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Metabolic syndrome is negatively associated with cognition among endothelial nitric oxide synthase (*eNOS*)- 786C carriers in schizophrenia-spectrum disorders

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ABSTRACT

Although metabolic syndrome and cognitive inefficiencies are well-described common complications of schizophrenia, their association remains inconsistent, potentially due to poorly understood mechanisms underlying their relationship. Variability in the endothelial nitric oxide synthase (*eNOS*) gene, specifically the T-786C variant, has been separately associated with cognition and metabolic syndrome, with worse outcomes for *eNOS*-786C carriers likely occurring via negative effects on blood vessel functioning. However, the interaction between *eNOS* and metabolic syndrome in cognition among adults with schizophrenia is unknown. This study aimed to test the main and interaction effects of the *eNOS*-786C allele in cognition using hierarchical regression analyses controlling for age, sex, education, race, and antipsychotic exposure. Metabolic syndrome, *eNOS* T-786C genotype, and cognitive performance were assessed in 226 community-dwelling participants with chronic schizophrenia-spectrum disorders. Results demonstrated a significant interaction between metabolic syndrome and the *eNOS*-786C allele. Specifically, among *eNOS*-786C carriers only, metabolic syndrome was independently associated with lower scores in processing speed and verbal fluency, and predicted 12.5% and 15.8% of variance in performance, respectively. These results suggest that the additive negative effects of *eNOS*-786C and metabolic syndrome on blood vessel functioning may be severe enough to negatively impact cognition. The finding that metabolic syndrome is associated with worse cognition *only* in the presence of the *eNOS*-786C allele may clarify extant inconsistencies in the literature. These findings provide preliminary evidence that may inform interventions to reduce cognitive morbidity among adults with schizophrenia.

1. Introduction

Emerging research in schizophrenia has focused on identifying the relationship between metabolic syndrome and associated cognitive dysfunction due to high rates of metabolic disturbances documented in this population (Kraal et al., 2017; Meyer et al., 2008). A well-developed body of literature has associated metabolic syndrome with lower performance on measures of global cognition, attention, speed of processing (Li et al., 2014; Lindenmayer et al., 2012), and verbal fluency (Oh et al., 2011; Goughari et al., 2015). However, contrasting findings have been documented (Meyer et al., 2005) which emphasizes the need for research aimed at clarifying mechanisms underlying metabolic syndrome-cognition relationships.

In the general population, presence of metabolic syndrome is associated with genetic variability in the endothelial nitric oxide synthase (*eNOS* or *NOS3*) gene, specifically the *eNOS* T-786C variant that lies in the promoter region (Alkharfy et al., 2012; Miranda et al., 2013). Compared to the *eNOS* −786T allele, the C allele is associated with reduced *eNOS* activity, possibly through reduced mRNA expression and nitric oxide synthesis, resulting in lower levels of circulating nitric oxide (Miyamoto et al., 2000; Metzger et al., 2005). Previous studies have linked the *eNOS* −786C allele to metabolic syndrome among obese children (Miranda et al., 2013) and adults without psychiatric disorders (Alkharfy et al., 2012). Preliminary research in patients with

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schizophrenia, however, is mixed. Specifically, in patients with metabolic syndrome, the −786CC genotype has been linked to worse lipid dysregulation compared with TT carriers (Fattakhov et al., 2018). However, our work has shown no differences in cardiovascular risk between the CC and TT genotype carriers with concomitant metabolic syndrome (Burghardt et al., 2014). Altogether, the *eNOS* gene may mechanistically represent a potentially important moderator of metabolic risk particularly because nitric oxide increases vasodilatation and prevents atherosclerotic plaque formation (Perrotta et al., 2009). High rates of metabolic syndrome in schizophrenia coupled with inconsistent findings highlight the need for additional research to clarify the association between the *eNOS* gene and metabolic syndrome.

Furthermore, evidence from mice models has shown that endothelial nitric oxide functions as a neurovascular protective molecule, and that *eNOS* inactivation exacerbates age-related processes, leading to worse cognition (Katusic and Austin, 2016). However, studies on the relationship between the *eNOS* gene and cognition is sparse. Therefore, additional research is needed to determine whether these findings can be extended to humans, particularly given the well-documented cognitive dysfunction seen in patients with schizophrenia and evidence documenting contrasting relationships with metabolic syndrome (Luckhoff et al., 2019).

