EUROPEAN JOURNAL OF
PSYCHO-
TRAUMATOLOGY
THE OFFICIAL JOURNAL OF THE EUROPEAN SOCIETY FOR TRAUMATIC STRESS STUDIES

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CLINICAL RESEARCH ARTICLE

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Adiponectin gene polymorphisms and posttraumatic stress disorder symptoms among female rape survivors: an exploratory study

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ABSTRACT

Background: Rape is a common traumatic event which may result in the development of posttraumatic stress disorder (PTSD), yet few studies have investigated risk biomarkers in sexually traumatised individuals. Adiponectin is a novel cytokine within inflammatory and cardiometabolic pathways with evidence of involvement in PTSD.

Objective: This prospective exploratory study in a sample of female rape survivors investigated the association of single nucleotide polymorphisms (SNPs) in the adiponectin gene (*ADIPOQ*) and posttraumatic stress symptom (PTSS) severity, and the interaction of these SNPs of interest with childhood trauma in modifying the association with PTSS severity.

Method: The study involved 455 rape-exposed black South African women (mean age (SD), 25.3 years (±5.5)) recruited within 20 days of being raped. PTSS was assessed using the Davidson Trauma Scale (DTS) and childhood trauma was assessed using a modified version of the Childhood Trauma Scale-Short Form Questionnaire. Eight *ADIPOQ* SNPs (rs17300539, rs16861194, rs16861205, rs2241766, rs6444174, rs822395, rs1501299, rs1403697) were genotyped using KASP. Mixed linear regression models were used to test additive associations of *ADIPOQ* SNPs and PTSS severity at baseline, 3 and 6 months following rape.

Results: The mean DTS score post-sexual assault was high (71.3 ± 31.5), with a decrease in PTSS severity shown over time for all genotypes. rs6444174TT genotype was inversely associated with baseline PTSS in the unadjusted model ($\beta = -13.6$, 95% CI [−25.1; −2.1], $p = .021$). However, no genotype was shown to be significantly associated with change in PTSS severity over time and therefore *ADIPOQ* SNP x childhood trauma interaction was not further investigated.

Conclusion: None of the *ADIPOQ* SNPs selected for investigation in this population were shown to be associated with change in PTSS severity over a 6-month period and therefore their clinical utility as risk biomarkers for rape-related PTSD appears limited. These SNPs should be further investigated in possible gene-gene and gene-environment interactions.

Highlights
- Women who are sexually assaulted are at increased risk of PTSD.
- The adiponectin gene (*ADIPOQ*) has been linked to cardiometabolic disease which frequently co-occurs with PTSD.
- *ADIPOQ* variants were not shown to predict PTSD symptom severity post-rape in this population.

Polimorfismos del gen de adiponectina y síntomas del trastorno de estrés postraumático en mujeres sobrevivientes a una violación sexual: Un estudio exploratorio

Antecedentes: La violación sexual es un evento traumático común que puede resultar en el desarrollo del trastorno de estrés postraumático (TEPT); no obstante, pocos estudios han investigado biomarcadores de riesgo en personas sexualmente traumatizadas. La adiponectina es una citocina recientemente involucrada en vías inflamatorias y cardiometabólicas que tienen evidencia de compromiso en el TEPT.

Objetivo: Este estudio prospectivo exploratorio, realizado en una muestra de mujeres sobrevivientes a violación sexual, investigó la asociación entre polimorfismos de nucleótido único (SNPs por sus siglas en inglés) en el gen de la adiponectina (*ADIPOQ*) y la severidad de los síntomas de estrés postraumático (SEPT), así como también cómo la interacción de estos SNPs sobre el trauma infantil modifica la asociación con la severidad de los SEPT.

Método: El estudio incluyó a 455 mujeres sudafricanas de raza negra expuestas a una violación sexual (edad promedio de 25,3 años ± 5,5) reclutadas 20 días después de haber sido violadas sexualmente. Los SEPT se evaluaron empleando la Escala de Trauma de Davidson (DTS por sus

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ⓘ Supplemental data for this article can be accessed online at https://doi.org/10.1080/20008066.2022.2107820.

siglas en inglés) y el trauma infantil se evaluó empleando una versión modificada de la Escala de Trauma Infantil – Cuestionario de versión corta. Se realizó la genotipificación de ocho SNPs del gen *ADIPOQ* (rs17300539, rs16861194, rs16861205, rs2241766, rs6444174, rs822395, rs1501299, rs1403697) empleando el KASP. Se emplearon modelos de regresión lineal para evaluar las asociaciones aditivas entre los SNPs del gen *ADIPOQ* y la severidad de los SEPT de base, a los tres y a los seis meses luego de la violación sexual.

Resultados: El promedio del puntaje en la DTS luego de una violación sexual fue alto (71,3 ± 31,5) con una disminución en la severidad de los SEPT evidenciada a lo largo del tiempo para todos los genotipos. El genotipo rs6444174TT se encontró inversamente asociado a los SEPT de base en el modelo no ajustado ($\beta = -13,6$, 95% CI [−25.1; −2.1], $p = .021$). Sin embargo, ningún genotipo mostró estar asociado significativamente con cambios en la severidad de los SEPT a lo largo del tiempo y, por tanto, ya no se investigó la interacción entre los SNPs del gen *ADIPOQ* y el trauma infantil.

Conclusiones: Ninguno de los SNPs del *ADIPOQ* elegidos para esta investigación mostraron tener alguna asociación entre los cambios en la severidad de los SEPT en un periodo de seis meses y, por tanto, su utilidad clínica como marcadores de riesgo para el TEPT asociado a violación sexual es limitada. Se debería investigar más estos SNPs para evaluar las posibles interacciones gen-gen y gen-ambiente.

