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Incidence of *HNFI*A and *GCK* *MODY* Variants in a South African Population

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Background and Aim: Maturity-onset diabetes of the young (MODY) is the result of single gene variants. To date, fourteen different MODY subtypes have been described. Variants in genes coding for glucokinase (*GCK*, *MODY2*) and hepatic nuclear factor 1 alpha (*HNFI*A, *MODY3*) are most frequently encountered. MODY patients are often misdiagnosed with type 1 or type 2 diabetes, resulting in incorrect treatment protocols. At the time of reporting, no data are available on MODY prevalence in populations from Africa. Our study aimed to investigate and report on the incidence of MODY-related variants, specifically *HNFI*A variants, in a population from the Western Cape.

Methods: Study participants were recruited (1643 in total, 407 males, 1236 females) and underwent anthropometric tests. Thereafter, blood was collected, and real-time PCR was used to screen for specific variants in *HNFI*A and *GCK* genes.

Results: Ninety-seven individuals (5.9%) were identified with a specific *HNFI*A gene polymorphism (rs1169288) and twelve (0.9%) with a *GCK* polymorphism (rs4607517).

Conclusion: In total, 6.6% of the study population expressed MODY variants. To our knowledge, we are the first to report on MODY incidence in Africa. This research provides the basis for MODY incidence studies in South Africa, as well as data on non-Caucasian populations.

Keywords: MODY, *HNFI*A, *GCK*, diabetes mellitus, monogenic diabetes, South Africa

Introduction

Maturity onset diabetes of the young (MODY) is a monogenic form of diabetes, caused by variation in a single gene, and type 1 (T1DM) and type 2 diabetes mellitus (T2DM) are polygenic in nature. While T1DM is caused by an autoimmune-mediated destruction of pancreatic β -cells in the islets of pancreatic glands, a complex interaction of multiple genes and environmental factors are thought to be drivers of T2DM.¹ MODY is associated with pathogenic variants in one of fourteen different genes, resulting in β -cell dysfunction, which causes a defect in insulin secretion in response to glucose stimulation.² Pathogenic variants in these genes (*HNFI*A, *GCK*, *HNFI*A, *PDX1*, *HNFI*B, *NEURO1*, *KLF11*, *CEL*, *PAX4*, *INS*, *BLK*, *ABCC8*, *KCNJ11*, and *APPL1*) determine the type of MODY (MODY1–14), age of onset, treatment responses, and associated extra-pancreatic complications, such as microvascular disorders.¹

MODY is characterised by an early age of onset (before 35 years), a strong familial history of diabetes, and often, a lack of insulin resistance.³ Further, patients diagnosed with MODY often present with normal body mass indexes (BMI).³ The illness is inherited in an autosomal dominant manner, where 63% of carriers

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develop diabetes before 25 years of age, and 96% develop diabetes before 55 years of age.⁴ MODY is thought to account for roughly 1–3% of all diabetes mellitus (DM) cases,⁵ where the most prevalent forms involve pathogenic variants in hepatocyte nuclear factor (*HNF1A*, *HNF1B*, *HNF4A*) and glucokinase (*GCK*) genes, accounting for ~99% of all MODY cases.⁶ However, prevalence estimates vary by ethnicity, hence the need for more comprehensive prevalence studies, especially in countries where genetic testing is often overlooked.

HNF1A (MODY3 [MIM: 600496]) pathogenic variants affect mitochondrial function in pancreatic β -cells, often causing progressive dysfunction of β -cells and insulin secretory defects.⁷ Additional clinical features in MODY3 patients include glycosuria and decreased renal absorption of glucose.⁸ Whilst the general consensus has been that heterozygous highly penetrant loss-of-function mutations in *HNF1A* give rise to MODY3, this genotype-phenotype correlation is true for a subset of *HNF1A* variant carriers, as it represents one end of a broad spectrum of *HNF1A* variant effects.⁹ *GCK* (MODY2) mutations prevent an appropriate response to rising glucose levels, thereby disrupting the normal secretion of insulin and increasing the glucose threshold. This translates to an increased fasting glucose level, delaying insulin secretion.⁷ While pathogenic variants in the *HNF1A* and *GCK* genes each account for ~20–70% of all MODY cases, pathogenic variants in *HNF4A* and *HNF1B* account for ~5%.⁶

MODY is very difficult to diagnose for several reasons, namely, the low prevalence in a population, shared symptoms with DM, and limited awareness of MODY.¹⁰ Further, genetic testing is not common practice in most countries, particularly low-middle income countries. Correct diagnosis could considerably alter treatment protocols and patient quality of life. Treatment could be amended to glucose lowering medication in the case of MODY1 (*HNF4A*) or MODY3 (*HNF1A*) diagnoses,¹¹ while withdrawal of medication would be appropriate for patients diagnosed with MODY2 (*GCK*).¹²

As most genetic studies have been conducted in Caucasian populations, it is vital to determine the specific prevalence of MODY in populations of varied ethnicity.¹³ The goal of this study was to report on MODY incidence in a mixed-ancestry population of the Western Cape, South Africa, by prevalence of MODY gene variants previously associated with MODY or T2D risk.¹⁴ To the best of our knowledge, we are the first research group to report on

MODY population prevalence in Africa. We further describe clinical characteristics of South African individuals carrying MODY variants.

Methods

Ethics

The current cross-sectional study forms part of the Vascular and Metabolic Health (VMH) study registered at the Cape Peninsula University of Technology, Bellville South, Cape Town, South Africa. Ethical approval for the study was obtained from the Research Ethics Committees of the Cape Peninsula University of Technology (CPUT) and Stellenbosch University (respectively, NHREC: REC - 230 408–014, CPUT/HW-REC 2015/H01 and N14/01/003). Further ethics approval was specifically granted for MODY study analysis (CPUT/HW-REC 2015/H01). The study was carried out in accordance with the Declaration of Helsinki. Prior to the commencement of this study, all participants signed a consent form after the study principles had been fully explained in the language of their choice. Thereafter, they were free to ask any questions pertaining to the study and their involvement.

