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ORIGINAL RESEARCH

Associations of TCF7L2 rs11196218 (A/G) and GLP-1R rs761386 (C/T) Gene Polymorphisms with Obesity in Chinese Population

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Introduction: This study aimed to investigate the genetic polymorphism associations with obesity of the transcription factor 7-like 2 (*TCF7L2*) gene rs11196218 (A/G) and glucagon-like peptide 1 receptor (*GLP1-R*) gene rs761386 (C/T) in the Chinese population.

Patients and Methods: This was a case–control pilot study involving 60 patients with obesity and 69 non-obesity Chinese adults, and the two groups were sex and age matched. Anthropometric indices of obesity, fasting blood glucose, blood pressure, and blood lipids were assessed. Both polymorphisms were genotyped using matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF).

Results: There were significant differences in the allelic frequencies of the *TCF7L2* rs11196218 and *GLP1-R* rs761386 between obesity and non-obesity groups (P = 0.003, OR = 2.32, 95% CI [1.31~4.09]; P = 0.034, OR = 1.94, 95% CI [1.05~3.60], respectively). In allele model, the genotypic frequencies of *TCF7L2* rs11196218 and *GLP1-R* rs761386 also differed between obesity and non-obesity groups (P = 0.014 and 0.033, respectively). In dominant model, the *TCF7L2* rs11196218 A-carrier (AA/AG) had a higher risk of obesity than GG genotype (P = 0.014, OR = 2.54, 95% CI [1.21~5.35]). Comparison of clinical and biochemical parameters between genotypes showed no significant difference.

Conclusion: These findings suggest that the rs11196218 (A/G) polymorphism of the *TCF7L2* gene and the rs761386 (C/T) polymorphism of the *GLP1-R* gene were associated with obesity in the Chinese population.

Keywords: obesity, genetic association, *TCF7L2*, *GLP1-R*, polymorphism, Chinese

Introduction

According to the World Health Organization (WHO), obesity is a medical condition where excess body fat has accumulated to an extent that may increase an individual's health risks.[1] The prevalence of obesity is high and ever-increasing worldwide – nearly 40% of adults were overweight and 10–15% were obese according to a report in 2016.[2] It has become a public health problem, causing severe negative effects on personal health and social development.[3–5] Obesity is a multifactor disease that is determined by both environmental and hereditary factors.[6,7] Simulation studies have suggested that SNPs account for around 30% of variance in BMI, indicating that SNP polymorphism is one of the hereditary factors that needs further study.[8] There is some evidence showing that the SNPs could have considerable biological effects. For instance, *FTO* SNPs variance could affect the gene expression by physically contacting the promoter or disrupting the binding

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sites of other genes, leading to the shifts of cell fates – from energy-burning beige adipocytes to energy-storing white adipocytes.[9] However, for many obesity-related genes, the associations between SNPs polymorphism and obesity are still paradoxical and insufficient, which also hampered the functional characterization of genetic associations.[10] This study mainly focuses on two genes: transcription factor 7-like 2 (*TCF7L2*) and glucagon-like peptide 1 receptor (*GLP1-R*).

TCF7L2 is a gene that encodes a high-mobility group (HMG) box-containing transcription factor that plays a key role in the Wnt signaling pathway. The protein has been implicated in blood glucose homeostasis. Several studies have found that genetic variants of this gene are associated with an increased risk of type 2 diabetes in Cameroonian and Danish individuals as well as gestational diabetes mellitus in Chinese individuals.[11–14] In an Asian Indian population study, *TCF7L2* polymorphism was also significantly associated with an increased risk of type 2 diabetes.[15] Considering the strong connection between type 2 diabetes and obesity, the possible association between *TCF7L2* and obesity has been explored.[16,17] *GLP1-R* encodes a 7-transmembrane protein that functions as a receptor for glucagon-like peptide 1 (*GLP-1*) hormone, which stimulates glucose-induced insulin secretion. *GLP1-R* polymorphisms are associated with diabetes, while the associations between *GLP1-R* polymorphisms and obesity in different countries and ethnic groups vary a lot.[18,19]

Important advances have been made regarding the understanding of the genetic mechanisms underlying obesity in previous decades, but the research remains insufficient, especially in Chinese people, who comprise nearly 1/5 of the global population. To the best of our knowledge, there are no published data for the Chinese population on the roles of *TCF7L2* or *GLP1-R* polymorphisms in obesity. This study aimed to investigate the associations of the *TCF7L2* rs11196218 (A/G) and *GLP-1R* rs761386 (C/T) polymorphisms with obesity to improve our understanding of the effect of single-nucleotide polymorphisms (SNPs) on obesity in Chinese individuals.