女性强奸幸存者脂联素基因多态性与创伤后应激障碍症状：一项探索性研究

背景：强奸是一种常见的创伤事件，可能导致创伤后应激障碍 (PTSD) 的发展，但很少有研究考查性创伤个体的风险生物标志物。脂联素是炎症和心血管代谢途径中的一种新型细胞因子，有证据表明它参与了 PTSD。

目的：本前瞻性探索性研究在一个女性强奸幸存者样本中，考查了脂联素基因 (*ADIPOQ*) 中的单核苷酸多态性 (SNP) 与创伤后应激症状 (PTSS) 严重程度的关联，以及这些感兴趣的 SNP 与童年期创伤在修饰 PTSS 严重性相关关联的交互作用。

方法：本研究纳入在被强奸后 20 天内招募的 455 名遭遇强奸的南非黑人女性（平均年龄 (SD)，25.3 岁 (±5.5)）。PTSS 使用戴维森创伤量表 (DTS) 进行评估，童年期创伤使用童年期创伤量表 – 简表修订版进行评估。使用 KASP 对八个 *ADIPOQ* SNP（rs17300539、rs16861194、rs16861205、rs2241766、rs6444174、rs822395、rs1501299、rs1403697）进行基因分型。使用混合线性回归模型在基线、强奸后 3 个月和 6 个月时考查 *ADIPOQ* SNP 和 PTSS 严重程度的加性关联。

结果：性侵犯后的平均 DTS 得分很高（71.3 ± 31.5），所有基因型的 PTSS 严重程度都随时间降低。在无调节的模型中，rs6444174TT 基因型与基线 PTSS 呈负相关（$\beta = -13.6$, 95% CI [−25.1; −2.1], $p = .021$）。然而，没有显示基因型与 PTSS 严重程度随时间的变化显著相关，因此没有进一步研究 *ADIPOQ* SNP x 儿童创伤的交互作用。

结论：在该人群中选择用于考查的 *ADIPOQ* SNP 均未显示与 6 个月期间 PTSS 严重程度的变化相关，因此它们作为强奸相关 PTSD 风险生物标志物的临床效用似乎有限。应该在可能的基因-基因和基因-环境相互作用中进一步研究这些 SNP。

1. Introduction

Posttraumatic stress disorder (PTSD) is disabling and often chronic psychiatric disorder that may develop following exposure to actual or threatened death, serious injury or sexual violence (American Psychiatric Association, 2013; Kessler et al., 2005). Compared to other traumas, sexual violence, including rape, is associated with the highest risk of developing PTSD (Dworkin, 2018; Scott et al., 2018). In South Africa, rape is prevalent, and disproportionately affects women (Abrahams et al., 2014; Ajayi et al., 2021; Steele et al., 2019). Despite experiencing the same trauma, post-sexual assault, the severity, and course of PTSD symptoms (PTSS) vary across individuals (Dworkin et al., 2021). Most individuals experience severe PTSS in the immediate aftermath of a sexual assault, with most recovery from PTSS occurring within the first 3 months post-sexual assault (Dworkin et al., 2021). Variability in individual risk for, and persistence of PTSS is likely due to underlying differences

in biological processes, possibly genetically driven. The heritability of PTSD is estimated to range from 30 to 40% (Duncan et al., 2018; Koenen, 2007; Nugent et al., 2008). Although a number of studies have examined psychosocial correlates of PTSS in female assault victims (Mgoqi-Mbalo et al., 2017; Nöthling et al., 2022; Tiihonen Möller et al., 2014), few biological, including genetic studies exploring mechanisms underlying differential susceptibility for PTSD have been conducted (D'Elia et al., 2021; Nöthling et al., 2021; Thurston et al., 2021). A biomarker that could predict PTSD symptom trajectory after sexual trauma may facilitate early detection and intervention for PTSD and may also advance our understanding of underlying biological mechanisms.

Among several proteins secreted by adipocytes (fat cells), adiponectin is prominent because of its protective metabolic properties, including insulin-sensitising, antiatherogenic (preventing formation of fatty deposits in arteries) and anti-inflammatory effects

(Ohashi et al., 2012). Adiponectin is encoded by *ADIPOQ* which spans approximately 15.8 kb, comprises three exons, two introns and is located on chromosome 3q27 (Maeda et al., 1996). Low circulatory levels of adiponectin are considered risk factors for cardiometabolic diseases (CMD) such as Type 2 diabetes mellitus (T2DM) and metabolic syndrome (Kadowaki et al., 2006; Lee & Shin, 2020; von Frankenberg et al., 2017). Likewise, various single nucleotide polymorphisms (SNPs) of *ADIPOQ* have been linked to MetS, T2DM, and cardiovascular disease (Farooq et al., 2018; Vionnet et al., 2000; Yuan et al., 2016) all common comorbidities in individuals with PTSD (Lihua et al., 2020; Scherrer et al., 2019). Inflammatory and metabolic mechanisms may play a role in the neurobiology of PTSD (Farr et al., 2014; Mellon et al., 2018; O'Donovan, 2016). Specifically, PTSS severity has been associated with higher levels of inflammation (Fonkoue et al., 2020).

Adiponectin can cross the blood–brain barrier and exerts neurotrophic and neuroprotective effects in various brain regions (Bloemer et al., 2019; Formolo et al., 2022). Adiponectin stimulates hippocampal neurogenesis (Zhang et al., 2016) and in a mouse model of PTSD, adiponectin infusions into the dentate gyrus of the hippocampus facilitated context-specific fear extinction learning (Zhang et al., 2017). Biomarker studies in human have shown that, compared to healthy controls, individuals with PTSD symptomatology (Na et al., 2017) and childhood trauma exposure (Lehto et al., 2012) exhibit decreased adiponectin levels. In addition, associations between *ADIPOQ* gene variants and other neuropsychiatric disorders that are mechanistically linked to PTSD, such as depression, have been shown (Awofala et al., 2020; Raheja et al., 2017; Wang et al., 2015). This makes *ADIPOQ* an interesting candidate gene to explore in relation to PTSD.

No human genetic study of the association between *ADIPOQ* and PTSD exists. Genome-wide association studies (GWAS) represent the current most robust and unbiased method to assess associations between genetic variants and complex diseases, such as PTSD (Uffelmann et al., 2021). Although PTSD GWASs have led to the identification of several novel risk variants not previously explored using biologically driven candidate-gene approaches, GWASs are not without limitations (Duncan et al., 2018; Nievergelt et al., 2019; Stein et al., 2021). To date, large-scale PTSD GWASs have not identified any genetic variants that exceeded genome wide significance (Duncan et al., 2018; Nievergelt et al., 2019; Stein et al., 2021). Furthermore, although one of the largest PTSD-GWAS to date, published by the Psychiatric Genomics Consortium (PGC)-PTSD, included South African samples in their analyses ($N = 387$); predominantly, samples analysed were of European ancestry ($N = 9954$) (Duncan et al., 2018). Studies among diverse population groups, specifically of African descent is a well-recognised research need and priority (Dalvie et al., 2015; Popejoy & Fullerton, 2016). Other limitations of GWASs include examining PTSD as a binary outcome (Duncan et al., 2018; Nievergelt et al., 2019). PTSD symptom severity and trajectories differ according to the index trauma type (Graham et al., 2016; Kessler et al., 2017). In addition, no GWAS has included cohorts that have exclusively focused on sexual trauma, and it remains unknown whether genetic risk for PTSD differs by trauma-type (Stein et al., 2021). Thus, a gap in knowledge exists regarding the genetic contribution to PTSS in sexually traumatised individuals, specifically of African descent.