Study Setting

This cross-sectional, descriptive study enrolled participants who reside in Bellville South, located in the Northern Suburbs of Cape Town, Western Cape, South Africa. This population largely consists of mixed-ancestry individuals. According to South African census data of 2011, the population is comprised of 76.0% mixed ancestry, 18.5% Black, 1.0% Asian, 0.5% Caucasian, and 4.0% individuals from other ethnicities.¹⁵ The aim of this study was to determine MODY variants in a South African community. MODY has been estimated to account for 1–5% of all diabetes mellitus cases world-wide. However, the incidence of MODY is unknown in the South African population. A study conducted by Erasmus et al reported on the increase in diabetes incidence in this population, thus providing the ideal setting to investigate MODY prevalence.¹⁶ Therefore, the prevalence of diabetes in the South African population, which has been reported as 28% by Erasmus et al (2012), was used for the sample size calculation. The formula used to calculate the sample size for this study is as follows:

$n = z^2(pq)/e^2$. Where: n = the sample size, z = standard error associated with the chosen level of confidence

(1.96), p = estimated population percentage, $q = 100 - p$, e = acceptable sample error (5%).

Calculation:

$$n = z^2(pq)/e^2$$

$$n = \{1.96^2(28.2*(100 - 28.2))\}/5^2$$

$$n = 311$$

The minimum sample size required was 311 participants. The study cohort comprised of individuals who voluntarily participated in the VMH study conducted between 2014 and 2016. A total of 1643 individuals were recruited. All participants were screened for MODY, as misdiagnosis with T1DM or T2DM could have occurred.

Inclusion/Exclusion Criteria

Only participants of mixed-ancestry descent were included. Participants had to be 20 years of age or older, and both males and females were included (both diabetic and non-diabetic). Pregnant women, severely ill individuals, and those who declined to participate were excluded from the study.

Anthropometric Measurements

Anthropometric measurements were recorded for all participants. These included height (cm), weight (kg), and hip (HipC, cm) and waist (WaistC, cm) circumferences. The measurements were performed three times, with the average used for final analysis. In addition, blood pressure (BP) readings were obtained. Blood pressure measurements were performed by a registered nurse according to World Health Organization (WHO) guidelines.¹⁷ The Omron M6 Comfort-preformed Cuff Blood Pressure Monitor (Omron, Japan) was used for the measurement. Readings were taken three times with three-minute intervals between each reading. The lowest systolic (SBP) and corresponding diastolic (DBP) readings were used.

Blood Sample Collection and Biochemical Analysis

Blood samples were collected by trained, registered nurses. Participants were requested to fast overnight according to WHO guidelines,¹⁷ in order to enable the collection of fasting samples. Samples were collected after the two-hour oral glucose tolerance test (OGTT). Participants who had reported T2DM and/or those using medication had only the fasting blood sample taken. All other participants performed the two-hour OGTT. Fasting and 2hr postprandial blood

samples were collected for serological tests, namely serum cotinine, insulin, lipid profile analysis, and measurement of glycated haemoglobin (HbA1c) levels. DNA was extracted using the salt extraction method. The Nanodrop™ One (Thermo Fisher Scientific, Waltham, MA, USA) was used to quantify DNA concentrations, thereafter DNA was stored at -80°C . Blood samples were transported to PathCare Reference Laboratory (Cape Town, South Africa) for further processing and biochemical analysis. Samples were processed and stored at -80°C for future use.

Biochemical Analysis

Plasma glucose concentrations (mmol/L) were measured using the hexokinase method (Beckman Coulter). Glycated haemoglobin (%) was measured using high performance liquid chromatography (HPLC) (Variant™ II Turbo System, BioRad, Hercules, CA, USA). Insulin (mIU/L) was measured using a paramagnetic particle-based chemiluminescent system. The lipid profile (mmol/L) was analysed using an enzymatic selective protection-endpoint assay (Beckman Coulter) for LDL-cholesterol, an enzymatic immuno-inhibition-endpoint assay (Beckman Coulter) for HDL-cholesterol, and a glycerol phosphate oxidase in the presence of peroxidase (GPO-POD) endpoint assay (Beckman Coulter) for triglycerides.

Definitions and Calculations

Body Mass Index (BMI) was calculated as weight per square meter (kg/m^2). According to the Global Report on Diabetes,¹⁸ DM is diagnosed if the fasting blood glucose (FBG) measures $\geq 7.0\text{mmol}/\text{L}$ or the post-2hr blood glucose measures (2hr BG) $\geq 11.1\text{mmol}/\text{L}$. Impaired fasting glucose (IFG) is diagnosed when the FBG measures between 6.1 and 6.9mmol/L and, if analysed, the post-2hr BG measures $< 7.8\text{mmol}/\text{L}$. Impaired glucose tolerance (IGT) is classified as a FBG measured at $< 7.0\text{mmol}/\text{L}$ and post-2hr BG measured between $\geq 7.8\text{mmol}/\text{L}$ and $< 11.1\text{mmol}/\text{L}$. Hyperglycaemia includes individuals with T2DM, IFG, and/or IGT.

Real-Time Polymerase Chain Reaction (RT-PCR) Single-Nucleotide Polymorphism (SNP) Genotyping

Six different SNPs (rs140491072 (p.Y322C), rs115080759 (p.L389V), rs142318174 (p.G52A), rs137853245 (p.A276D), rs1169288 (p.I27L), and rs4607517; [Supplementary Table 1](#)) were analysed using PCR techniques performed in two different laboratories, thereafter

results were confirmed by sequencing. Firstly, real-time PCR was carried out using the Applied Biosystems® QuantStudio™ 7 Flex Real-time PCR system (Thermo Fisher Scientific) and TaqMan® Universal PCR Master Mix, according to the manufacturer's protocol. The initial denaturation occurred at 95°C (10min), followed by 50 cycles of denaturation (95°C, 15s), annealing (60°C, 90s), and extension (60°C, 90s). Thereafter, 1643 genomic DNA samples were sent to Inqaba Biotechnical Industries (Pretoria, South Africa) for SNP genotyping and sequencing. Inqaba Biotechnical Industries employed an in-house protocol, which included an initial locus-specific PCR reaction, followed by single-base extension using mass-modified dideoxynucleotide terminators of an oligonucleotide primer. Reagents and primers (TaqMan® SNP Genotyping Assays) were sourced from Thermo Fisher Scientific.