Patients and Methods

Study Sample

We conducted a case–control study involving subjects of Chinese origin, aged 18 years old and above. The patients with obesity (body mass index [BMI] ≥28 kg/m^2 and/or male WC≥90 cm, female WC≥85 cm) were recruited from the Outpatient Clinic and the non-obese controls (BMI 18.5–23.9 kg/m^2) were recruited from the Physical Examination Center of Xiangya Hospital of Central South University. We only included patients who had a fasting blood glucose (FBG) level <5.6 mmol/L and without a history of diabetes. We finally invited 60 subjects with obesity and 69 normal-weight controls to participate in this study, all of whom agreed.

Clinical and Biochemical Data Collection and Genotyping

Clinical and biochemical data were collected. The data included sex, age, height, weight, BMI, waist-to-hip ratio (WHR), FBG, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), total triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). The *TCF7L2* rs11196218 (A/G) and *GLP-1R* rs761386 (C/T) polymorphisms were genotyped using MassARRAY® MALDI-TOF System (Sequenom, Inc) after the PCR amplification.[20] The primers used for rs11196218 are 5′-ACGTTGGATGCTCTTAACCAACATGGCTTG-3′ and 5′-ACGTTGGATGAATAAGTGTGCAAACGAGGG-3′; the primers for rs761386 are 5′-ACGTTGGATGGAGTGGCAGCTATGATAGGG-3′ and 5′-ACGTTGGATGAGATGAGGAAGTTCACCTGC-3′. The cycling parameters were 94 °C for 3 min; 40 cycles at 94 °C for 30 s, 56 °C for 25 s, 72 °C for 30 s; and a final extension step at 72 °C for 3 min. The detailed procedure is documented (https://www.gene-quantification.de/sequenom/).

Statistical Analysis

Statistical analysis was performed using SPSS 20.0, tests for deviation from the Hardy–Weinberg equilibrium as well as allelic and genotypic frequencies were performed with the online analysis tool SHEsis (http://analysis.bio-x.cn/myAnalysis.php).[21] Continuous variables are expressed as mean ± standard deviation and categorical variables are expressed as frequencies and percentages. Differences in clinical and biological parameters were compared between groups using independent-sample t-tests (continuous variables) and chi-square tests (categorical variables). We adjusted confounding factors including sex and age in the regression analysis. The significance level was set at P-value < 0.05. Three different modes of inheritances (allele model, dominant model and recessive model) were analyzed. We

performed the post hoc analysis of statistical power using the power calculator (https://clincalc.com/stats/Power.aspx).

Results

Clinical and Biochemical Characteristics of the Participants

We evaluated 129 Chinese participants, comprising 69 non-obese individuals and 60 patients with obesity (all of whom had a normal FBG level). Table 1 shows the clinical and biochemical characteristics of the subjects, comprising 78 women and 51 men. There were no significant differences between the two groups concerning sex composition, age and FBG (P> 0.05). BMI, WHR, SBP, DBP, TC, TG, and LDL-C were significantly higher in the obese group than in the non-obese group (P< 0.001). In contrast, HDL-C was significantly lower in the obese group compared to the non-obese group (P< 0.001).

