Are Glucose and Insulin Metabolism and Diabetes Associated with Migraine? A Community-Based, Case-Control Study

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Aims: To investigate the association between glucose and insulin metabolism and migraine, as well as between diabetes mellitus (DM) and migraine, at a Chinese community level. **Methods:** A community-based, case-control study was performed in Heihe City, China. A survey was conducted door to door by eight trained investigators. Migraine was diagnosed using the International Classification of Headache Disorders (ICHD-III) beta criteria. A total of 2,023 participants completed a questionnaire, underwent a physical examination, and donated fasting blood. After excluding 191 with reported DM, 1,832 participants were included in the study. Of these, 86 participants with migraine and 95 without migraine participated in a 75-g oral glucose tolerance test. Glycosylated hemoglobin (HbA1c) was assessed at 0 minutes and serum glucose and insulin levels were measured at 0, 30, 60, and 120 minutes after glucose loading. Data with skewed distributions were compared using rank sum test, and the associations between DM and migraine were analyzed with logistic regression. **Results:** There were no significant differences in HbA1c, homeostatic model assessment-insulin resistance (HOMA-IR), β-cell function index of HOMA, or quantitative insulin sensitivity check index (QUICKI) between the participants with migraine and without migraine. When participants without migraine were classified into DM, prediabetes, and normal glucose subgroups and compared with the corresponding migraine subgroups, participants in the migraine subgroup with prediabetes presented higher levels of fasting insulin and HOMA-IR and a lower QUICKI than the nonmigraine subgroup with prediabetes. Moreover, DM was negatively associated with migraine in the 181 subjects who participated in the OGTT; however, no association was found when all 1,832 participants were considered. **Conclusion:** Insulin resistance seems to exist in individuals with both migraine and prediabetes, and there is a possible negative association between DM and migraine. *J Oral Facial Pain Headache 2017;31:240–250. doi: 10.11607/ofph.1843*

Keywords: *association, diabetes mellitus, insulin resistance, migraine*

Migraine is a highly prevalent condition that presents a heavy burden on the patient, and its cause remains unclear.[1,2] Cavestro et al[3] reported that patients with migraine presented significantly higher insulin levels than control patients during an oral glucose tolerance test (OGTT). Adashi et al[4] suggested that insulin could stimulate the release of gonadotropin in rats, and Sachs et al[5] reported that beta-estradiol and progesterone, which can be stimulated by gonadotropin, enhanced the repetition rate and the amplitude of the cortical spreading depression wave, which has been reported as one of the possible mechanisms of migraine.[6] Additionally, some studies have shown that the use of oral contraceptives, which can induce hyperinsulinism and hypoglycemia, can increase frequency and worsen headache severity in subjects with migraine.[7,8] Other studies have indicated that polymorphisms in the insulin receptor gene are associated with migraine and that migraine is likely to occur in patients with low activation of the insulin receptor.[9–11] Therefore, it could be suggested that insulin and glucose metabolism are related to migraine.

OGTT is a widely utilized test for the assessment of glucose and insulin metabolism among patients.[12] However, the number of studies using OGTT to investigate the association between glucose and insulin metabolism and migraine is limited, and these studies have presented inconsistent results.[3,13] The study conducted by Cavestro et al showed that glucose and insulin levels in migraine patients during OGTT were all higher than those in healthy controls[3]; however, Rainero et al found that insulin levels during OGTT were comparable between migraine and control participants.[13] Furthermore, in studies investigating the association between glucose and insulin metabolism and migraine, patients with migraine were mainly recruited from headache centers, and the manner to deal with participants with newly diagnosed diabetes mellitus (DM) and prediabetes has not been clarified.[3,13–15] Given the high prevalence of diabetes and prediabetes in the general population in China,[16] it is necessary to clarify the association between glucose and insulin metabolism and migraine in different glucose metabolism states. Furthermore, while several studies have suggested that DM is negatively associated with migraine,[17–19] inconsistent results have been reported.[20,21] Until now, few studies on the association between migraine and glucose and insulin metabolism have been conducted in China, particularly at the community level. Therefore, a community-based, case-control study was conducted to evaluate the association between glucose and insulin metabolism and migraine, as well as between DM and migraine, in Heihe City, north Heilongjiang province, China.