Statistical Analysis

Data were analysed using Statistica version 13.5 (StatSoft, Southern Africa Analytics) and SPSS v.24 (IBM Corp, 2011). General characteristics of the study participants are summarized as mean \pm standard deviation (SD) or median (25th, 75th) percentiles for continuous variables and number (%) for categorical variables. Analysis of variance was used to calculate the mean and standard deviation values. SNPs were assessed using the Hardy-Weinberg Equilibrium (HWE) expectation with a Chi square goodness-of-fit test. Linear regression models were used for the analysis of quantitative traits assuming the dominant, recessive, and additive genetic models. A p -value of < 0.05 was considered statistically significant.

Results

Study Population Characteristics

In total, 1643 individuals participated in the study (407 males, 1236 females). Characteristics of the study population are indicated in Table 1. Females (50.0 \pm 15.1 years) were significantly older than males (47.0 \pm 15.6 years; $p = 0.0008$) and exhibited significantly greater glycaemic measurements. Consequently, the incidence of diabetes (males 15% vs females 20%) and pre-diabetes (pre-DM; males 10.8% vs females 15.8%) was significantly greater in females ($p = 0.0539$ and $p = 0.0313$, respectively). The BMI (males 24.7 \pm 6.6 vs females 30.8 \pm 8.0), waist circumference (WaistC, cm; males 86.2 \pm 16.8 vs females

95.1 \pm 16.9), and hip circumference (HipC, cm; males 94.5 \pm 12.5 vs females 107.9 \pm 16.4) measurements were significantly greater in females as compared to males ($p < 0.0001$ for all three measurements; Table 1).

Allele and Genotype Distribution Amongst Study Participants

The SNP frequency was tested for Hardy-Weinberg Equilibrium (HWE). Table 2 indicates the genotype distribution and minor allele frequencies within the study population. Ninety-seven individuals (5.9%) presented with the C/C genotype for *HNF1A* (rs1169288), while 557 individuals (34.3%) presented with the C/A genotype. The allele percentage was calculated at 23.1% for rs1169288 (751/3246; HWE $p = 0.1576$). Twelve individuals (0.7%) presented with the G/T genotype for *HNF1A* (rs115080759), with a rare allele percentage of 0.4% (12/3280; HWE $p = 0.8818$). The *GCK* SNP (rs4607517) results indicated that 28 individuals (2.1%) presented with the A/G genotype, while 12 presented with A/A (0.9%), indicating a rare allele percentage of 1.9% (52/2722; HWE $p < 0.0001$; Table 2).

Participant Characteristics Compared Across *HNF1A* rs1169288 SNP Genotypes According to Gender

Ninety-seven participants expressed the *HNF1A* p.I27L SNP (C/C), with 557 expressing A/C and 969 expressing A/A (Table 3). No significant difference was observed between genotypes and the percentage of diabetic, hyperglycaemic, and normoglycaemic participants. No age difference was observed between participants and the three varying genotypes. Similarly, no significant differences were observed between BMI, WaistC, HipC, and glycaemic measurements, as well as cholesterol profiles across the genotypes. Interestingly, C-reactive protein (CRP, mg/L) levels were significantly lower in participants with the C/C genotype (5.62 \pm 6.36) compared to participants with the A/A (9.47 \pm 17.43) and C/A (7.33 \pm 13.64) genotypes ($p = 0.0068$; Table 3). Regression analysis indicated decreased CRP levels across the models (Table 4), with significantly decreased CRP observed in the dominant and additive models ($p = 0.04$ and $p = 0.017$, respectively). Additionally, significantly increased LDL cholesterol levels were observed in the dominant and additive models ($p = 0.019$ and $p = 0.019$, respectively; Table 4), while HDL cholesterol appeared to decrease across all three

Table I Characteristics of the Study Population According to Gender

| | Total -N1643 | Males - N407 | Females - N1236 | p-value |
|----------------------------|--------------|--------------|-----------------|----------|
| | Mean±SD | Mean±SD | Mean±SD | |
| Hyperglycaemia, Yes, N (%) | 549 (33.4) | 105 (25.8) | 444 (35.9) | 0.0068* |
| Diabetes, Yes, N (%) | 310 (18.9) | 61 (15.0) | 249 (20.1) | 0.0539 |
| Pre-DM, Yes, N (%) | 239 (14.5) | 44 (10.8) | 195 (15.8) | 0.0313* |
| Age (years) | 49.2±15.3 | 47.0±15.6 | 50.0±15.1 | 0.0008* |
| BMI | 29.3±8.1 | 24.7±6.6 | 30.8±8.0 | <0.0001* |
| WaistC (cm) | 92.9±17.3 | 86.2±16.8 | 95.1±16.9 | <0.0001* |
| HipC (cm) | 104.6±16.6 | 94.5±12.5 | 107.9±16.4 | <0.0001* |
| WHR | 0.89±0.09 | 0.91±0.09 | 0.88±0.09 | <0.0001* |
| SBP (mmHg) | 127.2±23.9 | 126.6±24.3 | 127.5±23.7 | 0.5441 |
| DBP (mmHg) | 81.9±13.8 | 80.9±15.3 | 82.2±13.2 | 0.0851 |
| FBG (mmol/L) | 5.74±2.76 | 5.39±2.18 | 5.85±2.92 | 0.0029* |
| Post-2hr BG (mmol/L) | 6.61±2.93 | 5.75±2.99 | 6.90±2.85 | <0.0001* |
| HbA1c (%) | 6.19±1.53 | 5.92±1.25 | 6.28±1.61 | 0.0001* |
| Fasting BI (mIU/L) | 9.5±11.8 | 7.6±9.7 | 10.2±12.3 | 0.0001* |
| Post-2hr BI (mIU/L) | 55.5±53.6 | 33.7±38.3 | 63.1±56.1 | <0.0001* |
| Glucose/Insulin ratio | 1.00±0.88 | 1.32±1.07 | 0.90±0.79 | <0.0001* |
| Triglycerides-S (mmol/L) | 1.47±1.07 | 1.55±1.57 | 1.44±0.85 | 0.0886 |
| LDL Cholesterol (mmol/L) | 3.23±1.03 | 2.95±0.97 | 3.32±1.03 | <0.0001* |
| HDL Cholesterol (mmol/L) | 1.32±0.36 | 1.25±0.37 | 1.35±0.36 | <0.0001* |
| Cholesterol (mmol/L) | 5.17±1.17 | 4.83±1.12 | 5.29±1.17 | <0.0001* |
| Cholesterol/HDL ratio | 4.11±1.20 | 4.07±1.33 | 4.13±1.15 | 0.4149 |
| CRP (mg/L) | 8.5±15.7 | 8.1±17.2 | 8.6±15.2 | 0.6328 |
| Cotinine (ng/mL) | 141.7±160.7 | 157.6±153.1 | 136.4±162.8 | 0.0231* |
| Gamma GT-S (IU/L) | 46.2±70.6 | 54.1±97.1 | 43.6±59.2 | 0.0097 |

Note: *Chi-square.

