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Crosstalk between FTO gene polymorphism (rs9939609) and obesity-related traits among Bangladeshi population

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Abstract

Background and Aims: Obesity is a growing public health concern in Bangladesh, which is influenced by a complex interplay of genetic and environmental factors. The genetic variant rs9939609 of the FTO (fat mass and obesity-associated) gene has been found to be associated with an increased risk for obesity, depending on the population studied. The purpose of this cross-sectional study is to examine the relationship between the FTO gene polymorphism (rs9939609) and lifestyle-related risk factors, and their impact on obesity-related traits and biochemical parameters in the Bangladeshi population.

Methods: A total of 280 participants were enrolled in this study, comprising of 140 individuals with overweight and obesity (body mass index [BMI] ≥ 23.0) and 140 non-overweight healthy individuals (18.5 ≤ BMI ≥ 22.9). Demographic information, dietary behaviors, and physical activity-related data were collected using a structured questionnaire. Additionally, anthropometric assessments and measurements of biochemical parameters such as lipid profile and C-reactive protein were performed. The amplification refractory mutation system-polymerase chain reaction technique was used to identify single-nucleotide polymorphism in the FTO gene. Descriptive statistics, χ^2 and one-way ANOVA were performed to evaluate the relationships between independent and dependent variables.

Results: The presence of rs9939609 was strongly associated with the obesity risk factors of increased BMI, cholesterol, triglycerides, and low-density lipoprotein. We also found a significant association ($p < 0.05$) of *rs*9939609 with overweight and obesity in codominant AA versus TT (odds ratio [OR] = 0.299, 95% CI: 0.129–0.695) and AA versus AT (OR = 2.273, 95% CI: 1.023–5.053), recessive TT versus AA+AT (OR = 5.154, 95% CI: 2.463–10.782), and overdominant AT versus AA+TT (OR = 0.244, 95% CI: 0.122–0.488) models.

Conclusion: FTO variant rs9939609 is significantly linked to obesity and an increased risk of hyperlipidemia in the Bangladeshi population. However, this association is intertwined with environmental factors such as diet and physical activity.

KEYWORDS

Bangladesh, FTO gene, hyperlipidemia, obesity, single-nucleotide polymorphism

1 | INTRODUCTION

Obesity is a complex, multifactorial disease that is influenced by a combination of genetic and environmental factors.[1] Obesity is dubbed the "disease of diseases" because it is linked to numerous other disorders, including type-2 diabetes mellitus, cardiovascular disease, dyslipidemia, hypertension, respiratory dysfunction, and several cancers.[2] Obesity can have a range of negative impacts on a person's physical and mental health, including potential issues such as micropenis, unstable bladder, poor body image, decreased quality of life, anxiety, and sexual problems.[3–5] According to the World Health Organization, more than a billion people worldwide are overweight, and 300 million are obese, which is not confined to the developed world.[6]

The rise in obesity has become an increasing concern for the public health of developing countries like Bangladesh. Since the early 2000s, there has been a steady rise in the percentage of obese adults in Bangladesh, with around 20% of the adult population considered to be obese.[7] Factors contributing to this trend include shifting toward a more sedentary lifestyle, increased consumption of processed and high-calorie foods, and limited access to healthy food options.[8] Additionally, there is a lack of awareness about healthy eating and physical activity among the population.[9]

Genetics is one part of the complex picture, as specific genes have been linked to an increased risk of the condition, and it is important to consider environmental and lifestyle factors as well. One example of a gene linked to obesity is the FTO gene. The FTO (fat mass and obesity-associated) gene is a genetic variant that has been linked to an increased risk for obesity.[10] Studies have shown that individuals with specific variations in the FTO gene have a higher likelihood of becoming obese, particularly when combined with a high-calorie diet and a lack of physical activity.[11,12] The exact mechanism by which the FTO gene influences weight and body fat is not fully understood, but it is thought to regulate energy metabolism and appetite, possibly by influencing the production of certain hormones that regulate hunger and fullness.[13] Significant associations between FTO gene and body mass index (BMI) have been observed in different populations like Europeans, Americans, and Asians.[14–16]

Overall, while the research on FTO polymorphism and obesity in the Bangladeshi population is limited, the available studies suggest a possible association between the FTO gene and obesity in this population.[17] However, Kar et al. did not find any association between FTO polymorphism and obesity in Bangladeshi adults.[18] Extensive research with larger sample sizes, as well as more biochemical and behavioral parameter, is needed to better understand about the relationship between FTO polymorphism and obesity in the Bangladeshi population.

