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Increased levels of serum glucose-dependent insulinotropic polypeptide as a novel risk factor for human colorectal adenoma

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ABSTRACT

Obesity and insulin resistance are thought to be risk factors for colorectal adenoma. Glucose-dependent insulinotropic polypeptide (GIP) stimulates insulin secretion from the pancreas and promotes fat accumulation in adipocytes. The association between serum GIP and the risk of colorectal adenoma has not been examined previously. We investigated this association in 370 subjects who underwent total colonoscopy during thorough physical checkups between January and December 2008. We used a cross-sectional design and classified the subjects into a colorectal adenoma group and a control group without adenoma according to their endoscopic findings. Serum GIP concentrations in samples of venous blood obtained after an overnight fast were measured using a sandwich enzyme-linked immunosorbent assay kit. The mean levels of fasting GIP (34.9 ± 49.5 vs 25.0 ± 20.1 pg/mL, $P = .04$), triglyceride, glucose, and insulin and the values of the homeostasis model assessment of insulin resistance in the colorectal adenoma group were significantly higher than those in the control group. Multiple logistic regression analysis showed that the highest quartile of fasting GIP levels was associated with a significantly high risk of colorectal adenoma (odds ratio, 2.1; 95% confidence interval, 1.08-3.96; $P = .01$) in comparison with the lowest quartile. Quartile analysis demonstrated that increased levels of GIP were related to increased levels of fasting insulin and values of homeostasis model assessment β-cell. These results suggest that an increased level of fasting GIP is associated with an increased risk of colorectal adenoma.

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1. Introduction

Colorectal cancer is a common and highly frequent cause of cancer death worldwide [1]. During the past few decades, particularly in Asian countries, there has been a remarkable increase in the incidence of colorectal cancer, most likely because of the adoption of a Western-style diet associated with increased intake of animal fat, and the reduction of physical activity levels [2]. Most colorectal cancers arise from colorectal adenomas through the well-known adenoma-carcinoma sequence [3]. Therefore, for the prevention and early detection of colorectal cancer, it is important to identify the risk factors for colorectal adenoma.

Several studies have indicated that metabolic syndrome increases the risk for both colorectal adenoma and cancer by approximately 50% [4,5]. High levels of insulin-like growth factor–1, insulin [6,7], and glucose [8] and hypertriglyceridemia [9] are known to increase the risk of colorectal adenoma. Insulin resistance is an integral feature of metabolic syndrome [10]. Recently, we have also demonstrated that low levels of plasma adiponectin are associated with colorectal adenoma [11] and early colorectal cancer [12]. Furthermore, a prospective nested case-control study has shown that adiponectin levels are inversely associated with risk for colorectal cancer [13].

Glucose-dependent insulinotropic polypeptide (GIP or gastric inhibitory polypeptide), one of the incretins, is released from K cells of the proximal small intestine in response to meal ingestion and potentiates glucose-stimulated insulin secretion [14]. As well as its role as an important insulin-stimulating intestinal hormone, recent data indicate that GIP exerts effects on insulin resistance, lipid metabolism, and obesity [15,16].

Therefore, although it seems likely that GIP would be associated with colorectal adenoma, this possibility has not been investigated. Therefore, in the present cross-sectional study, we examined the association between fasting GIP levels and the incidence of colorectal adenoma.

2. Subjects and methods

2.1. Subjects

We screened 830 subjects who underwent colonoscopy at Tohoku Central Hospital during thorough physical checkups between January and December 2008. A total of 499 subjects were eligible for this study on the basis of the following exclusion criteria: a history of bowel resection, inflammatory bowel disease, and chronic disease such as chronic hepatitis, thyroid disease, chronic myeloid leukemia, collagen diseases, and renal failure; incomplete colonoscopy because of poor bowel preparation or failure to carry out cecal intubation; and regular use of antihypertensive drugs, antidiabetic drugs, antilipemic drugs, and nonsteroidal anti-inflammatory drugs including aspirin. None of the subjects had colorectal adenocarcinoma. From among 390 individuals who were found to be free of adenomatous polyps throughout the entire large intestine, we excluded 129 who had a history of colorectal polyp resection to yield a control group. Thus, our final total of 370 study subjects comprised an endoscopically diagnosed colorectal adenoma group (n = 109) and a control group (n = 261).