Materials and Methods

Participants

Permanent residents (defined as residents living in Heihe city for at least 1 year) between the ages of 18 and 65 years were included in the study. Participants who reported to have a history of DM or took medicine that interfered with glucose or insulin metabolism were excluded. All participants provided informed consent, and the study was approved by the Ethics Committee of Harbin Medical University (No. 2014001).

Questionnaire

A questionnaire was used that comprised six parts: *(1)* informed consent; *(2)* sociodemographics of participants, including age, sex, nationality, marital status, education level, and total household income; *(3)* lifestyle (ie, alcohol consumption and smoking habits); *(4)* Chinese version of ID-Migraine[22]; *(5)* migraine characteristics (ie, course, frequency, and duration of migraine attack); and *(6)* medical history (ie, history of hypertension and family history of DM).

Study Design

Heihe City is located on the south bank of the Amur River on the Russian border in the north Heilongjiang province, China, and experiences long and bitter cold winters.[23] Heihe City is a multiethnic gathering place including 38 minor nationalities (mainly the Manchu and Daur nationalities), which account for approximately 2.90% of the general population.[24]

This was a community-based, case-control study comprising two stages. The selection procedure for participants is shown in Fig 1. The first stage included two parts. The first part, for the rural participants, was conducted between December 20, 2014 and March 6, 2015. It comprised a typical investigation, mainly focused on the Daur and Manchu nationalities. All of the residents (both Han and minority nationalities) were from 7 Daur nationality villages and 5 of 11 Manchu nationality villages in the Aihui district (villages that had 300 or more residents were asked to participate in this investigation). The survey was performed door to door by eight trained investigators comprising four medical interns, two nurses, one neurologist who worked in the Department of Neurology at the First People's Hospital in Heihe City (Y.D.), and one PhD candidate majoring in epidemiology (X.W.). All the investigators were trained in all of the content of the questionnaire, including the Chinese version of the ID-Migraine.[22] During the survey, the investigators were required to transfer the participants who had reported to experience two or more headaches in the past 3 months to the neurologist for further diagnosis. The diagnosis of migraine was made by the neurologist with the International Classification of Headache Disorders (ICHD-III) beta criteria.[25] After a fasting period of 10 hours, 5 mL of blood were collected from each participant in the village committee building.

The second part of the first stage, for urban participants, was conducted between April 9 and June 20, 2015, with residents from 5 of 12 neighborhood communities (mainly Han and Hui nationalities). Residents were randomly selected using a simple random sampling method with the randomization process of SAS (SAS Institute Inc) according to the number of residents who completed a questionnaire, underwent a physical examination, and produced fasting blood samples for fasting blood glucose (FBG) and blood lipid assessments at the health examination center of the First People's Hospital, Heihe City.

In the second stage, all participants who had been diagnosed with or without migraine using

ICHD-III criteria[25] in the first stage were requested to fast overnight for 10 hours to undergo OGTT the next morning.[12] The 5-mL blood samples were collected at 0, 30, 60, and 120 minutes after 75-g glucose loading for blood glucose and insulin level measurements. Glycosylated hemoglobin (HbA1c) was also assessed at the same time.

Participants with and without migraine were further divided into three subgroups according to the DM diagnosis and classification criteria proposed by the American Diabetes Association (ADA) in 2010[26]:

1. Undiagnosed DM subgroup (newly diagnosed as DM: participants with FBG ≥ 7.0 mmol/L, 2-hour blood glucose in OGTT ≥ 11.1 mmol/L, or HbA1c ≥ 6.5%)
2. Prediabetes subgroup (FBG: 5.6–6.9 mmol/L, 2-hour blood glucose in OGTT 7.8–11.1 mmol/L, or HbA1c 5.7% to 6.5%)[26]
3. Normal glucose level subgroup (participants with FBG < 5.6 mmol/L, 2-hour blood glucose in OGTT < 7.8 mmol/L, and HbA1c < 5.7%)

Body Measurement Indicators

Anthropometric data included height, weight, and blood pressure. Body mass index (BMI) was calculated by the formula: weight (kg)/(height[m]^2).