While preliminary evidence supports an association between the *eNOS* −786C allele and presence of metabolic syndrome, the role of *eNOS* in cognition, and importantly, the interaction between *eNOS* and metabolic syndrome in cognition is unclear. Research delineating this relationship may be particularly important in clarifying mechanisms underlying metabolic syndrome-associated cognitive dysfunction, particularly in the context of inconsistent metabolic syndrome-cognition associations.

The current study aimed to examine the main effects of and corresponding interaction between the *eNOS* T-786C variant and metabolic syndrome in cognition among individuals with a schizophrenia-spectrum disorder. Based on previous research, we hypothesized main effects of metabolic syndrome and the *eNOS* −786C allele such that participants with either a metabolic syndrome diagnosis or the *eNOS* −786C allele would have worse cognition compared with those without. Additionally, we hypothesized that among participants with the *eNOS* −786C allele, those with metabolic syndrome would have worse cognition in comparison to participants without metabolic syndrome.

2. Materials and methods

2.1. Participants

Participants included in this analysis were part of an ongoing larger study of cardiovascular disease risk. Inclusion criteria for this parent study included being aged 18–90 years old (age range in current study: 19–70; $M_{\text{age}} = 44.72 \pm 11.31$ years), having a schizophrenia-spectrum disorder, and taking an antipsychotic medication for at least 6 months. Participants were excluded if they were unable or unwilling to give informed consent, pregnant or nursing, or had a current substance dependence diagnosis. Full inclusion and exclusion criteria are available at https://clinicaltrials.gov/ct2/show/NCT00815854. This study was approved by the University of Michigan Medical School Institutional Review Board, Washtenaw County Health Organization, Ann Arbor Veterans Affairs Medical Center, and Detroit–Wayne County Community Mental Health Agency. This study was conducted in accordance with the latest version of the Declaration of Helsinki. Participants were recruited from outpatient psychiatric clinics in Southeastern Michigan. The study was conducted at the Michigan Clinical Research Unit (MCRU) at the University of Michigan. After a discussion of the study's risks, purpose, and procedures, participants provided written informed consent. The following assessments and laboratory measures were then recorded.

2.2. Procedure

Clinical assessment. Current and past medical and medication histories as well as demographic information were obtained. Antipsychotic exposure was calculated using chlorpromazine equivalents (Andreasen et al., 2010). Primary schizophrenia-spectrum diagnosis was determined using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID; First et al., 1997). Level of education was obtained from the SCID, with possible responses ranging from 1 (completed grade 6 or less) to 8 (completed graduate/professional school).

Metabolic assessment. Participants underwent an 8-h fasting blood draw to examine levels of triglycerides, high-density lipoproteins (HDL), and glucose. Blood pressure and waist circumference were also measured. The National Cholesterol Education Program's (NCEP) Adult Treatment Panel III criteria (Grundy et al., 2004) were used to identify participants who met criteria for metabolic syndrome.

Cognitive assessment. Cognition was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004) by trained study staff. The BACS measures six cognitive domains: verbal memory, working memory, motor speed, processing speed, phonemic and semantic verbal fluency, and executive function. Z-scores for each cognitive domain were calculated using means and standard deviations from the overall sample. A composite global cognition z-score was calculated by averaging z-scores across domains.

***eNOS* genotyping.** DNA was extracted from whole blood samples using a Puregene kit (Qiagen, Hilden, Germany). Genotyping was completed for the *eNOS* T-786C (rs2070744) variant using Pyrosequencing™ Technology (Qiagen) which allows sequencing of a single strand of DNA by synthesizing the complementary strand alongside it, one base pair at a time. Methods for this assay are available upon request.

2.3. Statistical analyses

Group differences in participant characteristics were determined using analysis of variance (ANOVA) and Chi-Square tests as statistically appropriate. Hierarchical linear regression tested the main effects of and interaction between metabolic syndrome diagnosis and *eNOS* −786C carrier status, controlling for age, sex, educational attainment, race, and chlorpromazine equivalents. For regression analyses, age and chlorpromazine equivalents were centered at their respective means, race was dichotomized into White and non-White, and educational attainment was dichotomized based attainment of a high school diploma or GED.