This study was approved by the ethics committee of Tohoku Central Hospital. Written informed consent was obtained from all subjects.

2.2. Clinical and laboratory evaluations

From all subjects, we collected clinical information concerning smoking, alcohol consumption, and history of treatment and medication using a self-completed questionnaire that was distributed at the time of the physical checkup. We defined *current smoking* as at least one cigarette daily for the previous 12 months and *alcohol consumption* as more than 25 g of alcohol daily. Trained nurses measured waist circumference at the midpoint between the lower border of the rib cage and the iliac crest and determined blood pressure using a standardized protocol. Samples of venous blood were drawn from all subjects after an overnight fast before bowel preparation for colonoscopy. These samples were then taken immediately for analysis of serum high-density lipoprotein (HDL), low-density lipoprotein (LDL), serum triglyceride, hemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG), and fasting plasma insulin (FPI) levels. The indices of insulin secretion and sensitivity were evaluated by homeostasis model assessment (HOMA) and calculated as follows: HOMA β-cell = FPI × 360/(FPG − 63) and homeostasis model assessment of insulin resistance (HOMA-IR) = FPI × FPG/405, where FPI is expressed in micro–international units per milliliter and FPG in milligrams per deciliter [17,18]. Residual serum samples were immediately stored at –80°C for GIP assay. We measured the serum total GIP concentration, including intact GIP (1-42) and metabolite GIP (3-42), using a commercial sandwich enzyme-linked immunosorbent assay kit (Human GIP [Total] ELISA Kit; Millipore, Billerica, MA) in duplicate.

2.3. Detection of colorectal adenoma by colonoscopy

Nine experienced gastroenterologists performed colonoscopic examinations using conventional videoendoscopes (PCF-240I, PCF-Q260I, CF-240I, CF-240AI, CF-Q260AI, CF-H260AI; Olympus Medical Systems, Tokyo, Japan). All subjects underwent bowel preparation using 2 L of polyethylene glycol electrolyte solution (MUBEN; Nihon Pharmaceutical, Tokyo, Japan). These endoscopists were unaware of the clinical and laboratory findings at the time of the colonoscopic examinations. To obtain an accurate endoscopic diagnosis of whether lesions were adenomatous polyps, endoscopists sprayed indigo carmine solution on the surface of each lesion and analyzed the pit pattern during colonoscopic examination. This procedure, as described previously [19], is known to be highly accurate for differential diagnosis of neoplastic (adenoma and adenocarcinoma) and nonneoplastic (hyperplastic) polyps. All of the colonoscopy recordings were double-checked by the chief gastroenterologist (HS) at Tohoku Central Hospital.

2.4. Statistical analyses

Data are presented as the mean ± SD of the mean. For comparison between the colorectal adenoma group and the

Table 1 – Comparison of characteristics between subjects with colorectal adenoma and controls

Characteristic	Control group (n = 261)	Adenoma group (n = 109)	P value
Age (y)	47.7 ± 7.9	51.7 ± 5.7	<.001
Male, n (%)	178 (68.2)	95 (87.2)	<.001
Current smoking, n (%)	52 (19.2)	31 (29.0)	.059
Alcohol consumption, n (%)	147 (57.4)	73 (68.2)	.057
Body mass index (kg/m^2) [a]	23.6 ± 3.3	24.2 ± 3.3	.096
Waist circumference (cm)	84.6 ± 9.2	86.9 ± 9.2	.019
Blood pressure			
Systolic (mmHg)	117.7 ± 15.3	120.2 ± 16.4	.208
Diastolic (mmHg)	73.9 ± 10.0	76.3 ± 11.0	.029
HDL cholesterol (mg/dL)	63.3 ± 16.2	60.1 ± 15.9	.053
LDL cholesterol (mg/dL)	130.6 ± 33.3	131.7 ± 30.3	.631
Triglyceride (mg/dL)	135.7 ± 111.6	164.9 ± 104.7	<.001
Fasting glucose (mg/dL)	90.1 ± 12.1	95.3 ± 21.8	<.001
Fasting insulin (μIU/mL)	4.8 ± 3.2	6.2 ± 5.4	<.001
HOMA-IR [b]	1.1 ± 0.9	1.5 ± 1.9	.013
HOMA β-cell [c]	69.8 ± 60.5	78.7 ± 67.9	.486
HbA_{1c} (%)	5.2 ± 0.5	5.4 ± 0.7	.104

Values are expressed as mean ± SD or number (percentage). P values were evaluated by the 2-tailed Wilcoxon rank sum test or the χ^2 test.

