for neuroticism and low neuroticism is plotted at 1 SD below the mean. Very high neuroticism is plotted at 2 SD above the mean for neuroticism and very low neuroticism is plotted at 2 SD below the mean. Absolute values of insulin are plotted for ease of interpretation.

is flatter among obese people and that a flatter decrement is positively associated with neuroticism [26]. Moreover, once obesity is present, adrenomedullary activity has been implicated in the development of glucose dysregulation [5].

Although we found support for the hypothesis that neuroticism compounds the effect of BMI on glucose regulation, our study was constrained by its cross-sectional design that does not allow for determination of causal directionality. However, it seems less plausible that poor glucose regulation contributes to obesity or neuroticism than vice versa. Nevertheless, our analyses point to neuroticism as one specific personality trait that acts together with BMI to influence the progression to disease. Overall, the findings suggest that neuroticism deserves further attention as a psychological vulnerability factor which may aggravate the morbidity associated with hyperinsulinemia and insulin resistance.

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