This prospective exploratory study investigated (i) whether selected single nucleotide polymorphisms (SNPs) of the *ADIPOQ* gene are associated with change in PTSD symptom (PTSS) severity over 6 months and, (ii) given previous associations shown between adiponectin levels and childhood trauma (Lehto et al., 2012), sought to examine whether these SNPs modify the associations between childhood trauma exposure and PTSS severity in a sample of female rape survivors. Identification of genetic variants that are linked to PTSD development may provide insights into underlying disease mechanisms and assist in identifying individuals at risk early.

2. Materials and methods

2.1. Participants and phenotyping

The data for the present study are derived from the Rape Impact Cohort Evaluation (RICE) study, a large prospective comparative cohort study evaluating the impact of rape on adult women's physical and mental health and their use of health services in South Africa over a 3-year period (Abrahams et al., 2017). The design and selection of participants for the RICE study have previously been described in detail (Abrahams et al., 2017). Briefly, rape-exposed participants were enrolled within 20 days post-rape incident, on average 12 days from rape care centres in the KwaZulu Natal Province of South Africa. Assessments were conducted at baseline and every 3 months in the 1st year and every 6 months thereafter. Recruitment was restricted to female participants between 16 and 40 years. Participants were excluded from the RICE study if they were too emotionally distressed at the time of enrolment to provide informed consent, intellectually disables or more than 14 weeks pregnant. For this sub-study, we included a total of 455 rape-exposed (RE) participants for whom baseline DNA as well as physical and mental health information was available for the baseline, 3- and 6-month visits.

2.2. Data collection

At the baseline and follow-up visits, participants completed a set of mental health assessments, including self-reported measures of risk and protective factors for the development of PTSD. Questionnaires were administered by trained research assistants who were supervised by a senior psychiatrist. Participants also underwent a physical examination and provided blood samples.

For this sub-study, we included a total of 455 rape-exposed participants for whom baseline DNA as well as physical and mental health information was available for the baseline, 3- and 6-month visits.

2.2.1. Genetics
2.2.1.1. Genome extraction.
Genomic DNA was extracted from 3 ml of whole blood samples collected in an EDTA tube according to the manufacturer's instructions, using the Gentra Puregene Blood kit (Qiagen). Following DNA extraction, DNA quantification (ng/μl) and quality (absorbance ratio: 260/280 and 260/230) were determined using a Nanodrop spectrophotometer (ThermoFisher Scientific). DNA was subsequently diluted to 20 ng/ul.

2.2.1.2. Selection and genotyping of polymorphisms.
Eight *ADIPOQ* SNPs were selected a priori after reviewing the literature: rs16861194, rs16861205, rs17300539, rs2241766, rs6444174, rs822395, rs1402697 and rs1501299. These SNPs were selected based on the following criteria: (1) they capture variations in the major blocks of the gene, (2) are functionally relevant and have been studied by others in relation to cardiometabolic diseases such as diabetes and MetS (all of the selected SNPs) (de Luis et al., 2016; Howlader et al., 2021; Siitonen et al., 2011; Wu et al., 2014; Yuan et al., 2016), (3) they have previously been associated with neuropsychiatric disorders related to PTSD, such as depression (rs2241766, rs1501299) (Awofala et al., 2020; Raheja et al., 2017; Wang et al., 2015) and (4) they have a minor allele frequency (MAF) ≥5% in African populations (all of the selected SNPs).

The MAF for all SNPs was obtained from Ensemble 1000 genomes project (http://www.ensembl.org/Homo_sampiens/Info/Index). The African (AFR) MAF was determined using published data from seven sub-population, including Yoruba and Esan in Nigeria, Luhya in Webuye, Kenya, Gambian in Western Divisions, Gambia, Mende in Sierra Leone, Americans of African Ancestry in South-West U.S.A. and African Caribbean in Barbados, Supplemental File S1.

The SNPs were genotyped using Kompetitive allele-specific PCR (KASP) genotyping (LGC Biosearch Technologies), according to the manufacturer's instructions.

KASP is a novel, fluorescence-based method of SNP genotyping that only requires a few SNP markers to genotype various samples (He et al., 2014). Linkage disequilibrium (LD) was assessed using Haploview version 4.2 (Barrett et al., 2005) and haploblocks were determined using the confidence bound method of Gabriel et al (Gabriel et al., 2002).

2.2.1.3. Genotyping quality control (QC) procedures.
Quality control evaluations were undertaken for all laboratory procedures. Data were automatically quality control checked on a per SNP basis. No template controls (NTCs) were included on each plate to enable the detection of contamination or non-specific amplification. In addition, SNPs with a MAF ≤ 0.01 or those that deviated from the expected Hardy-Weinberg equilibrium ($p < .05$) and SNPs with a call rate <90% were removed. After an initial 35 cycles of PCR, all genotypic reaction plates run at LGC were read on a BMG PHERAStar plate reader and visually inspected to assess the progression of the PCR reaction. Plates were then recycled (3 cycles per recycle step) and read after each recycle step. Read data were visually inspected by a laboratory operator after each recycle step until they were satisfied that the PCR reaction had reached endpoint. After genotyping was complete and prior to statistical analysis being performed, genotypes were reviewed by a programmer.

2.2.2. Mental health measures
2.2.2.1. Posttraumatic stress symptoms.
The Davidson Trauma Scale (DTS) is a 17-item self-report questionnaire of posttraumatic stress symptoms and was used to determine PTSS severity at all time points (Davidson et al., 1997). RE participants completed the DTS in relation to the recent rape event. From the 17 items, participants were first asked to record 'the trauma that is most disturbing to you'. Participants were then asked, for all items, to 'consider how often in the last week the symptom troubled you and how severe it was.' The first five items specifically refer to reexperiencing or avoiding the disturbing event. Reponses were measured on a 5-point Likert scale for symptom frequency ranging from 0 ('not at all') to 4 ('every day') and symptom severity ranging from 0 ('not at all distressing') to 4 ('extremely distressing'). The DTS total score was computed by adding all item responses together, i.e. both frequency and severity scores, with a possible range of 0–136. A total score of 40 or more is considered indicative of PTSD (Davidson et al., 1997). The DTS showed excellent reliability in this study at each timepoint with a Cronbach alpha score of .92 at baseline, .91 at 3 months and .93 at 6 months post-rape.