3. Results

3.1. Participant characteristics

A total of 226 participants with a primary diagnosis of schizophrenia ($n = 101$), schizoaffective disorder ($n = 102$), and psychosis not otherwise specified (NOS) ($n = 23$) were included in the current study. Specific participant characteristics are provided in Table 1. A total of 115 (50.9%) participants were diagnosed with metabolic syndrome and 110 (48.7%) participants were carriers of the *eNOS* −786C allele. Overall, participants with metabolic syndrome were on average seven years older than those without metabolic syndrome, $F(1, 223) = 24.93$, $p < 0.001$. There were also racial differences in the *eNOS* genotype, with the C allele being more common in White participants compared with Black participants (69.7% vs 22.9%, respectively). This is in line with previous reports (Tanus-Santos et al., 2001).

3.2. Main and interaction effects

Results from the hierarchical linear regression analyses

Table 1
Participant characteristics.

Variable	N = 226	Metabolic syndrome		eNOS -786Callele	
		Yes (n = 115)	No (n = 111)	C Carrier (n = 110)	Non-C Carrier (n = 116)
Age in years M (SD)	44.7 (11.3)	48.2 (9.4)*	41.1 (12.0)*	45.3 (11.1)	44.0 (11.5)
Female n (%)	84 (37.2)	49 (42.6)	35 (31.5)	45 (40.9)	39 (33.6)
Race n (%)					
White	118 (52.2)	62 (53.9)	56 (50.5)	77 (70.0)*	41 (35.3)*
Black	85 (37.6)	44 (38.3)	41 (36.9)	25 (22.7)*	60 (51.7)*
Other	23 (10.2)	9 (7.8)	14 (12.6)	8 (7.3)	15 (12.9)
Education n (%)					
1	28 (13.4)	20 (18.0)	8 (8.2)	15 (14.4)	13 (12.4)
2	59 (28.2)	31 (27.9)	28 (28.6)	23 (22.1)	36 (34.3)
3	122 (58.3)	60 (54.1)	62 (63.3)	66 (63.5)	56 (53.3)
Diagnosis n (%)					
Schizophrenia	101 (44.7)	51 (44.3)	50 (45.0)	44 (40.0)	57 (49.1)
Schizoaffective	102 (45.1)	49 (42.6)	53 (47.7)	57 (51.8)	45 (38.8)
Psychosis NOS	23 (10.2)	15 (13.0)	8 (7.2)	9 (8.2)	14 (12.1)
Metabolic syndrome diagnosis n (%)	115 (49.6)	–	–	58 (52.7)	57 (49.1)
eNOS C carriers n (%)	110 (48.7)	58 (50.4)	52 (46.8)	–	–
AAP Use n (%)	193 (85.4)	97 (84.3)	96 (86.5)	96 (87.3)	97 (83.6)
CPZe M (SD)	716.1(792.9)	662.6(765.4)	766.1(816.1)	738.8(869.3)	694.9(712.4)
Mood Stabilizer Use n (%)	152 (67.6)	82 (71.3)	70 (63.6)	83 (75.5)*	69 (60.0)*

Note. * = $p < 0.05$; AAP = atypical antipsychotics (i.e., risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, clozapine, paliperidone, iloperidone, asenapine, lurasidone, and amisulpride); CPZe = Chlorpromazine equivalency; *eNOS* = Endothelial Nitric Oxide Synthase; Education: 1 = Did not complete high school or obtain GED, 2 = Completed high school or obtained GED, 3 = Completed more than high school or GED; Metabolic syndrome = metabolic syndrome; NOS = Not Otherwise Specified; Other = Asian, Bi/Multi-Racial, Native American, Native Hawaiian/Other Pacific Islander, Unknown; *SD* = Standard Deviation.

Table 2
Results of hierarchical regression analyses for cognition scores.