Laboratory Analyses

Blood glucose, HbA1c, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were measured on an OLYMPUS AU640 automatic biochemical analyzer (OLYMPUS OPTICAL Co, Ltd). Insulin levels were evaluated using the MAGLUMI 2000 Plus (SNIBE Co, Ltd) via the chemiluminescent immunoassay method.

Insulin resistance was evaluated using the fasting-based indicator of homeostatic model assessment-insulin resistance (HOMA-IR; FBG × serum insulin/22.5),[27] β-cell function index of HOMA (HOMA-B; 20 × serum insulin/[FBG − 3.5]),[28] and quantitative insulin sensitivity check index (QUICKI; 1/[log insulin + log blood glucose]).[29] Two-hour glucose and insulin areas under the curve (△AUC) were calculated as follows: 0.25 × glucose (insulin) at 0 minutes, + 0.5 × glucose (insulin) at 30 minutes, + 0.75 × glucose (insulin) at 60 minutes, + glucose (insulin) at 120 minutes.

Statistical Analyses

Data with skewed distributions were described as medians ± quartile deviations and compared using the Wilcoxon rank sum test or Kruskal-Wallis test. For multiple group comparisons between skewed data, these variables were first converted using rank transformation and compared using one-way analysis of variance (ANOVA). The differences between groups were tested by the Student–Newman–Keuls test. Repeated measures of ANOVA were performed for group comparisons of total glucose and insulin levels. Categorical variables were presented as counts and percentages, and differences between groups were evaluated using Pearson's chi-square test. In addition, the association between DM and migraine was analyzed using logistic regression. Statistically significant differences were accepted at $P < .05$. All statistical analyses were conducted with SAS statistical software, version 9.1 (SAS Institute Inc).

Results

Representativeness of OGTT Participants

A total of 2,023 participants completed the questionnaire, underwent the physical examination, and donated fasting blood. After excluding 191 with history of DM, 1,832 subjects were included in the study. Of these, 125 were diagnosed as having migraine and 1,707 were diagnosed as nonmigraine control (90 with nonmigraine headache and 1,617 with no headache). Ultimately, 86 of the subjects with migraine (migraine with aura = 2, migraine without aura = 82, chronic migraine = 2) and 95 of the subjects without migraine participated in the OGTT (Fig 1).

There were no significant differences in the proportions of undiagnosed DM, prediabetes, and normal glucose subgroups between the total nonmigraine population (n = 1,707) and the nonmigraine patients who participated in the OGTT (n = 95) (defined as the control group) ($\chi^2 = 4.4$; V = 2; $P = .11$) (Figs 2a and 2b). In regard to participants with migraine, there were also no differences in the distribution of these three subgroups between the total migraine group (n = 125) and those with migraine who participated in the OGTT (n = 86) ($\chi^2 = 0.5$; V = 2; $P = .77$) (Figs 2c and 2d).

When the demographic characteristics and body measurement indicators were compared between the control group and the total nonmigraine population, there were no significant differences in the factors, except for mean age and education level (see Appendix 1 at https://pan.baidu.com/s/1nvDH5cl). In addition, there were no differences in the factors between the total migraine group and those with migraine who participated in the OGTT (Appendix 2 at https://pan.baidu.com/s/1nvDH5cl).

Basic Demographic and Clinical Features in Selected Participants with Migraine and Controls

The data analysis procedure is shown in Fig 3.