Abbreviations: WaistC, waist circumference; HipC, hip circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; BI, blood insulin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; Gamma GT, gamma glutamyl transferase; BMI, body mass index; Chol, cholesterol.

models, with significance observed in the additive model ($p = 0.097$). The odds ratios were calculated for *HNFI1A* (rs1169288) regarding potential determinants of MODY, such as C-reactive protein, FBG, HbA1C, and lipid profile components ([Supplementary Table 2](#)).

Participant Characteristics Compared Across *HNFI1A* rs115080759 SNP Genotypes

Participants expressed the normal T/T (N=1628) genotype and the MODY-associated T/G (N=12) genotype ([Table 5](#)). No participants expressed the G/G variation. No significant differences were observed between the genotypes and the percentage of diabetic, hyperglycaemic, and normoglycaemic participants. No significant age difference was observed. Additionally, there were no significant differences between BMI, WaistC, HipC, and lipid profiles across the genotypes. However, significant differences

were observed in glycaemic measurements. Participants expressing the T/G genotype exhibited significantly increased FBG levels ($7.92±4.99$ vs $5.72±2.74$; $p = 0.0061$), increased HbA1c percentages ($7.30±2.73$ vs $6.18±1.52$; $p = 0.0116$), and an increased glucose to insulin ratio ($1.56±1.76$ vs $1.00±0.87$; $p = 0.0284$). A significant difference was observed in FBG ($p = 0.0098$), HbA1c % ($p = 0.0127$), and the glucose/insulin ratio ($p = 0.0213$) across genders and SNP genotypes ([Table 5](#)).

Participant Characteristics Compared Across *GCK* rs4607517 SNP Genotypes According to Gender

Twelve participants expressed the *GCK* rs4607517 SNP (A/A), with 28 expressing A/G, and 1321 expressing G/G ([Table 6](#)). No significant differences were observed in all participant parameters across SNP genotypes. However, participants expressing the MODY-associated allele (either

Table 2 Genotype Distributions and Minor Allele Frequencies

| <i>HNFI</i> A, rs1169288, p.I27L | N=1623 | <i>HNFI</i> A, rs115080759, p.L389V | N=1640 | <i>HNFI</i> A, rs137853245, p.A276D | N=1642 |
|------------------------------------|------------------|-------------------------------------|----------------|-------------------------------------|---------------|
| A/A, N (%) | 969 (59.7) | T/T, N (%) | 1628 (99.3) | C/C, N (%) | 1642 (100) |
| A/C, N (%) | 557 (34.3) | T/G, N (%) | 12 (0.7) | C/A, N (%) | 0 |
| C/C, N (%) | 97 (5.9) | G/G, N (%) | 0 | A/A, N (%) | 0 |
| C, N (%) | 751/3246 (23.1%) | G, N (%) | 12/3280 (0.4%) | G, N (%) | 0 |
| HWE (p-value) | 0.1576 | HWE (p-value) | 0.8818 | HWE (p-value) | N/A |
| <i>HNFI</i> A, rs142318174, p.G52A | N=1638 | <i>HNFI</i> A, rs140491072, p.Y322C | N=1641 | <i>GCK</i> , rs4607517 | N=1361 |
| G/G, N (%) | 1638 (100) | A/A | 1641 (100) | G/G, N (%) | 1321 (97.1) |
| G/C, N (%) | 0 | A/G, N (%) | 0 | A/G, N (%) | 28 (2.1) |
| C/C, N (%) | 0 | G/G, N (%) | 0 | A/A, N (%) | 12 (0.9) |
| C, N (%) | 0 | G, N (%) | 0 | A, N (%) | 52/2722 (1.9) |
| HWE (p-value) | N/A | HWE (p-value) | NA | HWE (p-value) | <0.0001 |

Abbreviation: HWE, Hardy–Weinberg equilibrium.

Table 3 Participant Characteristics Compared Across *HNFI*A rs1169288 SNP Alleles