[a] Body mass index is the weight in kilograms divided by the square of the height in meters.

[b] HOMA-IR = fasting plasma insulin (micro–international units per milliliter) × fasting plasma glucose (milligrams per deciliter)/405.

[c] HOMA β-cell = fasting plasma insulin (micro–international units per milliliter) × 360/[fasting plasma glucose (milligrams per deciliter) – 63].

control group, we analyzed continuous variables and categorical variables using the 2-tailed Wilcoxon rank sum test or the χ^2 test, respectively. The Kruskal-Wallis test or the χ^2 test was used to compare continuous variables or categorical variables in each of the quartile GIP groups, respectively. Spearman rank test was used to evaluate correlations between fasting GIP level and continuous variables. We computed the odds ratio (OR) and 95% confidence interval (95% CI) using logistic regression model analysis. Differences at a probability (P) value of less than .05 were considered to be significant. We carried out all statistical calculations using SAS Enterprise Guide v. 4.1 (SAS Institute, Cary, NC).

3. Results

3.1. *Baseline characteristics of the patients*

The baseline characteristics of the 370 enrolled subjects are summarized in Table 1. The proportion of male individuals (87.2% vs 68.2%, $P < .001$) and the mean age (51.7 ± 5.7 vs 47.7 ± 7.9 years, $P < .001$), waist circumference (86.9 ± 9.2 vs 84.6 ± 9.2 cm, $P = .019$), and diastolic blood pressure (76.3 ± 11.0 vs 73.9 ± 10.0 mmHg, $P = .029$) were significantly higher in the colorectal adenoma group than in the control group. There were no significant intergroup differences in the proportions of current smokers and current alcohol consumers, or mean body mass index. In comparison with the control group, individuals in the colorectal adenoma group had significantly higher mean levels of serum triglyceride (164.9 ± 104.7 vs 135.7 ± 111.6 mg/dL, $P < .001$), fasting glucose (95.3 ± 21.8 vs 90.1 ± 12.1 mg/dL, $P < .001$), fasting insulin (6.2 ± 5.4 vs 4.8 ± 3.2 μIU/mL, $P < .001$), and HOMA-IR values (1.5 ± 1.9 vs 1.1 ± 0.9, $P = .013$).

3.2. *Fasting GIP concentrations in patients with colorectal adenoma*

In all subjects, the mean concentration of serum GIP was significantly higher in the adenoma group (34.9 ± 49.5 pg/mL) than in the control group (25.0 ± 20.1 pg/mL, $P = .047$, Fig. 1A). When restricted to male subjects, the adenoma group