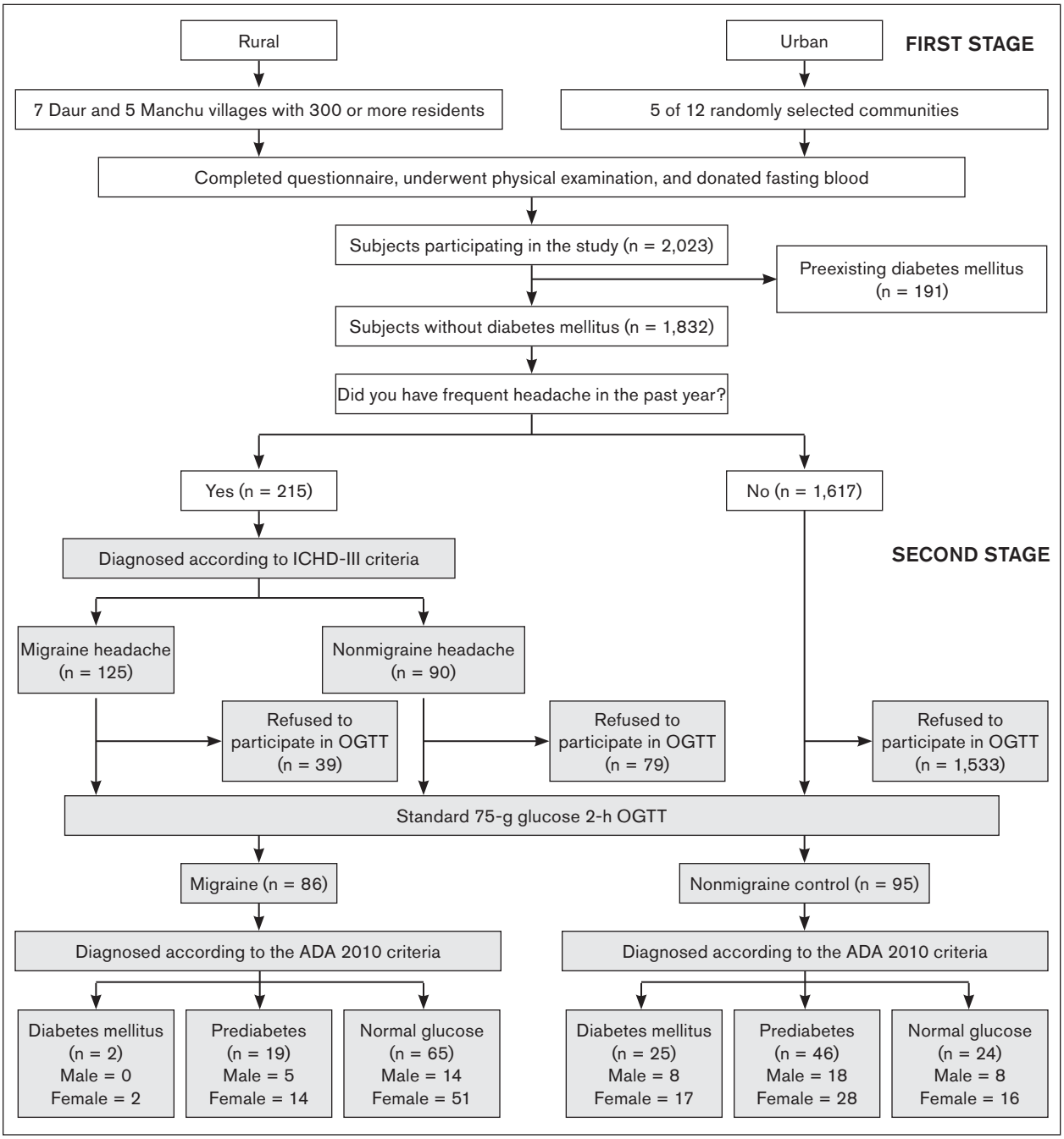

Fig 1 Flowchart of the selection procedure.

Total Migraine and Control Groups

The proportion of women was statistically higher in the migraine group than in the control group, and the proportions of participants with a history of hypertension and family history of DM were lower in the migraine group than in the control group. The waist circumference (WC), BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were significantly higher in the control group; however, the HDL-C was significantly higher in the migraine group (Table 1).

Total Migraine Group and Different Control Subgroups

The control subgroup with undiagnosed DM presented significantly higher WC, SBP, DBP, TG, and LDL-C than participants in the total migraine group. No significant differences were found in the other indices among these groups.