Predictor	Variable Statistics			Model Statistics		
	B	SE B	β	R^2	$\triangle R^2$	$\triangle F$
Processing Speed				0.259		
Age	−0.032	0.008	−0.358***		0.218	5.342***
Sex	−0.494	0.194	−0.233**			
Education	0.360	0.273	0.120			
Race	0.421	0.188	0.205**			
CPZe	0.000045	0.000	0.035			
eNOS C allele	0.111	0.200	0.054		0.003	0.159
MetS	−0.020	0.199	−0.010			
*eNOS**MetS	−0.808	0.369	−1.184**		0.038	4.791**
Verbal Fluency				0.140		
Age	−0.014	0.009	−0.157		0.060	1.243
Sex	−0.341	0.201	−0.169*			
Education	−0.067	0.283	−0.024			
Race	−0.180	0.195	−0.092			
CPZe	0.000	0.000	−0.098			
eNOS C allele	0.093	0.204	0.048		0.030	1.570
MetS	−0.349	0.203	−0.180*			
*eNOS**MetS	−0.876	0.376	−1.348**		0.050	5.412**
Global Cognition				0.180		
Age	−0.024	0.009	−0.274***		0.137	2.957***
Sex	−0.411	0.197	−0.204**			
Education	0.198	0.277	0.069			
Race	0.339	0.191	0.174			
CPZe	0.000047	0.000	0.038			
eNOS C allele	0.172	0.201	0.088		0.018	0.988
MetS	−0.226	0.201	−0.116			
*eNOS**MetS	−0.614	0.377	−0.942		0.024	2.656

Note. CPZe = Chlorpromazine equivalency; *eNOS* = Endothelial Nitric Oxide Synthase; MetS = metabolic syndrome. For ease of interpretation, variable statistics presented are values at its first inclusion in the hierarchical model (i.e., covariates at step 1, main effects at step 2, and interaction effect at step 3). $^{**}p < 0.05$. $^{***}p \leq 0.01$.

demonstrated a significant interaction between metabolic syndrome and *eNOS* in processing speed and verbal fluency scores (Table 2). Given *a priori* hypotheses regarding *eNOS* moderating metabolic syndrome-cognition associations, further analyses stratifying participants by *eNOS* −786C carrier status were conducted. Among C carriers, presence of metabolic syndrome was independently associated with lower scores on processing speed ($B = -0.73$, $t = -2.34$, $p = 0.03$), verbal fluency ($B = -0.90$, $t = -2.59$, $p = 0.01$), and a trend global cognition ($B = -0.68$, $t = -1.94$, $p = 0.06$) (Table 2; Fig. 1). Additionally, among C carriers, the contribution of metabolic syndrome to the variance in cognition scores was 12.5% in processing speed, 15.8% in verbal fluency, and 9.5% in global cognition. Metabolic syndrome was not associated with cognition among non C carriers. There were no main effects of either metabolic syndrome or *eNOS* −786C allele on cognition scores.

3.3. Sensitivity analyses

In the current study, post-hoc analyses showed that although 45.1% of participants met DSM-IV criteria for schizoaffective disorder, 67.3% of participants were prescribed a mood stabilizer medication, in line with previous research documenting the therapeutic potential of mood stabilizers beyond mania (Chiu et al., 2013). Sensitivity analyses with mood stabilizer medication use included as a covariate showed similar patterns of association between the interaction term and processing speed, verbal fluency, and global cognition.

4. Discussion

Despite high rates of metabolic syndrome and cognitive dysfunction in schizophrenia, research regarding mechanisms underlying the inconsistent associations between metabolic syndrome and cognition in chronic schizophrenia is lacking. Findings from this study suggest that in the presence of the *eNOS* −786C allele, metabolic syndrome is negatively associated with processing speed, semantic fluency, and, to a lesser extent, global cognition in outpatients with schizophrenia. This interaction was found to be independent of differences in age, race, sex, and education. Importantly, the finding that metabolic syndrome and *eNOS* −786C allele interactively, but not independently, predicted worse cognition sheds light on inconsistencies in metabolic syndrome-cognition associations.

Functionally, the *eNOS* −786C allele has been associated with reduced *eNOS* activity and nitric oxide synthesis compared to the T allele (Miyamoto et al., 2000). Nitric oxide's role in increasing vasodilatation