The aim of this study is to examine the potential association between the prevalent FTO gene polymorphism (rs9939609) and BMI, lipid profile, and lifestyle factors such as physical activity and dietary behavior in a selected Bangladeshi population.

2 | METHODS

2.1 | Study design and sampling

This cross-sectional study was conducted in conveniently selected five districts of Bangladesh (Dhaka, Cumilla, Noakhali, Gazipur, and Feni). The sample size was calculated using the EPIINFO program (http://www.cdc.gov/epiinfo).[19] The study included 140 obese and overweight group (case) with a BMI of ≥23 kg/m^2 and 140 healthy weight population (control) with a BMI of 18.5–22.9 kg/m^2.[20]

2.2 | Eligibility criteria

The study included participants who were 18 years or older and represented a diverse range of socioeconomic and educational backgrounds. Exclusions were made for individuals under 18 years of age and over 70 years of age. Additionally, female participants who were pregnant or lactating at the time of the survey were excluded.

2.3 | Data collection tools and procedure

We used a structured questionnaire to collect demographic and behavioral information. Demographic data like personal, anthropometric, socioeconomic, and dietary behavior-related information were collected. Total physical activity level was measured using the questionnaire of global physical activity questionnaire.[21] Household dietary diversity score (HDDS) and food consumption score (FCS) were measured using a validated questionnaire.[22] The questionnaire was pretested through pilot survey with a subset of the study population ($n = 30$) and internal consistency was measured by Cronbach's α. Cronbach α was 0.817 for global physical activity questionnaire, 0.785 for HDDS, 0.831 for FCS. The questionnaire's internal reliability was 0.81, which is ideal for field assessment.[23] Subjects were measured for anthropometrics, including weight, height, hip circumference, and waist circumference, using WHO-recommended techniques.[24]

2.4 | Blood collection and serum preparation

Three milliliters of whole blood was collected by venipuncture method. Serum was prepared for biochemical analysis by centrifuging the whole blood using 3000 rpm for 20 min and then stored in a freezer at −20°C.

2.5 | Biochemical analysis

The cholesterol oxidase (COD)/POD technique was used to assess the total cholesterol in the serum.[25] Triglyceride levels were determined using the glycerol phosphate oxidase/peroxidase method[26] and high-density lipoprotein (HDL-C) using the

precipitating method.[27] By using the Friedwald equation, low-density lipoprotein (LDL-C) was quantified.[28]

2.6 | DNA extraction and genotyping

Genomic DNA was extracted from whole blood using FavorPrepTM Blood Genomic DNA extraction micro kit (Favorgen). The FTO single-nucleotide polymorphism (SNP) rs9939609 was genotyped by amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) technique using tetra primers (Supporting Information: Table 1).[29] Gel doc (Alphalmager) was used to photograph and analyze bands.

2.7 | Statistical analysis

Statistical analyses were performed using SPSS 23.0. Disparities about demographic, anthropometric, and clinical characteristics between case and control group were assessed. Continuous variables were summarized using mean and standard deviations, whereas categorical data were summarized using number and proportion for all demographic, behavioral, anthropometric, and clinical and biochemical parameters of the study. To compare covariates between low-risk and high-risk participants, logistic regression, and χ^2 test (for categorical variables) were used. FTO rs9939609's correlation with anthropometric indices, demographics, and biomarkers was examined using ANOVA test. The genotype codominant, dominant, recessive, and overdominant model was utilized to calculate the odds ratio using basic logistic regression. p Value less than 0.05 was considered significant.