Table 1 Clinical and Biochemical Characteristics of the Studied Groups

Characteristics	Non-Obese (n=69)	Obese (n=60)	*P* value
Sex (F/M)	47/22	31/29	0.084
Age (year)	37.16±8.74	34.37±8.54	0.070
BMI (kg/m^2)	21.14±1.72	32.67±5.42	<0.001
WHR	0.79±0.05	0.95±0.06	<0.001
FBG (mmol/L)	5.06±0.29	5.08±0.37	0.783
SBP (mmHg)	110.22±10.94	120.30±20.28	<0.001
DBP (mmHg)	71.28±7.98	79.23±14.28	<0.001
TC (mmol/L)	4.44±0.49	5.06±0.82	<0.001
TG (mmol/L)	0.98±0.31	2.28±1.37	<0.001
HDL-C (mmol/L)	1.57±0.33	1.21±0.26	<0.001
LDL-C (mmol/L)	2.49±0.43	3.24±0.72	<0.001

Abbreviations: BMI, body mass index; WHR, waist-to-hip ratio; FPG, fasting plasma glucose; SBP, systemic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, serum total triacylglycerol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Allele and Genotype Distributions and Associations with Obesity

We performed the Hardy–Weinberg equilibrium test using the online tool SHEsis using the function "Single site analysis". The allelic and genotypic frequencies of rs11196218 and rs761386 in the study sample, which are presented in Tables 2 and 3, were consistent with Hardy–Weinberg equilibrium (P>0.05), which means there were no other evolutionary forces (such as natural selection). Regarding the *TCF7L2* rs11196218 polymorphism, the G allele was the major allele in the two groups (81.2% and 65.0%, respectively). There was a significantly higher proportion of A allele carriers in the obese group than the non-obese group (P=0.003), which indicates that the A allele of rs11196218 is probably a risk factor for obesity (OR=2.32, 95% CI [1.31~4.09]). Similarly, regarding the *GLP1-R* rs761386 polymorphism, the minor T allele was more frequent in the obese group compared with the non-obese group (P=0.034), which suggests that the T allele of rs761386 is a risk factor for obesity (OR=1.94, 95% CI [1.05~3.60]). Table 3 shows that the genotypic frequencies of rs11196218 and rs761386 between obesity and non-obesity group were also significantly different (χ^2 = 8.558, P = 0.014 and χ^2 = 6.795, P = 0.033, respectively). The frequency of *TCF7L2* rs11196218 A-carrier AA and AG in the obesity group was higher than in the non-obesity group, while GG showed a lower frequency. Regarding the *GLP1-R* rs761386, the genotypic frequency of T-carrier, CT and TT, is higher in the obesity group than in the non-obesity group. These results are compatible with the allele difference showed in Table 2. To explore

Table 2 Hardy–Weinberg Equilibrium Test and Allelic Frequencies

SNP	Allele	Non-Obese (n=69)	Obese (n=60)	*P* value	OR	95% CI
rs11196218	A G Total (2n) HWE *P*	26(0.188) 112(0.812) 138 0.665	42(0.350) 78(0.650) 120 0.843	0.003	2.32	1.31~4.09
rs761386	C T Total (2n) HWE *P*	117(0.848) 21(0.152) 138 0.136	89(0.742) 31(0.258) 120 0.502	0.034	1.94	1.05~3.60

Abbreviations: SNP, single-nucleotide polymorphism; *P*, Pearson's *P* value; HWE, Hardy–Weinberg equilibrium. The results are presented as n (%).

Table 3 Genotypic Frequencies Between Non-Obese and Obese Group

SNP	Genotype	Non-Obese (n=69)	Obese (n=60)	χ^2	*P* value
rs11196218	A/A A/G G/G	3(0.043) 20(0.290) 46(0.667)	7(0.117) 28(0.467) 25(0.417)	8.558	0.014
rs761386	C/C C/T T/T	48(0.696) 21(0.304) 0(0.000)	34(0.567) 21(0.350) 5(0.083)	6.795	0.033

Note: The results are presented as n (%).
Abbreviations: SNP, single-nucleotide polymorphism; *P*, Pearson's *P* value.