| <i>HNFI</i> A, rs1169288 (p.I27L) | Variant | | | | | |
|-----------------------------------|-------------|-------------|-------------|---------|---------|-----------------|
| | AA (N=969) | CA (N=557) | CC (N=97) | Gender | SNP | Gender* SNP |
| | Mean±SD | Mean±SD | Mean±SD | p-value | p-value | p-value |
| Hyperglycaemia, Yes, N (%) | 317 (32.7) | 187 (33.6) | 38 (39.2) | N/A | N/A | 0.4345* |
| Diabetes, Yes, N (%) | 177 (18.3) | 108 (19.4) | 22 (22.7) | N/A | N/A | Combined 0.7593 |
| Pre-DM, Yes, N (%) | 140 (14.4) | 79 (14.2) | 16 (16.5) | | | |
| Age (years) | 48.8±15.2 | 50.1±15.4 | 48.6±15.3 | 0.3736 | 0.2434 | 0.1626 |
| BMI | 29.5±8.4 | 29.0±7.7 | 30.1±8.1 | <0.0001 | 0.3227 | 0.6479 |
| WaistC (cm) | 92.8±17.2 | 92.9±17.5 | 94.6±17.4 | <0.0001 | 0.6016 | 0.3640 |
| HipC (cm) | 104.6±16.6 | 104.5±16.5 | 106.3±16.6 | <0.0001 | 0.6133 | 0.6557 |
| WHR | 0.89±0.10 | 0.89±0.09 | 0.89±0.08 | <0.0001 | 0.9717 | 0.2683 |
| SBP (mmHg) | 126.8±23.0 | 128.2±25.2 | 126.7±23.0 | 0.7523 | 0.5068 | 0.7031 |
| DBP (mmHg) | 81.8±13.6 | 82.3±14.3 | 82.2±13.0 | 0.6781 | 0.7869 | 0.1978 |
| FBG (mmol/L) | 5.70±2.67 | 5.77±2.86 | 5.79±2.34 | 0.0181 | 0.8532 | 0.3610 |
| Post-2hr BG (mmol/L) | 6.60±3.00 | 6.60±2.84 | 6.72±2.65 | 0.0002 | 0.9331 | 0.3948 |
| HbA1c (%) | 6.18±1.54 | 6.19±1.54 | 6.23±1.39 | 0.0055 | 0.9511 | 0.5368 |
| Fasting BI (mIU/L) | 9.9±13.7 | 8.9±8.2 | 10.2±7.9 | 0.0211 | 0.2719 | 0.9720 |
| Post-2hr BI (mIU/L) | 55.8±55.4 | 54.8±52.4 | 57.5±44.2 | <0.0001 | 0.8964 | 0.3691 |
| Glucose/Insulin ratio | 0.99±0.81 | 1.03±1.00 | 0.86±0.64 | <0.0001 | 0.2316 | 0.7501 |
| Triglycerides (mmol/L) | 1.43±0.96 | 1.51±1.17 | 1.58±1.57 | 0.0003 | 0.1936 | 0.0041* |
| LDL Chol (mmol/L) | 3.19±1.02 | 3.30±1.07 | 3.28±0.93 | 0.0095 | 0.1607 | 0.2502 |
| HDL Chol (mmol/L) | 1.33±0.38 | 1.32±0.35 | 1.28±0.29 | 0.0090 | 0.3706 | 0.4872 |
| Chol (mmol/L) | 5.14±1.16 | 5.24±1.22 | 5.23±1.11 | 0.0047 | 0.2266 | 0.1811 |
| Chol/HDL ratio | 4.09±1.25 | 4.15±1.10 | 4.20±1.22 | 0.8099 | 0.4792 | 0.7782 |
| CRP (mg/L) | 9.47±17.43 | 7.33±13.64 | 5.62±6.36 | 0.7075 | 0.0068 | 0.1964 |
| Cotinine (ng/mL) | 140.7±159.5 | 146.1±164.2 | 125.9±156.8 | 0.3616 | 0.5134 | 0.7389 |
| Gamma GT-S (IU/L) | 46.6±67.3 | 46.4±75.3 | 45.0±81.9 | 0.0019 | 0.9782 | 0.1113 |

Note: *Denotes significance ($p < 0.05$).

Abbreviations: WaistC, waist circumference; HipC, hip circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; BI, blood insulin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; Gamma GT, gamma glutamyl transferase; BMI, body mass index; Chol, cholesterol.

Table 4 Generalized Linear Regression Models Showing Phenotypes Associated with *HNFI*A rs1169288

| <i>HNFI</i> A rs1169288 (C) | Dominant | | Recessive | | Additive | |
|-----------------------------|------------------------|---------|------------------------|---------|------------------------|---------|
| | Effect Size (95% CI) | p-value | Effect Size (95% CI) | p-value | Effect Size (95% CI) | p-value |
| Age (years) | 0.001 (-0.001; 0.003) | 0.427 | 0.000 (-0.002; 0.001) | 0.365 | 0.001 (-0.001; 0.003) | 0.764 |
| Gender (Female) | -0.047 (-0.113; 0.019) | 0.165 | 0.003 (-0.029; 0.034) | 0.868 | -0.047 (-0.113; 0.019) | 0.285 |
| WaistC (cm) | 0.000 (-0.002; 0.002) | 0.752 | 0.000 (-0.001; 0.001) | 0.882 | 0.000 (-0.002; 0.002) | 0.841 |
| SBP (mmHg) | -0.001 (-0.002; 0.001) | 0.559 | 0.000 (-0.001; 0.001) | 0.692 | -0.001 (-0.002; 0.001) | 0.529 |
| DBP (mmHg) | 0.002 (-0.001; 0.005) | 0.310 | 0.001 (-0.001; 0.002) | 0.354 | 0.002 (-0.001; 0.005) | 0.236 |
| FBG (mmol/L) | -0.012 (-0.05; 0.025) | 0.521 | -0.001 (-0.018; 0.017) | 0.951 | -0.012 (-0.05; 0.025) | 0.584 |
| Post-2hr BG (mmol/L) | 0.008 (-0.007; 0.023) | 0.277 | 0.005 (-0.002; 0.012) | 0.178 | 0.008 (-0.007; 0.023) | 0.160 |
| HbA1c (%) | -0.032 (-0.089; 0.024) | 0.265 | -0.013 (-0.04; 0.014) | 0.348 | -0.032 (-0.089; 0.024) | 0.204 |
| Fasting BI (mIU/L) | -0.001 (-0.003; 0.002) | 0.670 | 0.000 (-0.001; 0.001) | 0.811 | -0.001 (-0.003; 0.002) | 0.798 |
| Post-2hr BI (mIU/L) | 0.000 (-0.001; 0.000) | 0.605 | 0.000 (0.000; 0.000) | 0.384 | 0.000 (-0.001; 0.000) | 0.449 |
| Triglycerides (mmol/L) | -0.016 (-0.051; 0.019) | 0.378 | 0.000 (-0.016; 0.017) | 0.990 | -0.016 (-0.051; 0.019) | 0.475 |
| LDL Chol (mmol/L) | 0.036 (0.006; 0.066) | 0.019* | 0.009 (-0.006; 0.023) | 0.233 | 0.036 (0.006; 0.066) | 0.017* |
| HDL Chol (mmol/L) | -0.059 (-0.141; 0.023) | 0.157 | -0.026 (-0.064; 0.013) | 0.189 | -0.059 (-0.141; 0.023) | 0.097* |
| CRP (mg/L) | -0.002 (-0.004; 0.000) | 0.040* | -0.001 (-0.002; 0.000) | 0.068 | -0.002 (-0.004; 0.000) | 0.017* |
| Gamma GT-S (IU/L) | 0.000 (-0.001; 0.000) | 0.611 | 0.000 (0.000; 0.000) | 0.803 | 0.000 (-0.001; 0.000) | 0.610 |

Note: *Denotes significance ($p < 0.05$).