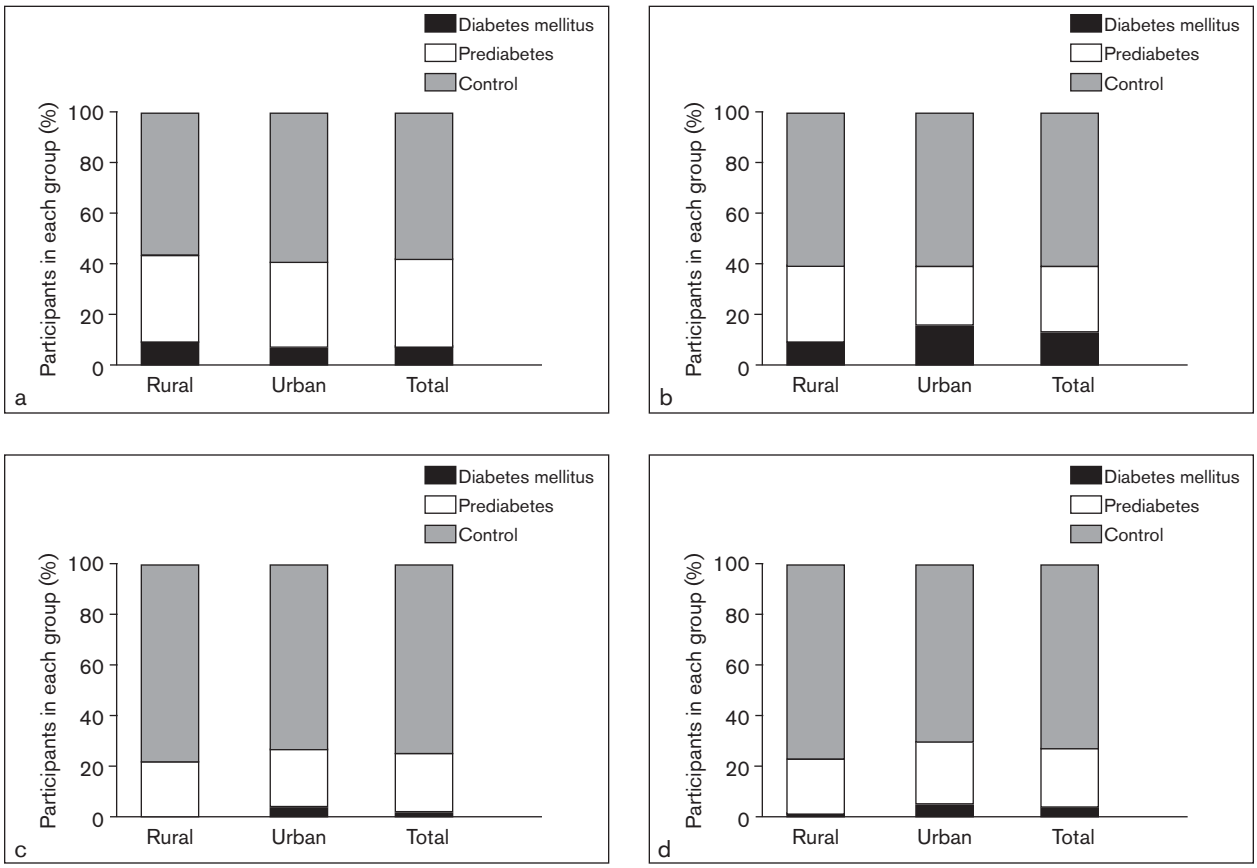

Fig 2 The proportions of undiagnosed DM, prediabetes, and normal glucose in total population and in the participants in the OGTT. *(a)* Refers to the participants without frequent headache (n = 1,617) and the ones with nonmigraine headache (n = 90). *(b)* Refers to 11 of 90 participants without frequent headache and 84 with nonmigraine headache who participated in the OGTT. *(c)* Refers to the participants who were diagnosed as migraine according to the ICHD-III criteria (n = 125). *(d)* Refers to the 86 migraineurs who participated in the OGTT.

Corresponding Subgroups Between Migraine and Control Groups

In the migraine subgroup with undiagnosed DM, subgroup analyses showed the SBP, DBP, and TG were significantly lower and the HDL-C was significantly higher than in the control subgroup with undiagnosed DM. No differences in other indices were found between any other corresponding subgroups. Results stratified by nationality (Han and minor nationality) and living areas (rural and urban) of the participants are shown in Appendices 3–6 (at https://pan.baidu.com/s/1nvDH5cl).

Glucose and Insulin Metabolism During OGTT in Migraine and Control Groups

When diagnosed according to OGTT and ADA criteria, the distribution of undiagnosed DM (10.5%), prediabetes (53.5%), and normal glucose (36.0%) in the migraine group was different from that in the control group (DM = 26.3%; prediabetes = 48.4%; normal glucose = 25.3%) ($\chi^2 = 8.0$; V = 2; $P = .018$), and the proportion of undiagnosed DM in the migraine group was significantly higher than that in the control group ($\chi^2 = 6.3$; V = 1; $P = .01$).