further, we studied the dominant and recessive model, separated the genotype into two groups for each SNP location, executed a binary logistic regression and took sex and age into count (Tables 4 and 5). For the dominant model, we compared *TCF7L2* rs11196218 AA/AG with GG genotype, and *GLP1R* rs761386 CT/TT with TT genotype. In this regression, age, sex and genotype are independent variables, group (obesity or non-obesity) is the binary dependent variable. We found that in *TCF7L2* rs11196218, genotype AA/AG had 2.54 times more risk of obesity (P = 0.014, OR = 2.54, 95% CI [1.21~5.35]) compared with GG. For *GLP1-R* rs761386, genotype CT/TT showed a marginal higher risk than CC group (P = 0.208, OR = 1.61, 95% CI [0.77~3.39]), but no statistic significance. For the recessive model, we compared *TCF7L2* rs11196218 AA with AG/GG genotype, and *GLP1-R* rs761386 TT with CT/CC genotype. The results showed that for *TCF7L2* rs11196218, the AA genotype had no significantly higher risk of obesity than the AG/GG group (P = 0.097, OR = 3.43, 95% CI [0.80~14.71]). Regarding the *GLP1-R* rs761386, there was no TT genotype in our study group; hence, it was unavailable to get meaningful results or make conclusions from the recessive model. Taken together, in the allele model, we found the difference of *TCF7L2* rs11196218 and *GLP1-R* rs761386 polymorphisms between obesity and non-obesity groups; in the dominant model, *TCF7L2* rs11196218 AA/AG showed a higher risk of obesity; there is no significant difference in the recessive model, potentially because of the limited sample size.

Table 4 Binary Logistic Regression Analysis of Obesity and Genotype – Dominant Model

SNP	*β*	Se*β*	*P* value	OR	95% CI
rs11196218					
Age Sex (AA/AG vs GG)	0.029 −0.730 0.933	0.022 0.381 0.380	0.185 0.056 0.014	1.03 0.48 2.54	0.99~1.08 0.23~1.02 1.21~5.35
rs761386					
Age Sex (CT/TT vs CC)	0.038 −0.702 0.478	0.021 0.374 0.379	0.073 0.061 0.208	1.04 0.50 1.61	1.00~1.08 0.24~1.03 0.77~3.39

Note: Age, sex and genotype are independent variables, group (obesity or non-obesity) is the binary dependent variable.
Abbreviation: SNP, single-nucleotide polymorphism.

Characteristics of Different Genotypes Associated with Obesity

Table 6 shows the comparisons of clinical and biochemical parameters between A allele carriers (AA/AG) and those with the GG genotype of *TCF7L2* rs11196218, and

Table 5 Binary Logistic Regression Analysis of Obesity and Genotype – Recessive Model

SNP	*β*	Se*β*	*P* value	OR	95% CI
rs11196218					
Age Sex (AA vs AG/GG)	0.039 0.821 1.233	0.021 0.380 0.742	0.070 0.031 0.097	1.04 2.27 3.43	1.00~1.08 1.08~4.78 0.80~14.71
rs761386					
Age Sex (TT vs CT/CC)	0.047 0.685 21.554	0.022 0.382 17,509.348	0.035 0.073 0.999	1.048 1.984 2.295E9	1.00~1.10 0.94~4.19 0.00~.

Note: Age, sex and genotype are independent variables, group (obesity or non-obesity) is the binary dependent variable.
Abbreviation: SNP, single-nucleotide polymorphism.

Table 6 Comparison of Clinical and Biological Parameters Between Genotypes

	AA/AG (n= 58)	**GG (n= 71)**	***P* value**	***P*-adjusted**
rs11196218				
BMI (kg/m^2)	27.56±7.38	25.64±6.52	0.120	0.267
WHR	0.88±0.10	0.85±0.93	0.034	0.082
FBG (mmol/L)	5.08±0.32	5.06±0.33	0.679	0.556
SBP (mmHg)	116.16±12.42	113.89±19.54	0.445	0.601
DBP (mmHg)	75.66±8.91	74.42±14.05	0.563	0.749
TC (mmol/L)	4.85±0.67	4.64±0.77	0.108	0.138
TG (mmol/L)	1.71±1.27	1.38±1.06	0.257	0.270
HDL-C (mmol/L)	1.35±0.32	1.44±0.37	0.148	0.199
LDL-C (mmol/L)	2.97±0.69	2.73±0.68	0.059	0.072
	CT/TT (n= 47)	**CC (n= 82)**	***P* value**	***P*-adjusted**
rs761386				
BMI (kg/m^2)	27.14±6.31	26.14±7.32	0.436	0.616
WHR	0.88±0.10	0.86±0.10	0.322	0.466
FBG (mmol/L)	5.08±0.40	5.06±0.29	0.739	0.674
SBP (mmHg)	112.09±19.63	116.52±14.64	0.147	0.107
DBP (mmHg)	73.28±13.63	75.95±10.91	0.224	0.166
TC (mmol/L)	4.86±0.78	4.66±0.70	0.143	0.190
TG (mmol/L)	1.74±1.23	1.49±1.11	0.241	0.350
HDL-C (mmol/L)	1.34±0.33	1.43±0.36	0.181	0.289
LDL-C (mmol/L)	2.96±0.80	2.77±0.62	0.120	0.181