2.2.2.2. Past trauma.
A modified version of the Childhood Trauma Questionnaire (CTQ-SF), revised in

South Africa, was used to screen for trauma exposure before the age of 18 years (Bernstein et al., 2003; Chirwa et al., 2018). The modified version of the CTQ-SF consists of 14 items which are grouped into the following subthemes: (i) witnessing abuse of mother by father or boyfriend, and childhood experiences of (ii) sexual abuse, (iii) physical abuse, (iv) emotional abuse, and (v) parental neglect. All the items were measured on a 4-point scale (1 = never, 2 = sometimes, 3 = often, 4 = very often), total score range between 14 and 56.

A modified version of the Life Events Checklist (LEC) (Nduna et al., 2010; Weathers et al., 2013) was used to measure direct exposure to nine trauma type using a dichotomous 'yes/no' response. The trauma types measured were (1) imprisonment, (2) civil unrest/war, (3) serious injury, (4) being close to death, (5) murder of a family member or friend, (6) unnatural death of a family member or friend, (7) murder of a stranger(s), (8) robbed at gun- or knifepoint, (9) kidnapped and (10) sexual assault. The number of 'yes' responses were added together to yield a total score ranging from 0 to 10, indicating the cumulative lifetime trauma load of participants.

2.2.2.3. Depression.
The Center for Epidemiologic Studies Depression Scale (CES-D) was administered at all time points and used to screen for the presence of clinically significant depressive symptoms (Radloff, 1977). The CES-D is a twenty-item, self-report measure with responses measured on a 4-point Likert scale ranging from 0 ('rarely or none of the time') to 3 ('most or all of the time'), total score range between 0 and 60. A cut-off score of ≥16 has been recommended as indicative of depression caseness with good sensitivity, specificity and high internal consistency (Lewinsohn et al., 1997).

2.2.2.4. Previous rape exposure.
Women who reported previous (lifetime) exposure to sexual violence, other than the recent rape (within 20 days), were identified with three screening questions at the baseline interview. Participants were asked to indicate whether exposed to one/more of the following: intimate partner rape and/or non-partner rape and/or first sexual intercourse that was forced/rape. Non-partner rape (NPR) was measured using three items: (1) forced to have sex, (2) forced to have sex when under the influence of alcohol/drugs, and (3) gang raped. Intimate partner rape was measured through a single item, i.e. forced to have sex by a current or previous intimate partner.

2.2.3. Physical health
2.2.3.1. Clinical assessments for the presence of medical conditions.
The presence of medical conditions (specifically; hypertension, diabetes, and HIV) was determined through self-reported medical history on the administered questionnaires, clinical measurements, and biochemical assessments of blood samples collected by trained personnel.

2.2.3.2. Adiposity-measures.
We included body mass index (BMI) as a proxy indicator of generalised obesity. Trained fieldworkers measured height and weight using standard techniques. Weight was measured on a calibrated scale with participants in light clothing, without shoes, and recorded to nearest 0.5 kilograms (kg). Height was measured using a stadiometer in a standing upright position without shoes. BMI was calculated using Quetelet's formula as weight (kg) divided by height (in square metres) (Nishida et al., 2010). The BMI was classified into underweight (<18.5 kg/m^2), normal ($18–24.9$ kg/m^2), overweight ($25–29.9$ kg/m^2), obese (≥30 kg/m^2).

2.3. Ethics statement

All participants provided written informed consent, and the study protocol was reviewed and approved by the Health Research Ethics Committee at Stellenbosch University in Cape Town, South Africa (N08/02/040 and S17/10/265 for the parent- and this sub-study, respectively) and Human Research Ethics Committee at the South African Medical Research Council (EC019-10/2013). All methods were carried out in accordance with the Declaration of Helsinki 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/).

3. Statistical analyses

Simple descriptive statistics were computed to summarise patient characteristics and *ADIPOQ* SNPs using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Deviation from Hardy-Weinberg Equilibrium (HWE) ($p < .05$) was examined for each SNP using Fisher's exact test (Hosking et al., 2004; Xu et al., 2002). The evolution of PTSS up to 6 months was graphically explored using average profile plots for each *ADIPOQ* SNP.

3.1. Missing data and imputation process

Responses to questionnaires were recorded electronically and an interviewer could not proceed until an item response had been captured. This ensured that there were no missing values at an item level. However, an uploading error resulted in missing value sets for the symptom severity subscale of the DTS which was corrected once it was identified.

There were no missing values for the DTS frequency subscale, but 56% ($n = 254$) of the DTS symptom severity scores were missing at baseline, 46% ($n = 209$) were missing at 3 months and 37% ($n = 127$) were missing at 6 months post-rape. In the present study, participants with both severity and frequency scores (i.e. those participants without missing data in the DTS scale) had either the same score for severity as for frequency, or very close to their frequency score. Missing DTS symptom severity values were imputed in the RICE study using a multiple imputation model.

The multiple imputation method used follows a Bayesian iterative Markov chain Monte Carlo (MCMC) procedure which assumes that all the variables in the imputation model have a multivariate normal distribution and use a uniform prior distribution (Carlin & Chib, 1995). The imputation model included baseline previous traumatic experiences as covariates. Prior to using multiple imputation, missing data patterns were examined. The DTS overall score was then derived using imputed DTS frequency and severity score and bounded to follow the range of the original scale.

3.2. Genetic association analyses

Linear mixed models were used to evaluate the association between each of the selected *ADIPOQ* variants and PTSS severity (continuous DTS scores) over time. We considered a range of potential confounding factors which were a priori selected with reference as risk factors for PTSD. To prevent overfitting of the model, each of these variables was individually tested against the PTSS outcome at baseline and those variables displaying a significant association with PTSS at baseline were corrected for in the primary analyses (Supplemental file, S1). Models were adjusted for potential confounding by namely relationship status, depression (CES-D total score), lifetime trauma exposure (LEC total score), and previous rape exposure. An additive genetic model [two copies of the major allele (coded as 0) vs one copy of the major and minor allele (coded as 1) versus two copies of the minor allele (coded as 2)] were used for all models. Depending on the main effects in the linear mixed modelling, we sought to examine interaction effects of the genotype with childhood trauma on PTSS outcome over time (i.e. for SNPs that showed significant differences in the rate of change in PTSS in unadjusted and adjusted mixed linear models). Multiple testing was conducted using the Benjami Hochberg adjustment at 10% false discovery rate and the adjusted *p*-value ($p < .025$) was used to detect statistical significance (Benjamini et al., 2001). Statistical analyses were conducted using STATA 17.