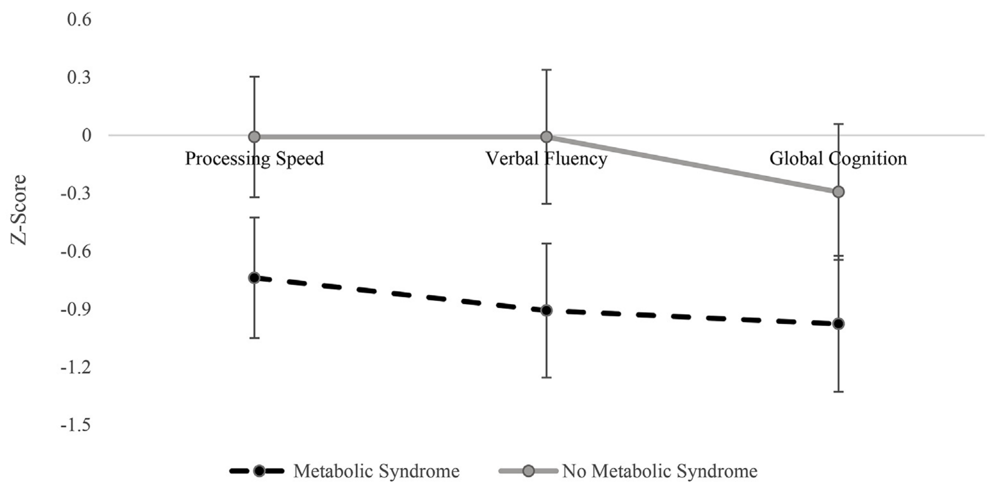

Fig. 1. Cognition z-scores of *eNOS* −786C carriers with and without metabolic syndrome. Error bars represent standard error values.

and preventing atherosclerotic plaque formation (Perrotta et al., 2009) indicates that the *eNOS* gene represents a potentially important moderator of metabolic risk. Findings from studies in mice with partial or full *eNOS* deficiency suggest that *eNOS* may protect against risk of metabolic syndrome and cognitive decline (Cook et al., 2003; Tan et al., 2015). Furthermore, studies have demonstrated that *eNOS* −786C carriers have genotype-associated nitric oxide decreases, contributing to blood vessel tonus dysregulation (Karantzoulis-Fegaras et al., 1999; Shesely et al., 1996).

However, the current study's findings suggest that *eNOS*-related dysregulated pathways alone may not be associated with poor cognition. Among those with the risk allele, the addition of metabolic syndrome may heighten dysregulation and potentially increase risk for peripheral resistance (Lind and Lithell, 1993). Given that poor blood vessel functioning has been negatively associated with cognitive function, the potentially additive effects of metabolic syndrome and the *eNOS* risk allele may lead to blood vessel dysregulation severe enough to negatively impact cognition.

Clarifying the role of *eNOS* may better characterize patterns of association between physical health and cognition. The T-786C variant occurs in the promoter region of the *eNOS* gene and the C allele has been associated with lower circulating levels of NO (Metzger et al., 2005). Cardiovascular risk factors such as metabolic syndrome are associated with increased oxidative stress and inflammation which in turn decreases the bioavailability of nitric oxide (Katusic and Austin, 2016; Sukhovershin et al., 2015). As heightened oxidative stress and inflammation lead to cognitive decline, endothelial nitric oxide may be a key molecule linking vascular function and cognition (Katusic and Austin, 2016). Ultimately, *eNOS -786*C allele carrier status may determine the levels of nitric oxide initially available whereas metabolic syndrome, through oxidative stress or inflammation, may further decrease the bioavailability of nitric oxide. Thus, mechanistically, *eNOS* may represent an important and novel genetic mechanism as it explains why individuals with metabolic syndrome have differing levels of cognition. This may be particularly relevant in schizophrenia given the high prevalence of both metabolic syndrome and cognitive inefficiencies, yet inconsistent metabolic syndrome-cognition associations documented in extant research.

Previous studies examining the relationship between metabolic syndrome and cognition in adults with schizophrenia, has not examined genetic risk as part of their investigations (Meyer et al., 2005; Luckhoff et al., 2019; MacKenzie et al., 2018). The current study's findings that the adverse cognitive consequences of metabolic syndrome occur only in the context of cardiovascular genetic risk corresponds to previous research by our group that similarly identified gene-moderated negative associations between metabolic health and cognition (Grove et al., 2015). The current study extends our previous work in schizophrenia disorders that linked endothelial dysfunction to poor cognition among those with risk alleles of methylenetetrahydrofolate reductase (*MTHFR*) C677T and catechol-O-methyltransferase (*COMT*) Val158Met in two ways. Firstly, the current study demonstrates metabolic syndrome-specific associations, which may be more relevant clinically and more easily replicated in research relative to endothelial functioning, as indices of the NCEP-derived criteria are frequently utilized whereas measures of endothelial functioning are rare due to prohibitively high costs. Secondly, the current study provides preliminary evidence regarding the role of *eNOS* -786T/C in linking metabolic risk to cognitive dysfunction and represents a potential area for further inquiry.