Note: *P*-adjusted, adjusted the confounder such as sex and age by multiple linear regression analysis.
Abbreviations: BMI, body mass index; WHR, waist-to-hip ratio; FPG, fasting plasma glucose; SBP, systemic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, serum total triacylglycerol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

between T allele carriers (CT/TT) and those with the CC genotype of *GLP1-R* rs761386. There was a significant difference in WHR between rs11196218 A allele carriers and those with the GG genotype. However, after the adjustment of sex and age, which were considered confounders, no significant difference was observed in these clinical characteristics (P>0.05) between the two groups.

Discussion

Although there are some studies on the effects of *TCF7L2* and *GLP1-R* gene polymorphisms on obesity, the SNP loci that have been studied are still sparse, and there are no data about Chinese people. Moreover, the associations between these genetic polymorphisms and obesity vary among different research, the reason contributing to this may be the ethical groups, sex, age, and additional modulation by diabetes.[22] Our study provides the first insight into the roles of the *TCF7L2* rs11196218 and *GLP1-R* rs761386 polymorphisms in obesity in Chinese individuals, taking the confounders such as sex, age and blood glucose into consideration. We found that the *TCF7L2* rs11196218 and *GLP1-R* rs761386 variants were associated with obesity.

In our study, we eliminated the interference of blood glucose in obese people on the results, the FBG level was normal in both obesity and non-obesity groups (Table 1). We also adjusted the effect of sex and age by logistic regression analysis. Thereafter, we found that there were significant differences in *TCF7L2* and *GLP1-R* allele frequency and genotypic polymorphisms between obese and non-obese people, which can be seen in Tables 2–3. In allele model (Table 3), with a two-sided significance level of 0.05 and frequency of the *TCF7L2* rs11196218 GG genotype of 66.7% in the non-obesity group and 41.7% in the obesity group, the power to detect the association of rs11196218 polymorphism and obesity reached 82.0%. For the *GLP1-R* rs761386, with the frequency of the rs761386 CC genotype of 69.6% in the non-obesity group and

56.7% in the obesity group, the power was 32.9%, which may lead to a false negative. In summary, the significant differences in the gene polymorphisms in our study are convincing, while the non-significant results could be false. The binary logic regression analysis indicated that in the recessive model, *TCF7L2* rs11196218-A was associated with an increased risk of obesity in Chinese individuals. Furthermore, as shown in Table 6, we studied whether multiple clinical and biochemical characteristics were associated with the genotypes that predicted obesity, but no significant difference was observed.

TCF7L2 and *GLP1-R* encode proteins that are implicated in blood glucose homeostasis and glucose-induced insulin secretion. *TCF7L2* and *GLP1-R* mechanistic studies suggested that *TCF7L2* could impair β-cell function and down-regulate the expression of glucagon-like peptide 1 receptor (*GLP-1R*) and glucose-dependent insulinotropic polypeptide receptor (*GIP-R*), thus reducing insulin level.[23] For the SNPs polymorphisms, recent studies have reported that variants in *TCF7L2* (rs7903146) and *WFS1* (rs10010131) could affect the response to exogenous *GLP-1*.[24] One study showed that the presence of the T allele compared to the CC genotype in rs7903146 SNP of the *TCF7L2* gene was associated with reduced fasting GV, suggesting that *TCF7L2* is associated with altered gastric functions that may predispose to obesity.[25] *GLP-1R* agonism enhances adjustable gastric banding in diet-induced obese rats and improves weight loss.[26] However, there was no investigation of the associations between *GLP1-R* genetic polymorphisms and obesity or the mechanisms behind that. In our study, the significant SNPs (*TCF7L2* rs11196218 and *GLP1-R* rs761386) were located within the intronic noncoding regions, and no previous studies have discovered any mechanisms of their actions, which awaits future investigation.