3 | RESULT

3.1 | Baseline characteristics and group differences at baseline

Mean differences between case and control regarding different parameters were shown in Table 1 following ANOVA test. There was a significant mean difference in waist circumference, hip circumference, and waist/hip ratio among healthy and obese people ($p < 0.05$). The mean differences of total cholesterol (mg/dL), total triglycerides (mg/dL), HDL-C, LDL-C, C-reactive protein (CRP) among healthy and obese people indicated that the risk factors of cardiovascular diseases were higher among obese people. But differences in total cholesterol and total triglycerides were not significant ($\chi^2 = 0.617$, $p = 0.735$ and $\chi^2 = 0.738$, $p = 0.691$, respectively) (Table 1).

TABLE 1 Comparison of demographic, anthropometric, and biochemical characteristics of respondents according to case and control.

Characteristics	Subjects (280)		
	Case ($n = 140$)	Control ($n = 140$)	p Value
Demographic profile			
Age (years)	37.42 ± 14.06	29.49 ± 12.74	<0.001
Sex (% males/females)	50.7/49.3	68.6/31.4	<0.05
Physical characteristics			
Weight (kg)	74.47 ± 10.86	62.85 ± 11.62	<0.001
Body mass index (kg/m^2)	29.62 ± 3.81	21.33 ± 2.12	<0.001
Waist hip circumference ratio	0.94 ± 0.06	0.91 ± 0.051	<0.001
Biochemical characteristics			
Total cholesterol (mg/dL)	222.56 ± 37.48	207.85 ± 37.39	<0.001
Total triglycerides (mg/dL)	212.64 ± 35.48	201.28 ± 24.07	<0.05
HDL-C (mg/dL)	55.02 ± 10.75	51.29 ± 8.26	<0.001
LDL-C (mg/dL)	125.56 ± 40.68	116.30 ± 38.18	0.051
CRP (%yes/no)	55/45	37.1/62.9	<0.05
Others			
HDDS score	7.65 ± 1.26	7.01 ± 1.45	<0.001
FCS score	53.99 ± 5.15	51.95 ± 6.02	<0.05
Total physical activity	638.07 ± 260.71	1556.31 ± 702.02	<0.001

Note: Values are expressed as means ± SD except where noted.
Abbreviations: CRP, C-reactive protein; FCS, food consumption score; HDDS, household dietary diversity score; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviations.

3.2 | Association of noncommunicable disease risk factors among healthy and obese people

Multinomial logistic regression showed that total triglycerides, total cholesterol, HDL-C, and CRP were significantly higher among people with obesity ($p < 0.05$). After adjusting with age and gender, the findings also remained the same ($p < 0.05$). Total triglycerides, total cholesterol, HDL-C, and LDL-C were found to be significantly higher among obese people in the fully adjusted model (Table 2).

3.3 | Association of demographic and biochemical parameters with genotype FTO SNP rs9939609

Figure 1 depicts ARMS-PCR analysis of FTO (rs9939609) SNP with Full Ranger 100 bp DNA ladder (cat. 11800) molecular weight marker (Thermo Fisher Scientific). Homozygous (AA) and heterozygous (AT) risk alleles. In the control population, the A allele was associated with higher total cholesterol, lower LDL-C, and HDDS ($p < 0.05$). While the A allele was associated with higher BMI, waist-hip ratio, total

cholesterol, and LDL-C in obese participants ($p < 0.05$) (Table 3). According to the dominant model, genotype did not significantly affect age, BMI, anthropometric indices, biochemical parameters in the two groups. However, we found a significant association between genotypes and physical activity in the control group. In the Codominant model (AA vs. AT and TT), the FTO (rs9939609) gene polymorphism's TT genotype was significantly lower in cases than in controls. Where for genotypes AT and AA, cases are significantly higher than controls (Supporting Information: Table 2). Regression analysis, the risk of obesity for AT genotype is more than two times higher, and for AA genotype is lower compared with the TT genotype. In the Dominant model (AA vs. AT+TT), the frequency of AT+TT genotype was also higher among the controls (72.2%) than in cases (68.8%). There was no significant difference among cases and controls. In the recessive model (TT vs. AA+AT) analysis, there was a significant difference in the genotype frequency of FTO (Rs9939609) gene polymorphism. The risk of obesity for AA+AT genotype was significantly five times more likely among cases (83.8%) compared with controls (50%) (Table 4).