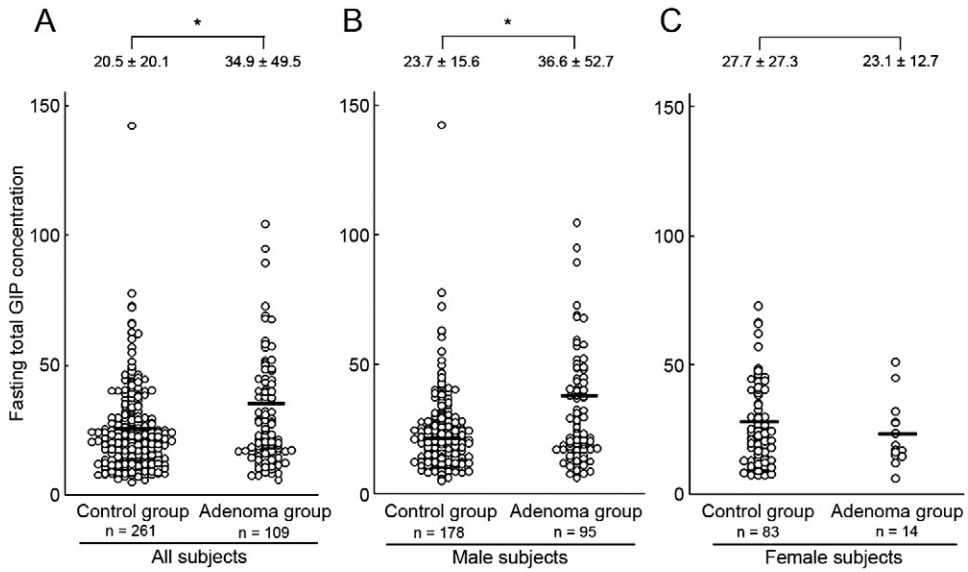

Fig. 1 – Comparison of fasting GIP concentrations between control subjects and patients with colorectal adenoma. A, All subjects. B, Male subjects. C, Female subjects. Values are expressed as means ± SD. Black bar: mean fasting GIP concentration. *P < .05 compared with control group.

Table 2 – Fasting GIP levels and risk of colorectal adenoma

GIP concentration (pg/mL)		Univariate analysis			Multivariate analysis [a]		
		OR	95% CI	P value	OR	95% CI	P value
Quartile 1	GIP < 14.0	1 (reference)			1 (reference)		
Quartile 2	14.0 ≤ GIP < 21.1	1.6	0.82-3.00	.39	1.5	0.78-2.89	.42
Quartile 3	21.1 ≤ GIP < 31.8	0.9	0.43-1.75	.05	0.9	0.42-1.73	.07
Quartile 4	31.8 ≤ GIP	2.3	1.20-4.31	<.01	2.1	1.08-3.96	.01
GIP, per 10 pg/mL increase		1.1	1.01-1.23	.03	1.0	1.00-1.02	.03

The ORs were evaluated by logistic regression analysis.
[a] Adjusted for age, sex, current smoking, alcohol consumption, BMI, waist circumference, insulin, triglyceride, and glucose.

(36.6 ± 52.7 pg/mL) had a significantly higher fasting GIP concentration than the control group (23.7 ± 15.6 pg/mL, P = .027, Fig. 1B). In contrast, in female subjects, no significant difference in GIP concentration was observed between the groups (Fig. 1C).

3.3. GIP level and risk of colorectal adenoma

By means of logistic regression analysis models, we examined whether the fasting GIP level was a risk factor for colorectal adenoma (Table 2). Based on the results of univariate analysis, the highest GIP quartile (OR, 2.3; 95% CI, 1.20-4.31; P < .01) and GIP concentration as a continuous variable (OR, 1.1; 95% CI, 1.01-1.23; P = .03) were significantly associated with the incidence of colorectal adenoma. In addition, the multivariate analysis model, including age, sex, current smoking, alcohol consumption, BMI, waist circumference, insulin, triglyceride, and glucose, showed that the highest GIP quartile had a 2.1-fold higher risk of colorectal adenoma than the lowest quartile (95% CI, 1.08-3.96; P = .01).

3.4. Factors associated with an increased GIP level

We performed quartile analysis of the GIP level to assess the factors associated with high GIP levels in control subjects (Table 3). No significant differences in the proportions of men, current smokers, or current alcohol consumers or the mean body mass index and waist circumference were observed among the quartiles. The mean level of fasting insulin (P = .045) and the value of HOMA β-cell (P = .025) were significantly higher in the highest GIP quartile than in the lowest quartile. Furthermore, the mean levels of fasting insulin and the HOMA β-cell levels increased as the GIP quartile became higher, and showed a weak positive correlation with GIP as a continuous variable (Spearman correlation coefficient of 0.122 between triglyceride and GIP, 0.124 between insulin and GIP, and 0.122 between HOMA β-cell and GIP; all P values < .05). The value of HOMA-IR tended to become higher as the GIP level increased (P = .05, Spearman correlation coefficient of 0.119 between HOMA-IR and GIP).