Abbreviations: WaistC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; BI, blood insulin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; Gamma GT, gamma glutamyl transferase.

heterozygous A/G or homozygous A/A) exhibited slightly elevated glycaemic measurements compared to participants expressing the G/G genotype (Table 6), although non-significant. Linear regression analysis indicates significantly increased levels of triglycerides across the three models ($p = 0.001$ (dominant), $p < 0.001$ (recessive and additive); Table 7). The odds ratios were calculated for *GCK* (rs4607517) regarding potential determinants of MODY, such as C-reactive protein, FBG, HbA1C, and lipid profile components (Supplementary Table 3).

Discussion

MODY is a rare form of diabetes caused by single-gene defects, and is often misdiagnosed as T1DM or T2DM, thereby compromising treatment protocols.¹⁰ Mutations in *GCK* and *HNFI*A genes are most common, accounting for approximately 99% of MODY diagnoses, representing 1–5% of all DM cases. Previous research on the South African study population reported a high incidence of diabetes and cardiovascular disease,^{16,19} providing a suitable setting for an investigation into MODY incidence. To our knowledge, this is the first study to identify individuals carrying pathogenic variants for monogenic diabetes in South Africa and Africa in general. We aimed to determine the presence of MODY by the risk allele frequency of five *HNFI*A SNPs, one common (MAF > 5%) and four rare (MAF < 1%), of which the four have

been found in an African population alone, according to Gnomad, and one *GCK* SNP, and their association with cardiometabolic traits in a general South African population characterised by a high DM prevalence.

For the common *HNFI*A variant, we observed the presence of a dominant genotype in *HNFI*A rs1169288 (p.Ile27Leu), which affected 97 (5.9%) individuals, while 12 (0.9%) individuals were affected with *GCK* rs4607517, and only one participant carried both, resulting in MODY-associated variants amounting to 6.7%. Another 554 (34.3%) and 28 (2.1%) participants were carriers of *HNFI*A rs1169288 and *GCK* rs4607517, respectively. No carriers of *HNFI*A rs140491072, rs142318174, and rs137853245 were observed, however, 12 (0.7%) participants carried the MODY-associated *HNFI*A rs115080759 (p.L389V) SNP.²⁰ Although the distribution of genotypes according to glycaemic status were not significantly different, a third of *HNFI*A rs1169288- or *GCK* rs4607517-positive individuals exhibited hyperglycaemia. In individuals with diabetes, the *HNFI*A SNP was observed in 7.1%, whilst the *GCK* SNP was observed in 0.6% of individuals. C-reactive protein (CRP) levels were significantly lower in participants expressing the *HNFI*A (rs1169288) common SNP ($p = 0.0068$), and this remained after linear regression model analysis, which showed that the presence of the C allele significantly reduced CRP and HDL-cholesterol,

Table 5 Participant Characteristics Compared Across *HNFI*A rs115080759 SNP Alleles

| <i>HNFI</i> A, rs115080759 | Variant | | | | | |
|----------------------------|-------------|------------|----------|---------|---------|-----------------|
| | TT (N=1628) | GT (N=12) | GG (N=0) | Gender | SNP | Gender*SNP |
| | Mean±SD | Mean±SD | Mean±SD | p-value | p-value | p-value |
| Hyperglycaemia, Yes, N (%) | 543 (33.4) | 5 (41.7) | 0 | N/A | N/A | 0.5430 |
| Diabetes, Yes, N (%) | 305 (18.7) | 4 (33.3) | 0 | N/A | N/A | Combined 0.4078 |
| Pre-DM, Yes, N (%) | 238 (14.6) | 1 (8.3) | 0 | | | |
| Age (years) | 49.2±15.3 | 49.0±13.9 | N/A | 0.8061 | 0.9609 | 0.8061 |
| BMI | 29.3±8.1 | 31.1±6.9 | N/A | 0.0287 | 0.4520 | 0.8760 |
| WaistC (cm) | 92.8±17.3 | 97.4±16.3 | N/A | 0.0421 | 0.3676 | 0.4897 |
| HipC (cm) | 104.5±16.6 | 108.6±13.4 | N/A | 0.0129 | 0.3962 | 0.7844 |
| WHR | 0.89±0.09 | 0.90±0.08 | N/A | 0.9765 | 0.8036 | 0.4571 |
| SBP (mmHg) | 127.2±23.9 | 126.9±22.0 | N/A | 0.8026 | 0.9619 | 0.7319 |
| DBP (mmHg) | 81.9±13.8 | 84.3±9.5 | N/A | 0.4625 | 0.5512 | 0.3169 |
| FBG (mmol/L) | 5.72±2.74 | 7.92±4.99 | N/A | 0.0339 | 0.0061 | 0.0098* |
| Post-2hr BG (mmol/L) | 6.62±2.93 | 5.47±0.85 | N/A | 0.5317 | 0.2705 | 0.8996 |
| HbA1c (%) | 6.18±1.52 | 7.30±2.73 | N/A | 0.0615 | 0.0116 | 0.0127* |
| Fasting BI (mIU/L) | 9.6±11.8 | 7.8±3.6 | N/A | 0.6059 | 0.6073 | 0.9581 |
| Post-2hr BI (mIU/L) | 55.5±53.7 | 52.7±39.5 | N/A | 0.4714 | 0.8822 | 0.7352 |
| Glucose/Insulin ratio | 1.00±0.87 | 1.56±1.76 | N/A | 0.0004 | 0.0284 | 0.0213* |
| Triglycerides (mmol/L) | 1.47±1.08 | 1.24±0.53 | N/A | 0.6385 | 0.4518 | 0.4686 |
| LDL Chol (mmol/L) | 3.23±1.03 | 3.33±1.00 | N/A | 0.4978 | 0.7311 | 0.7849 |
| HDL Chol (mmol/L) | 1.32±0.36 | 1.27±0.40 | N/A | 0.4065 | 0.5868 | 0.8687 |
| Chol (mmol/L) | 5.18±1.17 | 5.17±1.27 | N/A | 0.4942 | 1.0000 | 0.7262 |
| Chol/HDL ratio | 4.11±1.20 | 4.27±1.08 | N/A | 0.8717 | 0.6423 | 0.7716 |
| CRP (mg/L) | 8.5±15.8 | 6.0±7.3 | N/A | 0.6849 | 0.5902 | 0.7371 |
| Cotinine (ng/mL) | 142.3±160.9 | 57.1±90.7 | N/A | 0.3096 | 0.0797 | 0.4891 |
| Gamma GT-S (IU/L) | 46.2±70.7 | 49.1±68.2 | N/A | 0.7800 | 0.8897 | 0.5058 |

Note: *Denotes significance ($p < 0.05$).