4 | DISCUSSION

In this cross-sectional study, two distinct groups were identified with group allocation based on BMI: a case group (comprising obese individuals) and a control group (comprising individuals of healthy weight). The South Asian population is recognized to have a lower BMI cutoff when compared to other populations.[30,31] This distinction is attributed to a greater incidence of health problems associated with obesity, including cardiovascular and metabolic disorders, among South Asians at lower BMI levels than other populations. To address this, a BMI threshold of 23 kg/m² is typically employed as a diagnostic criterion for obesity in South Asian populations, in contrast to the standard threshold of 25 kg/m² employed for other populations.[32]

In this study, the case group exhibited a higher prevalence of multimorbidity compared to the control group. Obese individuals were identified to have a greater prevalence of comorbidities such as hypertension, heart disease, and arthritis, relative to the control group which is congruent with Agborsangaya et al.'s study.[30]

According to a Brazilian study,[33] obesity is the most prevalent risk factor for cardiovascular disease as it raises total cholesterol, triglycerides, and LDL levels. The present study corroborates this knowledge by revealing a significant association between obesity and modified levels of total cholesterol, triglycerides, LDL, and HDL. The study findings reinforce the notion that obese individuals tend to exhibit altered levels of these variables. In addition, the study identified elevated levels of CRP in obese individuals. This finding is consistent with a previous study that directly linked obesity to increased circulating CRP levels.[34] Owing to resource limitation, a comparative analysis of CRP concentrations in individuals classified

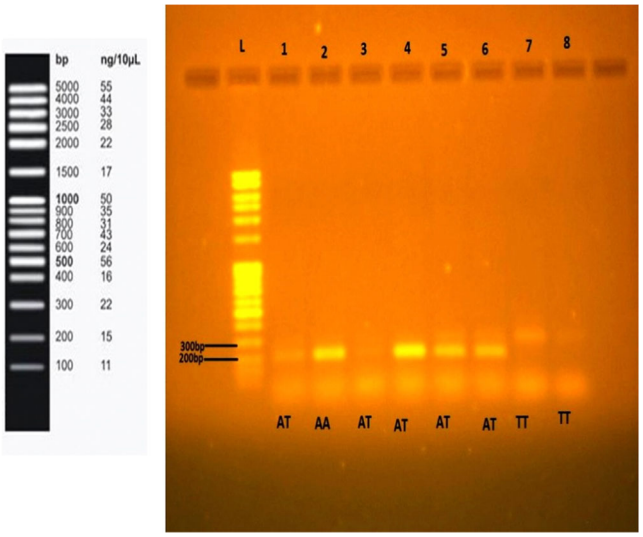

FIGURE 1 Agarose gel image of ARMS-PCR product. Figure 1 shows that in lanes 1, 3, 4, 5, and 6, AT heterozygous mutant; lanes 7 and 8, TT homozygous wild type and lane 2, AA homozygous mutant. ARMS-PCR, amplification refractory mutation system-polymerase chain reaction.

TABLE 2 Association of biochemical characteristics of respondents with obesity.

Variables	Bivariate OR (95% CI)	Multivariate[a] OR (95% CI)	Multivariate[b] OR (95% CI)
Total cholesterol (mg/dL)	1.01 (1.00–1.02)**	1.01 (1.0–1.02)**	0.66 (0.66–0.67)***
Total triglycerides (mg/dL)	1.01 (1.01–1.02)**	1.01 (1.00–1.18)*	1.09 (1.08–1.11)***
HDL-C (mg/dL)	1.04 (1.02–1.08)**	1.06 (1.03–1.09)***	1.65 (1.59–1.71)***
LDL-C (mg/dL)	1.01 (1.00–1.01)	1.01 (1.00–1.01)	1.53 (1.53–1.53)
CRP	2.07 (1.28–3.34)**	2.00 (1.19–3.35)*	1.25 (0.66–2.37)

Abbreviations: CRP, C-reactive protein; HDL-C, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio.

[a]Adjusted for age and gender.

[b]Fully adjusted.

*$p < 0.05$; **$p < 0.005$; ***$p < 0.001$.

TABLE 3 Comparison of demographic, anthropometric, and biochemical parameters among different genotypes of FTO SNP rs9939609 in healthy and obese population.