Table 3 – Factors associated with increasing GIP quartiles among the controls

	Quartile 1 GIP < 14.0	Quartile 2 14.0 ≤ GIP < 21.1	Quartile 3 21.1 ≤ GIP < 31.8	Quartile 4 31.8 ≤ GIP	P value	Correlation coefficient [a]
Age (y)	48.4 ± 7.8	48.5 ± 8.0	47.2 ± 7.6	46.6 ± 8.0	.370	–0.106
Male, n (%)	45 (65.2)	41 (71.9)	59 (74.7)	33 (58.9)	.221	
Current smoking, n (%)	12 (17.4)	12 (21.1)	15 (19.0)	13 (23.2)	.862	
Alcohol consumption, n (%)	38 (56.7)	32 (57.1)	52 (66.7)	25 (45.5)	.113	
Body mass index (kg/m^2) [b]	23.6 ± 3.0	23.7 ± 3.1	23.8 ± 3.3	24.0 ± 4.1	.981	0.026
Waist circumference (cm)	83.1 ± 8.3	85.1 ± 7.3	85.3 ± 9.5	85.1 ± 11.4	.533	0.047
Blood pressure						
Systolic (mmHg)	118.1 ± 13.0	115.5 ± 12.5	116.0 ± 15.1	120.6 ± 20.3	.705	0.016
Diastolic (mmHg)	74.4 ± 8.9	72.1 ± 7.8	73.8 ± 10.1	75.2 ± 12.9	.577	–0.005
HDL cholesterol (mg/dL)	65.8 ± 15.4	60.9 ± 16.1	63.4 ± 17.4	62.7 ± 15.8	.276	–0.075
LDL cholesterol (mg/dL)	125.2 ± 32.5	133.9 ± 35.8	131.3 ± 32.5	132.8 ± 33.1	.347	0.067
Triglyceride (mg/dL)	113.4 ± 56.8	125.9 ± 65.6	151.9 ± 166.4	150.1 ± 99.6	.269	0.122 *
Fasting glucose (mg/dL)	89.9 ± 10.5	89.8 ± 9.9	89.5 ± 7.6	91.7 ± 19.3	.875	–0.014
Fasting insulin (μIU/mL)	4.1 ± 2.8	4.8 ± 2.6	5.1 ± 2.8	5.5 ± 4.4	.045	0.124 *
HOMA-IR [c]	0.9 ± 0.7	1.1 ± 0.7	1.1 ± 0.7	1.3 ± 1.1	.054	0.119
HOMA β-cell [d]	56.6 ± 39.0	66.8 ± 36.5	72.2 ± 43.7	85.7 ± 104.1	.025	0.122 *
HbA_{1c} (%)	5.2 ± 0.3	5.2 ± 0.4	5.2 ± 0.3	5.4 ± 0.9	.839	0.033

Results are expressed as mean ± SD or number (percentage). P values were evaluated by the Kruskal-Wallis test or the χ^2 test. Spearman rank test was used to evaluate correlations.
[a] Spearman correlation coefficients of the continuous variables and GIP as a continuous variable.
[b] Body mass index is the weight in kilograms divided by the square of the height in meters.
[c] HOMA-IR = fasting plasma insulin (micro–international units per milliliter) × fasting plasma glucose (milligrams per deciliter)/405.
[d] HOMA β-cell = fasting plasma insulin (micro–international units per milliliter) × 360/[fasting plasma glucose (milligrams per deciliter) – 63].
* P < .05.

4. Discussion

The present study demonstrated that fasting concentrations of GIP, triglyceride, glucose, and insulin and values of HOMA-IR were higher in individuals with colorectal adenoma than in controls, and that the level of GIP was associated with the level of fasting insulin and the HOMA β-cell value. In addition, an increased level of fasting GIP was an independent risk factor for colorectal adenoma. To our knowledge, no previous study has investigated the association between GIP level and colorectal adenoma.

It is well known that patients with colorectal adenoma tend to have obesity and metabolic syndrome [4,20,21]. The primary physiologic role of GIP is to potentiate meal-stimulated insulin secretion [14]. In addition, GIP participates in the development of obesity and insulin resistance [15,16]. GIP receptor-knockout mice ($GIPR^{-/-}$) exhibit resistance to hyperphagia-induced obesity and reduced expansion of adipocyte mass upon high-fat feeding [16,22]. Lep^{ob}/Lep^{ob} mice lack functional leptin because of a mutation of the gene and become grossly overweight, with hyperphagia and insulin resistance [23]. Double-homozygous mice ($GIPR^{-/-}$, Lep^{ob}/Lep^{ob}) exhibit reduced weight gain and decreased adiposity [16]. These findings appear to be consistent with the association we observed in the present study between an increased level of GIP and obesity, insulin resistance, and hyperinsulinemia in patients with adenoma. Our findings are also supported by reports indicating high GIP levels in patients with type 2 diabetes mellitus [24,25]. However, further investigations are needed to clarify the nature of the association between GIP and the development of colorectal adenoma.