Abbreviations: WaistC, waist circumference; HipC, hip circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; BI, blood insulin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; Gamma GT, gamma glutamyl transferase; BMI, body mass index; Chol, cholesterol.

but increased LDL-cholesterol. This result agrees with previous research reporting on low CRP levels in MODY3 patients.²¹ Interestingly, participants expressing the rare allele for *HNFI*A mutation (rs115080759; p. Leu389Val) exhibited significantly increased fasting blood glucose and HbA1c levels, as well as increased glucose to insulin ratios ($p = 0.0061$, $p = 0.0116$, and $p = 0.0284$, respectively), indicating that the presence of the rare allele influences glycaemic measurements, although participants were not diagnosed with MODY. This is particularly important when considering the extra-hepatic complications associated with MODY3, such as microvascular and macrovascular issues.²² Although twelve participants expressed genotype variations of the *GCK* SNP, no anthropometric or biochemical differences were observed during comparisons between genotypes. Nonetheless, participants expressing the rare MODY

allele associated with a *GCK* mutation (rs4607517) exhibited slightly increased glycaemic measurements as compared to those without the rare allele; these results were non-significant.

The presence of the *GCK* rs4607517 A-allele non-significantly increased glycaemic indices, but significantly increased triglyceride levels. The reported incidence correlates with MODY research conducted globally.^{23–26} However, *GCK* variants in our study population disagrees with the current prevalence estimate of approximately 1 in 1000 people.¹² Our results report a 0.9% presence of the *GCK* rs4607517 AA-genotype in a population of 1361 people, demonstrating an incidence of 0.88%, as opposed to 0.1% cited in literature.¹² *HNFI*A, a human gene located on chromosome 12, comprising of 10 exons that span 23kb of genomic DNA (gDNA), contains mutations scattered throughout the entire gene, with the greatest numbers found in *HNFI*A

Table 6 Participant Characteristics Compared Across *GCK* rs4607517 SNP Alleles

| <i>GCK</i> , rs4607517 | Variant | | | | | |
|----------------------------|-------------|-------------|-------------|---------|---------|-----------------|
| | GG (N=1321) | AG (N=28) | AA (N=12) | Gender | SNP | Gender*SNP |
| | Mean±SD | Mean±SD | Mean±SD | p-value | p-value | p-value |
| Hyperglycaemia, Yes, N (%) | 453 (34.3) | 9 (32.1) | 2 (16.7) | N/A | N/A | 0.4290 |
| Diabetes, Yes, N (%) | 251 (19.0) | 7 (25.0) | 2 (16.7) | N/A | N/A | Combined 0.3847 |
| Pre-DM, Yes, N (%) | 202 (15.3) | 2 (7.1) | 0 | | | |
| Age (years) | 49.6±15.1 | 51.7±18.0 | 44.5±17.3 | 0.2449 | 0.7154 | 0.4318 |
| BMI | 29.3±8.1 | 30.9±9.0 | 29.2±9.3 | 0.2072 | 0.2976 | 0.0547 |
| WaistC (cm) | 93.0±17.4 | 95.0±15.5 | 91.1±18.4 | 0.0698 | 0.7338 | 0.9835 |
| HipC (cm) | 104.6±16.6 | 109.0±17.9 | 103.3±17.0 | 0.0013 | 0.3439 | 0.7761 |
| WHR | 0.89±0.09 | 0.87±0.07 | 0.88±0.06 | 0.1440 | 0.7944 | 0.7682 |
| SBP (mmHg) | 127.6±24.1 | 127.4±19.6 | 118.1±23.4 | 0.6729 | 0.6029 | 0.9138 |
| DBP (mmHg) | 82.1±13.8 | 81.6±13.7 | 76.9±17.3 | 0.3357 | 0.5378 | 0.5283 |
| FBG (mmol/L) | 5.75±2.73 | 5.58±1.58 | 6.77±6.82 | 0.1775 | 0.9047 | 0.6773 |
| Post-2hr BG (mmol/L) | 6.63±2.97 | 7.45±4.24 | 5.85±0.95 | 0.0723 | 0.5255 | 0.5543 |
| HbA1c (%) | 6.19±1.54 | 6.16±1.16 | 6.41±2.15 | 0.1256 | 0.9379 | 0.5609 |
| Fasting BI (mIU/L) | 9.5±12.5 | 10.6±13.8 | 9.6±6.3 | 0.8858 | 0.6692 | 0.5690 |
| Post-2hr BI (mIU/L) | 55.6±54.7 | 50.7±51.3 | 96.0±73.6 | 0.0420 | 0.2150 | 0.9815 |
| Glucose/Insulin ratio | 1.00±0.86 | 1.01±0.60 | 1.35±2.24 | 0.6457 | 0.9258 | 0.0765 |
| Triglycerides (mmol/L) | 1.46±1.07 | 1.59±0.87 | 1.57±0.92 | 0.8446 | 0.9652 | 0.5702 |
| LDL Chol (mmol/L) | 3.25±1.03 | 3.12±0.82 | 3.53±0.75 | 0.5195 | 0.5698 | 0.5491 |
| HDL Chol (mmol/L) | 1.32±0.37 | 1.30±0.33 | 1.33±0.36 | 0.0236 | 0.5923 | 0.3737 |
| Chol (mmol/L) | 5.19±1.18 | 5.10±0.94 | 5.74±0.85 | 0.9507 | 0.1095 | 0.2551 |
| Chol/HDL ratio | 4.12±1.17 | 4.16±1.27 | 4.16±0.90 | 0.5446 | 0.7093 | 0.4373 |
| CRP (mg/L) | 8.7±15.8 | 4.7±7.2 | 6.2±8.4 | 0.5067 | 0.2660 | 0.7580 |
| Cotinine (ng/mL) | 141.5±161.9 | 123.3±165.0 | 170.1±186.8 | 0.8643 | 0.8863 | 0.7621 |
| Gamma GT-S (IU/L) | 46.2±71.7 | 44.3±42.4 | 26.3±11.7 | 0.9285 | 0.6219 | 0.4450 |