4. Results

4.1. Sociodemographic characteristics of participants

The clinical characteristics of the study sample are presented in Table 1. The mean age of the 455 RE females included in this study was 25.3(5.5) years. Most participants were unemployed (73.6%, $n = 335$), and 48.6% ($n = 221$) tested positive for HIV infection at baseline. The mean PTSS score at baseline was high for the sample; 71.3(31.5). More than half of the participants (51.4%, $n = 234$) indicated a past rape experience other than the most recent rape event.

4.2. Genetics

A total of eight SNPs in *ADIPOQ* (rs16861194, rs16861205, rs17300539, rs2241766, rs6444174, rs822395, rs1403697 and rs1501299) were genotyped for each participant. rs1501299 and rs1403697 were found to not be in HWE and were therefore excluded from further analysis. SNP information including observed MAF and HWE *p*-values are shown in Table 2. The linkage disequilibrium (LD) plot for the

Table 1. General characteristics of the study cohort ($N = 455$).

Sociodemographic	Mean ± SD or n (%)
Age (years), mean ± SD	25.3 (5.5)
Age (years), median (IQR)	24.0 (21.0, 29.0)
Relationship status, N = 454, n(%)	
Single, separated or divorced	107 (23.6%)
Relationship, not cohabiting	34 (7.5%)
Married or cohabiting	313 (68.9%)
Socioeconomic status (SES), n(%)	
Secondary education completed,	256 (56.3%)
Employed	120 (26.4%)
Chronic medical illness, n(%)	
Hypertension	18 (4.0%)
Diabetes	72 (15.8%)
HIV infection	221 (48.6%)
Adiposity measures	
Body Mass Index, kg/m^2	26.6 (6.4)
Body Mass Index Categories, n (%)	
Underweight: BMI <18.5 kg/m^2	31 (6.8%)
Normal weight: BMI 18.5–24.9 kg/m^2	186 (40.9%)
Overweight: BMI 25–29.9 kg/m^2	111 (24.4%)
Obese: BMI ≥30 kg/m^2	127 (27.9%)
Previous trauma exposure	
Childhood trauma	
Childhood Trauma (CTQ-SF) score, mean ± SD	16.8 (3.7)
Childhood Trauma (CTQ-SF) score, median (IQR)	16.0 (14.0, 18.0)
Categories of childhood trauma, n (%)	
Physical abuse	200 (44.0%)
Emotional abuse	117 (25.7%)
Sexual abuse	94 (20.8%)
Neglect	194 (42.6%)
Witnessed abuse	66 (14.5%)
Lifetime trauma	
Lifetime Trauma (LEC), score, mean ± SD	2.1 (1.8)
Lifetime Trauma (LEC), score, median (IQR)	2.0 (1.0, 3.0)
Mental Health factors	
Posttraumatic stress score (DTS)	71.3 (31.5)
Depression score (CES-D), mean ± SD	33.9 (12.6)
Previous rape exposure, n(%)	234 (51.4%)

Notes: Data are expressed as mean (SD) for continuous variables with normal distribution, and further expressed as median (IQR) if distribution is skewed, and N, (percentage) for categorical variables, Davidson Trauma Scale (DTS).

Table 2. Characteristics of the eight SNPs genotyped in 455 participants.

Name	Position	Region in gene	ObsHET	PredHET	HW p-value	%Geno	MAF	Alleles (major/minor)
rs17300539	188042154	Promoter	0.012	0.012	1	99.8	0.006	G/A
rs16861194	188042119	Promoter	0.371	0.357	.3202	97.2	0.233	A/G
rs16861205	188044328	Intron 1	0.309	0.309	1	99.4	0.191	G/A
rs2241766	188053586	Exon 2	0.065	0.063	.8047	99.3	0.033	T/G
rs6444174	188055883	Intergenic	0.378	0.388	.4824	99.4	0.264	T/C
rs822395	188049501	Intron 1	0.478	0.478	1	99.3	0.396	C/A
rs1501299	188053817	Intron 2	0.568	0.5	8.75E-05	99.9	0.488	T/G
rs1403697	188059387	3′-UTR	0.311	0.29	.035	99.9	0.176	A/G

Notes: ObsHET, SNPs observed heterozygosity; PredHET, marker's predicted heterozygosity i.e. 2*MAF*(1-MAF); HW, Hardy-Weinberg; MAF, minor allele frequency; SNP, single nucleotide polymorphism; UTR, untranslated region.

six *ADIPOQ* polymorphisms in HWE is presented in Figure 1. No *ADIPOQ* haploblocks were identified, and thus no haplotype analysis was performed.

4.3. Associations between ADIPOQ *SNPs and PTSS*

The genotype distribution of the selected SNPs and corresponding PTSS scores at baseline, 3- and 6-month follow-up is shown in Table 3. Most of the improvement in PTSS severity occurred within the first 3 months followed by a slower rate of improvement between 3 and 6 months for all genotypes, except for participants with rs17300539GA and rs644174CC genotypes, who had a non-significant increase in PTSS severity (mean DTS increase score of 0.5, p = .954; 1.4, p = .806) between 3 and 6 months follow up. A graphical depiction of the PTSS trajectory over 6 months for all SNPs is presented in Supplemental file, S2. The association between the 6 SNPs (those in HWE) and PTSS scores was investigated using a linear mixed model at 3- and 6-month follow-up (Table 4). The rs6444174CC genotype was significantly

associated with PTSS at baseline (β = −13.6, 95% CI [−25.2; −2.1], p = .021). None of the genotypes were significantly associated with PTSS in the unadjusted or adjusted models at follow-up.

4.4. Gene × environment interaction analyses

We did not conduct further analysis investigating *ADIPOQ* SNP × childhood trauma interaction effects on PTSS, due to the absence of significant associations in linear mixed models.