Obesity is affected by genetic profile and environmental risk factors, in which heritability is estimated to 40–70%.[27] Previous studies of genetic associations with obesity suggested that many genes are related to obesity, including *MC4R, BDNF, PCSK1, POMC, SH2B1, LEPR, NTRK2, FTO, IL-33*, etc.[9] Regarding *TCF7L2* polymorphism, there was a study showing an absence of the association between rs12255372 variant and obesity in the Cameroonian population, as well as the European and American populations.[16] Another study in a European population indicated that the *TCF7L2* rs7903146 T allele was known to be a risk factor for type 2 diabetes, but not obesity.[28] A meta-analysis about *TCF7L2* rs11196218 suggested that there was an association between rs11196218 polymorphism and type 2 diabetes mellitus in the Asian population.[23] Khan IA et al investigated six SNPs in six genes including *TCF7L2*, which was involved in β-cell dysfunction and insulin pathway, and they found that the *TCF7L2* rs7903146 was associated with gestational diabetes in an Indian population.[29] However, the detailed information on sex, age, anthropometric measurements and metabolic measurements lacked, so the interactive effects of these factors could not be adequately addressed.[23] Another similar meta-analysis in the Chinese Han population did not show any association between the *TCF7L2* gene rs11196218 A/G polymorphism and T2DM risk.[30] As for *GLP1-R* gene polymorphism, a study in the European population revealed that rs2268641 in *GLP1-R* was significantly associated with BMI while rs9380825 is not.[18,19] And there have not been studies about the *GLP1-R* rs761386 variant on obesity yet. Overall, the gene polymorphism findings are insufficient and controversial, which may be due to the ethical difference, study group and lack of consideration of confounding effects, such as obesity, sex and age. Therefore, to address the question of whether *TCF7L2* rs11196218 is associated with obesity, it is important to have a well-matched obesity-specific gene polymorphism study and take confounders to count.

In summary, the study provides evidence and increases our understanding of the role of genetic polymorphisms in obesity. Our results suggest that the *TCF7L2* rs11196218 and *GLP1-R* rs761386 gene polymorphisms are associated with obesity in the Chinese population.

This is the first study to evaluate the effect of *TCF7L2* rs11196218 and *GLP1-R* rs761386 polymorphisms on obesity in the Chinese population. There are also several limitations. The number of SNP loci and the sample size may attenuate the power of our study. Since the genetic risk of obesity reflects the accumulation of multiple loci, each contributing a small portion of the total risk, large-scale screening of obesity-related gene candidates is required to better understand the genetic polymorphisms and the underlying mechanisms of genetic association in obesity. In addition, considering the connection between obesity and type 2 diabetes, longitudinal follow-up research would be helpful to understand the effect of these gene polymorphisms on the onset of type 2 diabetes and other metabolic diseases. In-depth studies with a larger scale and ethnic variation would help to elucidate the genetic associations with obesity in more detail.

Conclusion

Our study suggested that the allelic frequencies of *TCF7L2* rs11196218 and *GLP1-R* rs761386 in allele model both differed in the obesity and non-obesity groups in the Chinese population. In the allele model and the dominant model, *TCF7L2* rs11196218 A-carrier is a risk factor for obesity. In summary, the rs11196218 (A/G) polymorphism of the *TCF7L2* gene and the rs761386 (C/T) polymorphism of the *GLP1-R* gene were associated with obesity in the Chinese population.

Statement of Ethics

This study was approved by the ethics committee of Xiangya Hospital of Central South University (No. 201601029) and was monitored by an independent Data and Safety Monitoring Board. All participants provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki.

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Disclosure

The authors declare no conflicts of interest.

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