	Control ($n = 80$)				Case ($n = 80$)			
	SNP (rs9939609)				SNP (rs9939609)			
Parameters	AA	AT	TT	p Value	AA	AT	TT	p Value
Age (year)	28.52 ± 12.16	36.0 ± 14.10	30.0 ± 14.64	0.101	30.55 ± 12.06	37.77 ± 15.76	28.77 ± 11.51	0.238
Weight (kg)	63.41 ± 11.77	62.73 ± 12.34	59.12 ± 9.63	0.388	71.80 ± 10.97	74.83 ± 10.32	74.57 ± 11.39	0.694
Height (cm)	161.81 ± 8.67	158.19 ± 11.36	163.0 ± 7.89	0.269	159.47 ± 5.07	158.07 ± 8.01	159.47 ± 8.68	0.606
Waist hip ratio	0.90 ± 0.05	0.911 ± 0.046	0.92 ± 0.05	0.831	0.92 ± 0.06	0.94 ± 0.057	0.94 ± 0.067	0.574
Total cholesterol (mg/dL)	209.05 ± 40.51	210.55 ± 25.17	197.15 ± 20.38	0.476	227.08 ± 29.74	223.00 ± 33.21	211.42 ± 42.30	0.892
Total triglycerides (mg/dL)	202.19 ± 23.85	201.93 ± 20.32	194.49 ± 28.81	0.490	209.47 ± 23.76	214.77 ± 40.86	211.23 ± 31.99	0.815
HDL-C (mg/dL)	51.74 ± 8.83	51.40 ± 7.34	48.11 ± 2.83	0.261	57.55 ± 11.57	53.46 ± 7.83	55.99 ± 12.67	0.297
LDL-C (mg/dL)	116.86 ± 41.59	118.77 ± 22.91	110.14 ± 22.72	0.780	127.64 ± 36.40	127.30 ± 33.68	123.67 ± 47.03	0.868
Total HDDS	7.02 ± 1.41	6.40 ± 1.72	7.43 ± 1.45	0.136	8.0 ± 1.73	7.78 ± 1.13	7.50 ± 1.29	0.313
FCS	54.13 ± 6.31	49.40 ± 8.64	55.68 ± 5.37	**0.016***	51.50 ± 6.04	52.62 ± 4.85	53.33 ± 5.24	0.482
Total physical activity	1580.66 ± 738.72	1737.33 ± 547.76	1220.75 ± 447.83	0.091	550.91 ± 157.06	639.67 ± 257.02	650.74 ± 277.07	0.502
BMI	22.37 ± 2.05	22.41 ± 1.88	21.91 ± 2.82	0.705	28.29 ± 3.46	29.97 ± 3.76	29.52 ± 3.89	0.389

Abbreviations: BMI, body mass index; FCS, food consumption score; HDDS, household dietary diversity score; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SNP, single-nucleotide polymorphism.

*$p < 0.05$.

TABLE 4 Genotypes of FTO gene polymorphism model analysis.

SNP	Genotype	Case (80)		Control (80)		OR	95% CI	*p* Value
rs9939609	Codominant model (AA vs. AT and TT)							
	AA	25	31.2	23	28.8	1		
	AT	42	52.5	17	21.2	2.273	1.023–5.053	0.044
	TT	13	16.3	40	50.0	0.299	0.129–0.695	0.005
	Recessive model (AA vs. AT+TT)							
	AA	25	31.2	23	28.8	1.126	0.573–2.216	0.730
	Dominant model (TT vs. AA+AT)							
	AA+AT	67	83.8	40	50.0	5.154	2.463–10.782	0.000
	Overdominant model (AT vs. TT+AA)							
	TT+AA	38	47.5	63	78.8	0.244	0.122–0.488	0.000

Note: $p < 0.05$ is significant; reference group: control.