Total Migraine and Control Groups

The total blood glucose levels during OGTT were significantly higher in the control group than in the migraine group; however, no significant differences were found in total serum insulin levels during OGTT between these two groups. Two-hour glucose △AUC in the migraine group was significantly lower than in the control group; however, there were no differences in 2-hour insulin △AUC or HbA1c.

Total Migraine Group and Different Control Subgroups

Subgroup analyses showed that total blood glucose levels, total insulin levels, 2-hour glucose △AUC, 2-hour insulin △AUC, and HbA1c in the migraine group were significantly lower than those in the control subgroup with undiagnosed DM but similar to those in the prediabetes subgroup and significantly higher than those in the normal glucose subgroup. The results were consistent with Han subgroups (Appendix 7 at https://pan.baidu.com/s/1nvDH5cl),

minority nationality (Appendix 8 at https://pan.baidu.com/s/1nvDH5cl) subgroups, and those living in urban areas (Appendix 10 at https://pan.baidu.com/s/1nvDH5cl).

Corresponding Subgroups Between Migraine and Control Groups

There were no differences in the total glucose and insulin levels between the migraine and control DM and normal glucose subgroups. The migraine subgroup with prediabetes had significantly higher fasting and 30-minute insulin levels than in the control group; however, no differences were found in the other indices between any of the groups. These factors did not significantly differ in the comparisons between subgroups when stratified by participants' nationalities and places of residence (Appendices 7–10, at https://pan.baidu.com/s/1nvDH5cl).

Fasting Blood and Indicators of Insulin Resistance in Migraine and Control Groups

Total Migraine and Control Groups

The glucose level, insulin level, HOMA-IR, HOMA-B, and QUICKI values showed no significant differences between the migraine and control groups (Table 2).

Migraine Group and Different Control Subgroups

The fasting glucose and 2-hour glucose AUC, fasting insulin and 2-hour insulin AUC, HbA1c, and HOMA-IR in participants with migraine were significantly lower than in control participants with undiagnosed DM, similar to those in the control subgroup with prediabetes, and significantly higher than those in the control subgroup with normal glucose Furthermore, QUICKI in the migraine group was significantly higher than in the control subgroup with undiagnosed DM, similar to the control subgroup with prediabetes, and significantly lower than in the control subgroup with normal glucose. However, the HOMA-B was not different among the groups. These results were consistent with those for participants living in urban areas (Appendix 10 at https://pan.baidu.com/s/1nvDH5cl).

Corresponding Subgroups Between Migraine and Control Groups

The migraine subgroup with prediabetes presented a significantly higher HOMA-IR and lower QUICKI than the corresponding control subgroup. However, no differences were found between the other subgroups (Table 2). These factors did not significantly differ in the subgroup comparisons when stratified by participants' nationalities and places of residence (Appendices 7–10 at https://pan.baidu.com/s/1nvDH5cl).