5. Discussion

In the present study, the association between selected *ADIPOQ* SNPs and PTSS severity was explored longitudinally among adult female rape survivors. Consistent with previous research, we found a high prevalence of PTSS in this cohort in the days following the rape, with the majority of PTSS recovery occurring within the first 3 months post-sexual assault (Dworkin et al., 2021). At the baseline assessment, the mean DTS score was markedly higher than the
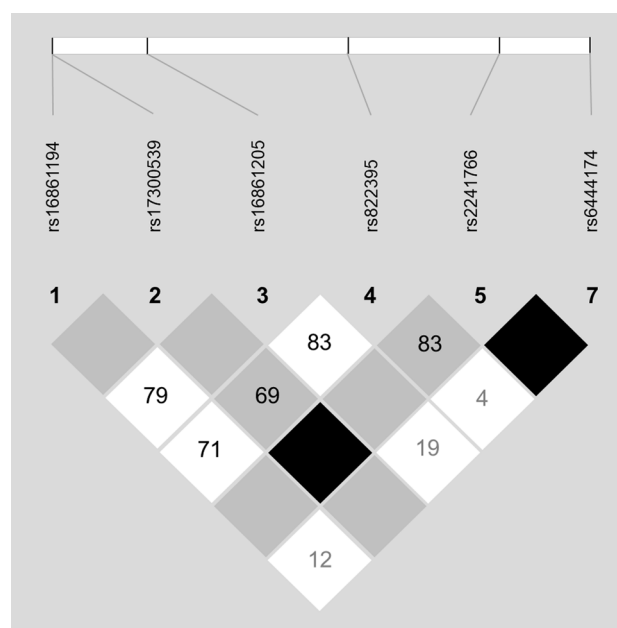
Figure 1. Linkage disequilibrium (LD) map. Linkage disequilibrium for the 8 *ADIPOQ* polymorphisms investigated. D' values are depicted in the diamonds, with darker colours depicting stronger LD. The LD map was created using the confidence interval of LD, implemented in Haploview version 4.2.

Table 3. Genotype distribution of the selected *ADIPOQ* SNPs with PTSS severity at baseline, 3 and 6 months.

Adiponectin SNP	Genotypes	N	%	PTSS at baseline Mean (95% CI)	PTSS at 3 months Mean (95% CI)	PTSS at 6 months Mean (95% CI)	Mean PTSS difference (baseline-3 months) Mean difference (95% CI)	p value	Mean PTSS difference (3–6 months) Mean difference (95% CI)	p value	Mean PTSS difference (baseline – 6months) Mean difference (95% CI)	p value
rs17300539	GA	6	1.3	74.4 (46.2; 102.6)	22.6 (8.0; 37.1)	23.1 (12.3; 33.9)	−51.8 (−82.6; −21.1)	.008	0.5 (−21.8; 22.8)	.954	−51.3 (−82.9; 19.7)	.009
	GG	445	97.8	71.5 (68.6; 74.4)	40.7 (37.7; 43.7)	32.9 (30.2; 35.6)	−30.8 (−34.3; −27.3)	<.001	−7.8 (−11.0; −4.6)	<.001	−39.6 (−42.0; −35.1)	<.001
	Missing[a]	4	0.9									
rs16861194	AA	252	55.4	70.6 (66.6; 74.6)	41.2 (37.1; 45.3)	32.4 (28.9; 35.9)	−29.4 (−33.9; −24.8)	<.001	−8.9 (−13.2; −4.6)	<.001	−38.2 (−42.8; −33.6)	<.001
	GA	165	36.3	72.3 (67.9; 76.8)	41.7 (36.7; 46.6)	33.4 (28.9; 37.8)	−30.7 (−36.3; −25.0)	<.001	−8.3 (−13.4; −3.1)	.002	−39.0 (−44.3; −3.6)	<.001
	GG	22	4.8	73.0 (56.7; 89.4)	35.9 (23.4; 48.5)	33.9 (19.8; 47.9)	−37.1 (−56.8; −17.4)	.001	−2.01 (−15.3; 11.2)	.749	−39.1 (−60.7; −17.6)	.001
	Missing[a]	16	3.5									
rs16861205	AA	18	4.0	73.9 (59.4; 88.4)	31.5 (18.1; 45.0)	19.2 (8.7; 29.7)	−42.4 (−62.6; −22.1)	<.001	−12.4 (−24.4; −0.3)	.045	−54.7 (−72.4; −37.1)	<.001
	AG	142	31.2	69.3 (64.3; 74.2)	41.8 (36.3; 47.3)	34.3 (29.4; 39.1)	−27.4 (−33.2; −21.7)	<.001	−7.6 (−13.3; −1.9)	.010	−35.0 (−40.8; −29.1)	<.001
	GG	290	63.7	72.8 (69.2; 76.5)	40.8 (37.1; 44.5)	33.4 (30.1; 36.7)	−32.0 (−36.6; −27.6)	<.001	−7.4 (−11.4; −3.4)	<.001	−39.5 (−43.8; −35.1)	<.001
	Missing[a]	5	1.1									
rs2241766	TG	24	5.3	75.3 (63.3; 87.3)	45.7 (30.5; 60.9)	36.0 (27.2; 44.8)	−29.6 (−44.6; −14.6)	.001	−9.7 (−22.0; 2.6)	.117	−39.3 (−49.3; −29.3)	<.001
	TT	426	93.6	71.1 (68.1; 74.1)	40.3 (37.2; 43.4)	32.7 (29.9; 35.4)	−30.8 (−34.4; −27.2)	<.001	−7.6 (−10.9; −4.4)	<.001	−38.5 (−42.0; −34.9)	<.001
	Missing[a]	5	1.1									
rs6444174	CC	32	7.0	60.1 (49.7; 70.6)	30.9 (21.7; 40.2)	32.3 (22.2; 42.5)	−29.2 (−43.7; −14.7)	<.001	1.4 (−10.0; 12.8)	.806	−27.8 (−41.1; −14.5)	<.001
	TC	169	37.1	70.4 (65.8; 74.9)	40.1 (34.9; 45.3)	29.8 (25.3; 34.3)	−30.3 (−35.9; −24.7)	<.001	−10.3 (−15.3; −5.3)	<.001	−40.6 (−46.3; −34.9)	<.001
	TT	250	55.0	73.8 (69.8; 77.7)	42.4 (38.4; 46.3)	34.7 (31.3; 38.1)	−31.4 (−36.1; −26.7)	<.001	−7.6 (−11.9; −3.4)	.001	−39.1 (−43.6; −34.5)	<.001
	Missing[a]	4	0.9									
rs822395	AA	81	17.8	70.4 (63.6; 77.2)	43.4 (36.1; 50.7)	33.2 (26.6; 39.8)	−27.0 (−34.4; −19.6)	<.001	−10.2 (−17.7; −2.7)	.008	−37.2 (−44.8; −29.6)	<.001
	CA	210	46.2	71.6 (67.5; 75.6)	36.8 (32.8; 40.9)	31.6 (27.8; 35.4)	−34.7 (−39.9; −29.6)	<.001	−5.2 (−9.5; −0.9)	.017	−40.0 (−45.1; −34.8)	<.001
	CC	158	34.7	71.4 (66.2; 76.6)	42.8 (37.5; 48.2)	33.9 (29.4; 38.4)	−28.6 (−34.5; −22.6)	<.001	−8.9 (−14.7; −3.1)	.003	−37.5 (−43.3; −31.7)	<.001
	Missing[a]	6	1.3									