Abbreviations: OR, odds ratio; SNP, single-nucleotide polymorphism.

as healthy and obese was not feasible. Notably, the state of obesity significantly escalates the susceptibility to cardiovascular disorders in adult cohorts, attributed to the contribution of hypertension, abnormal lipid profile, and anomalous glucose metabolism.[35,36]

The present study has revealed that diet is a crucial factor in the development of obesity. The FCS and HDDS were found to be significantly different between the case and control groups ($p < 0.05$), indicating that dietary habits are linked to obesity. In particular, a higher dietary diversity is associated with an increased risk of developing obesity, as it is often recommended to meet nutrient requirements. However, it is important to note that obesity can still develop even when consuming a high-diversity diet if energy intake is not adequately controlled. Thus, monitoring energy intake is critical in preventing obesity, even when following a nutrient-rich diet.[37]

Our study outcomes indicate that the FTO variant rs9939609 exhibits a significant correlation with obesity, total cholesterol, LDL-C, and HDL-C. These findings are in concurrence with the results reported in earlier research.[12,14] Despite extensive research on the FTO gene's role in promoting BMI and susceptibility to overweight and obesity, the underlying mechanisms of its influence remain inadequately understood.[38] However, this was explained by a study by the fact that this SNP was found in intron 1, the FTO gene region most frequently associated with obesity. The glucocorticoid receptor exhibits the strongest signal in this region, which is distinguished by a high DNase sensitivity and by the presence of numerous transcriptional factors attached to the obesity-associated region.[39] In a study conducted in Malaysia, significant variations were observed in the genotype distribution and allele frequencies of FTO rs9939609 among different ethnic groups. However, despite these disparities, no significant correlation with obesity was observed in this cohort.[40] Our study demonstrated that the homozygous (AA) and heterozygous (AT) alleles of the gene of interest were significantly more prevalent among individuals with higher levels of BMI, waist circumference, hip circumference, and total cholesterol. The presence of homozygous (AA) alleles may confer a higher risk of overweight and obesity in the studied population. The regression model showed significant association in the dominant and overdominant model ($p < 0.05$) (Table 4). Our findings align with those of Zdrojowa-Welna et al., who reported that individuals carrying the A allele of rs9939609, especially males, exhibited a greater propensity to develop obesity.[41] Individuals with obesity, particularly those carrying the A allele, exhibited significantly higher levels of total cholesterol, total triglycerides, and LDL-C. The presence of the A allele was found to increase the risk of developing cardiovascular disease. A systematic review and meta-analysis revealed a significant association between the FTO gene and the risk of cardiovascular disease.[42]

The present study's primary strength lies in being the first study conducted in Bangladesh to demonstrate the association between the FTO gene and obesity-related traits and metabolic diseases. However, this study also has several limitations. First, the data on noncommunicable diseases were based on self-reported information, which could lead to misclassification if participants provide inaccurate data regarding their hypertension or diabetes treatment. Second, this study did not incorporate noncommunicable disease risk factors. Lastly, ARMS-PCR has some drawbacks in SNP detection due to lower sensitivity, which may result in the failure to identify SNPs due to low levels of expression or limited abundance in the sample.[43] In addition, it is advisable to explore other variants of the FTO gene that may have a significant impact, either directly or indirectly, on the development of overweight/obesity within the Bangladeshi population.

5 | CONCLUSION

To summarize, our investigation has validated the significant correlation between the FTO gene (rs9939609) and obesity, as well as an increased risk of hyperlipidemia in Bangladeshi population. Notably, the presence of the A allele was found to be more prevalent in overweight or obese individuals than in the general population. It is

worth mentioning that the link between FTO gene and obesity is not deterministic, as there are many other factors that contribute to obesity, such as diet, lifestyle, environment, and cultural habits. In addition, genetic predisposition to obesity does not mean that an individual will inevitably become overweight or obese, but rather that they may be more susceptible to weight gain when exposed to certain environmental factors.

AUTHOR CONTRIBUTIONS

Lincon Chandra Shill: Data curation; formal analysis; investigation; software; validation; visualization; writing—original draft. **Mohammad Rahanur Alam**: Conceptualization; formal analysis; funding acquisition; methodology; project administration; resources; supervision; visualization; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data will be made available upon reasonable request.

ETHICS STATEMENT

The ethical approval was obtained from the institutional ethics committee of the Noakhali Science and Technology University. The authors hereby consent to publish this research article. This article has not been published or submitted elsewhere for publication. The authors also declare that this work does not libel anyone, violate anyone's copyright or common law rights.

TRANSPARENCY STATEMENT

The lead author Mohammad Rahanur Alam affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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