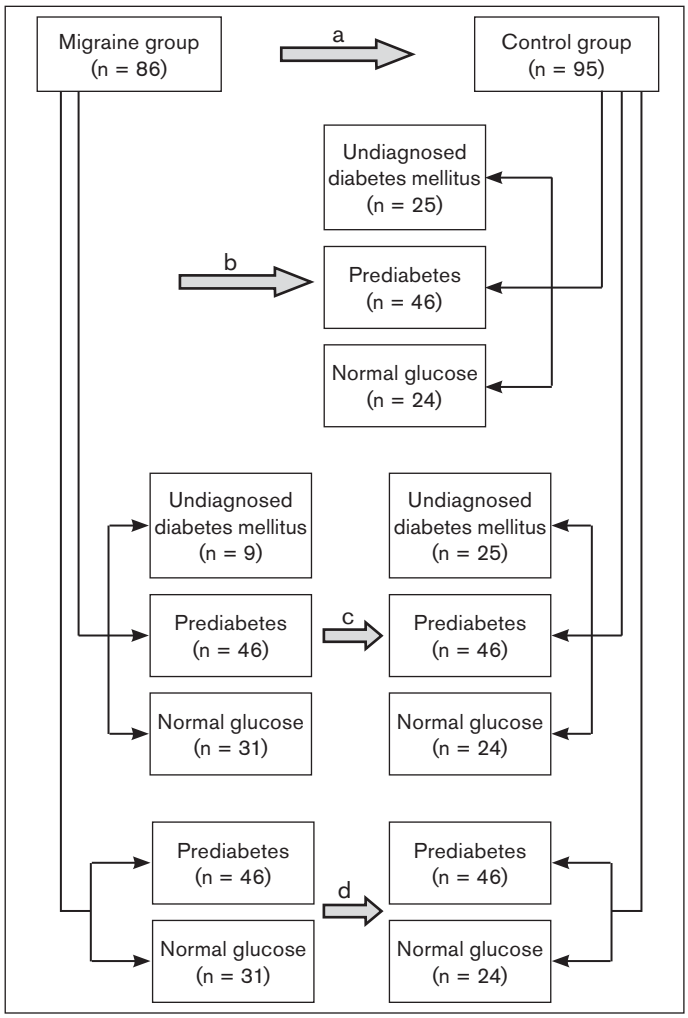

Fig 3 Detailed data analysis procedure. Data analyses were conducted in four steps: *(a)* Comparing total migraine (n = 86) and total control groups (n = 95); *(b)* Comparing total migraine group with control group stratified into undiagnosed DM (n = 25), prediabetes (n = 46), and normal glucose control (n = 24) subgroups; *(c)* Comparing migraine and control groups, stratifying both into undiagnosed DM, prediabetes, and normal glucose subgroups; *(d)* Comparing migraine and control groups after excluding participants with undiagnosed DM.

Migraine and Control Groups After Excluding Participants with Undiagnosed DM

When participants with undiagnosed DM were excluded, no differences were found in total glucose (P = .61) and insulin levels (P = .11) during OGTT or in the indicators of insulin resistance between the total migraine (n = 77) and control groups (n = 70). When the control group was classified into prediabetes and normal glucose subgroups, the glucose levels, HbA1c, and HOMA-IR values in the migraine group were similar to those in the control subgroup with prediabetes and significantly higher than those in the control subgroup with normal glucose (Table 3). These results were consistent when stratified by nationalities and by participants that lived in urban areas (Appendices 11–14 at https://pan.baidu.com/s/1nvDH5cl).

Table 1 Demographic and Clinical Characteristics of Migraine and Nonmigraine Control Participants

	Diabetes mellitus			Prediabetes		
	Control (n = 25)	Migraine (n = 9)	*P* value	Control (n = 46)	Migraine (n = 46)	*P* value
Female, n (%)	17 (68.0)	6 (66.7)	.94	28 (60.9)	36 (78.3)	.070
Married, n (%)	25 (100.0)	9 (100.0)	1.00	45 (97.8)	45 (97.8)	1.00
Nationality, n (%)			.21			.12
Ethnic Han	17 (68.0)	4 (44.4)		35 (76.1)	28 (60.9)	
Others	8 (32.0)	5 (55.6)		11 (23.9)	18 (39.1)	
Education level, n (%)			.89			.91
Middle school or less	4 (16.0)	2 (22.2)		10 (21.7)	11 (23.9)	
High school	7 (28.0)	2 (22.2)		19 (41.3)	20 (43.5)	
College or higher	14 (56.0)	5 (55.6)		17 (37.0)	15 (32.6)	
Household income (RMB/month), n (%)			.96			.031
< 2,000 yuan	9 (36.0)	3 (33.3)		14 (30.4)	26 (56.5)	
2,000–3000 yuan	7 (28.0)	3 (33.3)		21 (45.7)	11 (23.9)	
≥ 3,000 yuan	9 (36.0)	3 (33.4)		11 (23.9)	9 (19.6)	
Smoking habit, n (%)	6 (24.0)	1 (11.1)	.41	13 (28.3)	12 (26.1)	.81
Drinking habit, n (%)	7 (28.0)	0 (0.0)	.075	17 (37.0)	14 (30.4)	.51
Hypertension, n (%)	11 (44.0)	1 (11.1)	.077	15 (32.6)	10 (21.7)	.24
Family history of DM, n (%)	5 (20.0)	1 (11.1)	.55	6 (13.0)	2 (4.35)	.14
Age (y)	48.0 ± 4.0	55.0 ± 9.0	.28	51.5 ± 14.0	52.5 ± 10.0	.29
WC (cm)	91.0 ± 15.0[e]	88.0 ± 14.0	.08	90.0 ± 17.8	85.0 ± 16.0	.049
BMI (kg/m2)	24.8 ± 3.38	23.9 ± 1.2	.67	25.1 ± 6.0	23.6 ± 4.6	.086
SBP (mm/Hg)	140.0 ± 25.0[c,d,e]	105.0 ± 20.0	< .001	130.0 ± 28.0[b]	130.0 ± 20.0	.86
DBP (mm/Hg)	90.0 ± 14.0[e]	70.0 ± 10.0	< .001	80.0 ± 10.0	80.0 ± 20.0	.46
TC (mmol/L)	5.5 ± 1.6[c,d]	4. 9 ± 1.3	.21	4.9 ± 1.2[b]	5.3 ± 1.2	.20
TG (mmol/L)	1.7 ± 0.9[c,d,e]	1.0 ± 0.3	.033	1.2 ± 0.6[b]	1.2 ± 0.9	.74
LDL-C (mmol/L)	3.6 ± 1.0[c,d,e]	2.7 ± 0.9	.11	3.1 ± 1.1[b]	3.1 ± 0.9	.48
HDL-C (mmol/L)	1.3 ± 0.3	1.5 ± 0.1	.043	1.4 ± 0.3	1.4 ± 0.5	.27
Course of headache (y)		22.0 ± 15.0			15.5 ± 14.0	
Headache frequency (no. per mo)		3.0 ± 3.0			3.0 ± 2.0	
Headache duration (h)		8.0 ± 8.0			8.0 ± 5.0	