Abbreviations: WaistC, waist circumference; HipC, hip circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; BI, blood insulin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; Gamma GT, gamma glutamyl transferase; BMI, body mass index; Chol, cholesterol.

exons 2 and 4.²⁷ Although we did not screen the entire *HNFI*A gene, we observed a high frequency of common variant *HNFI*A rs1169288 (I27L) and less than 1% of one single low-frequency variant in the *HNFI*A gene. Interestingly, one participant exhibited both *GCK* rs4607517 and *HNFI*A rs1169288 common variants. However, the anthropometric measurements did not exhibit extreme diabetic symptoms. Further research regarding this participant is warranted, including an in-depth investigation into the family history of diabetes.

This study did not follow strict clinical criteria before genetic testing was performed. The models for pre-emptive MODY testing have been developed in primarily European Caucasian populations, as such, our study deviated from this model. Previous research highlighted the prevalence of MODY in Europe,^{25,26,28} therefore our study provides a foundation for MODY research in Africa. Accurate diagnosis of MODY is crucial for appropriate treatment protocols and management of associated complications. DM

misdiagnosis is common in MODY patients, which could result in inappropriate treatment and exacerbation of related illnesses. We hope that this research draws awareness to the subject of MODY and the number of people potentially affected by an undiagnosed illness. Our results further support the need for full genetic testing of DM patients and paediatric cases to accurately diagnose and appropriately treat MODY patients. Limitations to our study include the small study population and the investigation of only a few *HNFI*A and *GCK* SNPs. Further, the number of female participants was greater than that of male participants in this study, which is a common limitation in community-based studies in Africa, where women tend to be more interested in participating than men. Other MODY types were not screened, and our testing included six SNPs, demonstrating that numerous mutations could be overlooked. Future studies should address these limitations and include an investigation into family history of DM incidence.

Table 7 Generalized Linear Regression Models Showing Phenotypes Associated with GCK rs4607517

| GCK rs4607517 (A) | Dominant | | Recessive | | Additive | |
|------------------------|------------------------|---------|------------------------|---------|------------------------|---------|
| | Effect Size (95% CI) | p-value | Effect Size (95% CI) | p-value | Effect Size (95% CI) | p-value |
| Age (years) | 0.000(−0.001;0.001) | 0.923 | 0.000 (−0.001; 0.000) | 0.582 | 0.000 (−0.001; 0.001) | 0.882 |
| Gender (Female) | −0.002 (−0.027; 0.023) | 0.872 | 0.001 (−0.012; 0.015) | 0.837 | −0.001 (−0.035; 0.033) | 0.971 |
| WaistC (cm) | 0.000 (−0.001; 0.001) | 0.685 | 0.000 (−0.001; 0.000) | 0.528 | 0.000 (−0.001; 0.001) | 0.963 |
| SBP (mmHg) | 0.000 (−0.001; 0.001) | 0.621 | 0.000 (0.000; 0.000) | 0.589 | 0.000 (−0.001; 0.001) | 0.565 |
| DBP (mmHg) | 0.000 (−0.001; 0.001) | 0.845 | 0.000 (−0.001; 0.001) | 0.940 | 0.000 (−0.002; 0.001) | 0.862 |
| FBG (mmol/L) | −0.007 (−0.021; 0.007) | 0.335 | −0.002 (−0.01; 0.005) | 0.594 | −0.009 (−0.028; 0.010) | 0.359 |
| Post-2hr BG (mmol/L) | 0.000 (−0.005; 0.006) | 0.877 | −0.002 (−0.005; 0.002) | 0.334 | −0.001 (−0.009; 0.007) | 0.787 |
| HbA1c (%) | 0.015 (−0.006; 0.035) | 0.165 | 0.005 (−0.007; 0.016) | 0.425 | 0.019 (−0.009; 0.048) | 0.183 |
| Fasting BI (mIU/L) | 0.000 (−0.001; 0.001) | 0.667 | 0.000 (−0.001; 0.000) | 0.485 | 0.000(−0.001; 0.001) | 0.970 |
| Post-2hr BI (mIU/L) | 0.000 (0.000; 0.000) | 0.917 | 0.000 (0.000; 0.000) | 0.049* | 0.000 (0.000; 0.000) | 0.481 |
| Triglycerides (mmol/L) | 0.023 (0.010; 0.036) | 0.001* | 0.016 (0.008; 0.023) | <0.001* | 0.039 (0.020; 0.057) | <0.001* |
| LDL Chol (mmol/L) | −0.007 (−0.019; 0.004) | 0.199 | −0.001 (−0.007; 0.005) | 0.760 | −0.008 (−0.024; 0.007) | 0.288 |
| HDL Chol (mmol/L) | 0.003 (−0.027; 0.034) | 0.825 | 0.005 (−0.012; 0.021) | 0.565 | 0.008 (−0.033; 0.050) | 0.696 |
| CRP (mg/L) | 0.000 (−0.001; 0.000) | 0.211 | 0.000 (0.000; 0.000) | 0.868 | 0.000 (−0.001; 0.000) | 0.395 |
| Gamma GT-S (IU/L) | 0.000 (0.000; 0.000) | 0.301 | 0.000 (0.000; 0.000) | 0.257 | 0.000 (0.000; 0.000) | 0.228 |

Note: *Denotes significance ($p < 0.05$).

Abbreviations: WaistC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; BI, blood insulin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; Gamma GT, gamma glutamyl transferase.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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