In addition to mechanistic explanations regarding metabolic syndrome-cognition associations, the current study's findings may have important clinical implications. The prevalence of metabolic syndrome in this sample of outpatients with schizophrenia is almost twice as high relative to its prevalence in the general population (50.4% vs. 23.7%, respectively). While the utility of decreasing metabolic risk is manifold, findings from this study suggest that improving metabolic health may be particularly important for cognition among *eNOS* −786C allele carriers. However, findings in the current study do not warrant routine genetic screening for the *eNOS* gene particularly given the potential adverse psychological effects of positive test results for those with pre-existing elevated emotional distress, as shown in the multi-site *APOE* genotype disclosure study (Green et al., 2009).

From an intervention standpoint, a recent meta-analysis documented beneficial effects of exercise interventions on cognitive functioning in schizophrenia (Firth et al., 2017). However, the contribution of *eNOS* to intervention effects is unknown. Additionally, the extent to which inflammatory and/or oxidative stress pathways underlie associations and whether findings can be extended to adults with schizophrenia with metabolic syndrome remains unclear. Furthermore, a recent systematic review of randomized controlled trials involving non-pharmacological interventions, or so-called “natural medicines”, including vitamin B6, glycine, and omega-3 fatty acids showed that there was no substantial evidence that such strategies conferred *cognitive* benefits in psychotic disorders (Hoenders et al., 2018). Of note, the positive effects of dietary interventions such as vitamin B6 on cardiovascular risk (Ellingrod et al., 2015) and psychiatric symptoms (Roffman et al., 2013) in schizophrenia have been shown to be gene-dependent. Thus, additional research is needed to clarify the potential role of *eNOS* as a moderator of intervention outcomes in schizophrenia.

Limitations of this study include the small number of participants with the CC genotype (n = 5), which statistically prohibited further examination into TC vs CC differences. Nevertheless, we were able to demonstrate an effect in those carrying the C allele. Given our preliminary findings, further research should examine differences between homozygous and heterozygous C carriers. Furthermore, in the current study, only one SNP of the *eNOS* gene was studied and we were not able to utilize an independent sample to test whether results are replicable. Future research should investigate the association between multiple *eNOS* SNPs and additional indices of metabolic and cardiovascular health in cognitive functioning. Additionally, the current study's finding demonstrating a trend ($p = 0.06$) in metabolic syndrome-associated decreased global cognitive functioning among C carriers may be driven primarily by processing speed and verbal fluency. Future research is warranted to clarify both domain-specific and global cognition associations. Another limitation of the current study is its cross-sectional design. Future studies should employ longitudinal approaches to clarify temporal dynamics between *eNOS,* metabolic syndrome, and cognition. Additionally, although we employed statistical control for antipsychotic exposure, all participants had been receiving antipsychotic medication long term, and we were therefore unable to examine the contribution of these medications to these relationships. While the current study included participants with schizophrenia-spectrum disorders only, additional research should examine associations across other psychiatric disorders, particularly given increasing rates of metabolic disturbances in psychiatric illnesses (De Hert et al., 2009). While the current study conducted sensitivity analyses to test for the potential influence of mood stabilizer medication use in patterns of association, we did not examine the influence of other, co-morbid medical conditions and medication use due to limitations of available data. Future studies should test whether other medical conditions and medications may influence patterns of association between *eNOS*, metabolic syndrome, and cognition.

Major strengths of the current study include its assessment of multiple domains of cognition. Our broad eligibility criteria additionally increase generalizability of findings. Furthermore, this study extends our previous work on genotype-dependent associations between endothelial functioning and cognition by incorporating measures of metabolic risk routinely utilized in research and clinical settings. This study also contributes to research on mechanisms underlying metabolic syndrome-cognition associations, which is an underdeveloped area of study.

Altogether, the current study supports the potentially deleterious effects of *eNOS* −786C allele in the presence of high metabolic risk among individuals with a schizophrenia-spectrum diagnosis. Results may clarify factors contributing to cognitive dysfunction in schizophrenia and may additionally inform the development of interventions to reduce cognitive morbidity within this population.

Declarations of interest

None.

Conflicts of interest

The authors have no conflicts of interest.

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Appendix A. Supplementary data

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