Glucose-dependent insulinotropic polypeptide is secreted from intestinal K cells in response to ingestion of nutrient, especially fat or glucose [14]. However, the factors that modulate fasting GIP secretion remain unclear. In the Lep^{ob}/Lep^{ob} mouse model, an increased amount of dietary fat chronically stimulates the production and secretion of GIP and increases the density of intestinal K cells [26]. In humans, it has been reported that the level of GIP is correlated with that of plasma triglyceride [27]. In the present study, individuals with colorectal adenoma had significantly higher serum triglyceride levels. Recently, it has been shown that GIP release increases after a fat-rich meal, in contrast to a small or large carbohydrate-rich meal [28]. Further studies will be needed to examine the relationships between the carbohydrate and fat contents of the diet and fasting GIP concentrations in patients with colorectal adenoma.

It has been unclear how GIP is associated with the development of colorectal adenoma. The primary role of GIP is to potentiate meal-stimulated insulin secretion [14]. Insulin, as well as glucose, has been postulated to play a direct role in tumor promotion by acting as a growth factor [29,30]. Thus, the high level of GIP in the present patients with colorectal adenoma would seem to have contributed to adenoma development via high levels of insulin and glucose.

Glucose-dependent insulinotropic polypeptide is thought to be a growth and antiapoptotic factor for pancreatic β cells [31,32]. There has been no clear evidence that the GIP receptor is expressed in colorectal mucosa or adenoma, which makes it unlikely that GIP could play a direct role in promoting colorectal adenoma development. Recently, it has been reported that the GIP receptor is expressed in human colorectal cancer cells and that GIP induces a concentration-dependent increase in cell proliferation [33]. Glucose-dependent insulinotropic polypeptide may exert a growth-stimulating effect on mucosal epithelial cells in the colorectum, thus promoting the development of colorectal adenomas. Further investigations of this issue will be necessary.

Among the female subjects in the study population, no significant difference in GIP concentration was observed between those with adenoma and the controls. In addition, no significant differences in the mean levels of fasting triglyceride (99.1 ± 51.0 vs 103.6 ± 71.4 mg/dL, $P = .72$), glucose (89.8 ± 7.5 vs 88.3 ± 10.1 mg/dL, $P = .22$), and insulin (4.2 ± 2.4 vs 4.1 ± 2.6 μIU/mL, $P = .82$) and in the values of HOMA-IR (0.9 ± 0.6 vs 0.9 ± 0.6, $P = .83$) were observed between the patients and controls. Thus, it was suggested that, in women, the level of GIP may not be associated with a risk of colorectal adenoma in the absence of hypertriglyceridemia, hyperglycemia, hyperinsulinemia, and insulin resistance. However, in this study, the number of female patients with adenoma was too small to allow detailed analysis of sex differences. Further studies will be needed to confirm the mechanisms responsible for the sex differences between GIP level and the risk of colorectal adenoma.

Our study had several strengths. The presence of colorectal adenomas was assessed by total colonoscopy with the noninvasive chromoendoscopy technique. In addition, exclusion criteria based on detailed clinical information ensured that this analysis was conducted with as few potential confounding factors as possible.

On the other hand, this study was limited by its cross-sectional design. All the subjects underwent blood sampling and colonoscopy on the same day, making it difficult to establish a causal relationship between a variety of laboratory parameters and the development of colorectal adenoma. In addition, the association between the effect of high GIP over a long period and colorectal adenoma was not evaluable. Only cohort studies can incorporate a time sequence criterion for causality. Therefore, a prospective study with a larger number of individuals will be needed to clarify the essential role of GIP in the development of colorectal adenoma, especially in a background of metabolic syndrome. Furthermore, future studies on colorectal cancer would be useful.

In conclusion, our present findings suggest that a high level of fasting GIP is associated with a risk of colorectal adenoma, and may offer a new insight into the role of GIP in the development of human colorectal adenoma. Additional studies—hopefully, cohort studies—will need to replicate our results in this and other populations.

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