[a]Missing refers to missing genotype. PTSS, posttraumatic stress score according to the Davidson Trauma Scale.

Table 4. Linear mixed model of *ADIPOQ* SNPs and posttraumatic stress symptom (PTSS) severity at 3- and 6-month follow up.

	Unadjusted			Adjusted		
	β coefficient	95% CI for β Range(CI)	*p*-value	β coefficient	95% CI for β Range(CI)	*p*-value
rs17300539						
Time						
Baseline	Ref			Ref		
Month 3	−30.8	−34.1; −27.5	<.001	−30.8	−34.1; −27.5	<.001
Month 6	−38.6	−42.0; −35.2	<.001	−38.7	−42.0; −35.2	<.001
Genotype						
GG	Ref			Ref		
GA	2.9	−22.4; 28.2	.822	−2.2	−23.8; 19.4	.839
Time x Genotype						
Month 3 & GA	−21.0	−49.9; 7.8	.152	−21.1	−49.9; 7.7	.152
Month 6 & GA	−12.7	−42.5; 17.0	.401	−12.6	−42.4; 17.1	.404
rs16861194						
Time						
Baseline	Ref			Ref		
Month 3	−29.4	−33.8; −24.9	<.001	−29.4	−33.8; −24.9	<.001
Month 6	−38.2	−42.8; −33.7	<.001	−38.2	−42.8; −33.7	<.001
Genotype						
AA	Ref			Ref		
GA	1.8	−4.5; 8.0	.580	1.3	−4.0; 6.6	.622
GG	2.5	−11.4; 16.3	.728	2.1	−9.7; 13.9	.727
Time x Genotype						
Month 3 & GA	−1.3	−8.3; 5.7	.714	−1.3	−8.3; 5.8	.725
Month 3 & GG	−7.8	−23.3; 7.8	.329	−7.8	−23.3; 7.8	.329
Month 6 & GA	−0.7	−8.0; 6.5	.844	−1.0	−8.2; 6.3	.797
Month 6 & GG	−0.9	−17.0; 15.1	.909	−0.9	−17.0; 15.1	.909
rs16861205						
Time						
Baseline	Ref			Ref		
Month 3	−32.0	−36.2; −27.9	<.001	−32.0	−36.2; −27.9	<.001
Month 6	−39.5	−43.7; −35.2	<.001	−39.5	−43.7; −35.2	<.001
Genotype						
GG	Ref			Ref		
AG	−3.6	−9.9; 2.7	.266	−1.9	−7.4; 3.5	.483
AA	1.1	−14.0; 16.1	.890	1.0	−11.8; 13.8	.881
Time x Genotype						
Month 3 & AG	4.6	−2.6; 11.8	.211	4.7	−2.5; 11.9	.204
Month 3 & AA	−10.3	−27.4; 6.8	.236	−10.3	−27.4; 6.8	.236
Month 6 & AG	4.5	−2.9; 11.8	.236	4.2	−3.2; 11.6	.263
Month 6 & AA	−15.3	−32.8; 2.2	.087	−15.3	−32.8; 2.2	.087
rs2241766						
Time						
Baseline	Ref			Ref		
Month 3	−3.8	−34.2; −27.4	<.001	−30.8	−34.2; −27.4	<.001
Month 6	−38.5	−42.0; −35.0	<.001	−38.5	−42.0; −35.0	<.001
Genotype						
TT	Ref			Ref		
TG	4.2	−8.7; 17.1	.525	1.5	−9.6; 12.6	.793
Time x Genotype						
Month 3 & TG	1.2	−13.6; 15.9	.876	1.2	−13.6; 15.9	.878
Month 6 & TG	−0.9	−16.0; 14.3	.910	−0.8	−15.9; 14.4	.919
rs6444174						
Time						
Baseline	Ref			Ref		
Month 3	−31.4	−35.8; −27.0	<.001	−31.4	−35.8; −27.0	<.001
Month 6	−39.1	−43.6; −34.5	<.001	−39.2	−43.8; −34.6	<.001
Genotype						
TT	Ref			Ref		
TC	−3.4	−9.5; 2.7	.278	−2.5	−7.7; 2.8	.358
CC	−13.6	−25.2; −2.1	**.021**	−7.2	−17.1; 2.8	.158
Time x Genotype						
Month 3 & TC	1.1	−5.8; 8.1	.751	1.1	−5.9; 8.0	.758
Month 3 & CC	2.2	−10.9; 15.3	.740	2.2	−10.9; 15.3	.744
Month 6 & TC	−1.6	−8.7; 5.6	.672	−1.4	−8.6; 5.8	.702
Month 6 & CC	11.2	−2.3; 24.8	.103	11.4	−2.1; 24.9	.099
rs822395						
Time						
Baseline	Ref			Ref		
Month 3	−28.6	−34.1; −23.0	<.001	−28.6	−34.1; −23.0	<.001
Month 6	−37.5	−43.2; −31.7	<.001	−37.5	−43.2; −31.7	<.001
Genotype						
CC	Ref			Ref		
CA	0.2	−6.4; 6.7	.960	−0.2	−5.8; 5.4	.942
AA	−1.0	−9.5; 7.5	.816	−0.6	−7.8; 6.7	.873

(Continued)

Table 4. Continued.

	Unadjusted			Adjusted		
	β coefficient	95% CI for β Range(CI)	p-value	β coefficient	95% CI for β Range(CI)	p-value
Time x Genotype						
Month 3 & CA	−6.2	−13.5; 1.2	.099	−6.2	−13.5; 1.2	.099
Month 3 & AA	1.6	−8.0; 11.1	.748	1.7	−7.9; 11.3	.726
Month 6 & CA	−2.5	−10.1; 5.2	.524	−2.5	−10.1; 5.2	.524
Month 6 & AA	0.3	−9.6; 10.2	.956	−0.2	−10.1; 9.8	.975

Notes: Adjusted for relationship status, lifetime trauma, depression, and previous rape event. Values in bold indicate p-value ≤ .025 (adjusted for multiple testing) Abbreviations: *ADIPOQ*, adiponectin gene; SNP, single nucleotide polymorphism; PTSS, posttraumatic stress symptom; β, coefficient, CI; confidence interval.

recommended cut-off for clinically significant PTSS. Although two of the examined SNPs (rs17300539GA and rs6444174CC) were associated with non-significant increases in PTSS severity between 3 and 6 months; none of the six *ADIPOQ* SNPs were shown to be associated with PTSS severity over time.

To the best of our knowledge, this is the first study to investigate the association between *ADIPOQ* and PTSD. Adiponectin is best known for its associations with cardiometabolic diseases (Chen et al., 2012; Davis et al., 2015; Ghadge et al., 2018). Genetic variations in *ADIPOQ* have been shown to be associated with obesity, T2DM, hypertension and related phenotypes in various populations (Farooq et al., 2018; Wu et al., 2014; Yuan et al., 2016). High rates of cardiometabolic disease among individuals with PTSD suggest that there may be mechanistic links underlying these disorders. This is of relevance among victims of sexual assault who show an increased risk for both PTSD and cardiometabolic disease longitudinally (Ba & Bhopal, 2017; Dworkin, 2018; Oshodi et al., 2016). To date, *ADIPOQ* has not been linked with PTSD in PTSD-GWAS (Duncan et al., 2018; Gelernter et al., 2019; Nievergelt et al., 2019; Stein et al., 2021), however given differences in ethnicity, trauma types, trauma severity and gender distribution between currently published GWAS and our study, we undertook to investigate this gene in our population. In addition, GWAS cannot identify all genetic determinants of complex traits (Tam et al., 2019).

There are several potential reasons why our analysis did not reveal any significant association between examined SNPs and PTSS in this cohort. First, the relatively small sample may have increased risk of a Type II error which could have masked an association or decreased statistical power. Only a limited number of *ADIPOQ* SNPs were examined in this study; the investigated SNPs were not functional SNPs and thus unlikely to represent the causal SNPs. Gene-gene and gene-environment interactions may also contribute to PTSD risk, which were not accounted for in the present study. *ADIPOQ* SNP x dietary interactions have been shown to influence risk of MetS (Coltell et al., 2021; Ferguson et al., 2010). Epistatic (gene-gene) interactions are considered to play a major role in susceptibility to complex diseases

(Nagel, 2005; Wei et al., 2014). It has been proposed that epistasis could explain some of the 'missing heritability' undetected by PTSD-GWAS (Manolio et al., 2009; Zhang et al., 2019). There is a strong body of evidence showing that PTSD is associated with a dysregulated HPA-axis resulting in altered cortisol levels (Dunlop & Wong, 2019; Yehuda et al., 2000). The FK506 binding protein 5 (*FKBP5*) is a major regulatory protein of the HPA axis, which binds to glucocorticoid receptors and modulates glucocorticoid sensitivity (Fani et al., 2016; Zannas et al., 2016). SNPs in the *FKBP5* gene have been shown to be associated with reduced cortisol-levels (Velders et al., 2011) and PTSD (Kang et al., 2019; Zhang et al., 2020). Interestingly, cortisol has been shown to have an inhibitory effect on adiponectin (Fallo et al., 2004; Fernandez-Real et al., 2005; Gavrila et al., 2003). Given this reported negative correlation between circulating adiponectin and cortisol levels, the potential intermolecular epistatic interactions between *ADIPOQ* and *FKBP5* may be avenue of further study to identify individuals at risk for PTSD. However, investigation of such interactions would require a much larger sample size to attain optimal statistical power (Murcray et al., 2011). Future research could seek to determine whether epigenetic modification of the *ADIPOQ* locus influences PTSD risk. Of interest, the promotor region of *ADIPOQ* contains consensus sequences for the glucocorticoid receptor and could, therefore, be subject to environmental modifications in response to stress (Comuzzie et al., 2001). Lastly, rare variants, which were not investigated in the present study, may also affect disease risk. Replication of this analysis in a much larger sample is required to conclusively rule out an association between the investigated *ADIPOQ* SNPs and rape-related PTSD.

6. Strengths and limitations

Findings from this study should be interpreted in the context of several unavoidable limitations. First, this study used a candidate gene approach to assess the role of *ADIPOQ* variants in predicting PTSS development following rape. To data, candidate gene studies have largely been underpowered due to small sample sizes and GWAS approaches are increasingly favoured

in PTSD genetics research. Nevertheless, we believe our study has merit and utility given that it was conducted among sexually traumatised individuals of African ancestry, both understudied populations in genetic research. Second, we were unable to account for the genomic ancestral substructure of this sample as this information was not available (Tian et al., 2008). Third, the sample was small providing limited statistical power for detecting the effect of adiponectin genotype on PTSD status. Fourth, our study results may not be readily generalisable to male, other ethnic population groups or other trauma types. The strengths of our study include its prospective design, comprehensive assessment of known risk and predictive factors in a well characterised and a relatively understudied population in psychiatric genetics and a homogenous index trauma. Findings are considered preliminary, and replication is needed in large, well characterised samples exposed to other types of interpersonal trauma.

7. Conclusions

ADIPOQ polymorphisms were not associated with PTSS in this population of rape-exposed black South African women. These findings suggest that these SNPs may not be clinically helpful to predict PTSS severity post-sexual assault. Replications studies in larger, mixed sex trauma samples followed over a longer time course (> 6 months) are warranted as is the examination of other *ADIPOQ* variants. The role of these SNPs in possible gene-gene and gene-environment interactions also remains to be established.

Data availability statement

The data that support the findings of this study are being used to address additional study aims and cannot be shared publicly at this stage. The study collaborative team will review individual requests to access data.

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