RMB = renminbi; DM= diabetes mellitus; WC = waist circumference; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; TG = triglyceride; LDL-C = low-density lipoprotein-cholesterol; HDL-C = high-density lipoprotein-cholesterol.
[a]*P* value for the comparison between migraine and control groups after classifying the control group into undiagnosed DM, prediabetes, and normal glucose subgroups.
[b]*P* < .05 when compared to the undiagnosed DM control subgroup in control.
[c]*P* < .05 when compared to the prediabetes subgroup in control.
[d]*P* < .05 when compared to the normal glucose subgroup in control (n = 24).
[e]*P* < .05 when compared to the total migraine group (n = 86).

Table 2 Difference in Indicators of Glucose and Insulin Metabolism and Insulin Resistance Between

	Diabetes mellitus			Prediabetes		
	Control (n = 25)	Migraine (n = 9)	*P* value	Control (n = 46)	Migraine (n = 46)	*P* value
Glucose level (mmol/L)						
0 min	6.5 ± 1.7[c,d,e]	5.3 ± 1.1	.062	5.4 ± 0.7[b,d]	5.5 ± 0.7	.29
30 min	11.6 ± 2.6[c,d,e]	9.5 ± 3.1	.009	8.7 ± 2.5[b]	8.4 ± 2.0	.73
60 min	13.2 ± 3.4[c,d,e]	11.8 ± 6.1	.25	10.0 ± 5.2[b,d]	8.2 ± 3.1	.084
120 min	13.0 ± 3.3[c,d,e]	11.7 ± 6.6	.27	7.0 ± 2.7[b,d]	6.7 ± 2.2	.52
2-h glucose △AUC (mmol/L/min)	29.6 ± 8.0[c,d,e]	26.6 ± 11.4	.15	19.4 ± 8.5[b,d]	19.0 ± 4.7	.31
Insulin level (uIU/ml)						
0 min	12.2 ± 4.1[c,d,e]	11.8 ± 4.0	.58	7.8 ± 2.2[b]	9.3 ± 4.1	.034
30 min	49.4 ± 25.8[c,d]	42.1 ± 26.5	.076	36.4 ± 19.6[b]	46.5 ± 31.3	.035
60 min	72.4 ± 54.1[c,d,e]	58.7 ± 12.7	.14	52.8 ± 32.5[b]	48.3 ± 41.5	.59
120 min	57.3 ± 44.3[c,d,e]	62.9 ± 46.1	.79	33.1 ± 18.6[b]	33.6 ± 35.7	.27
2-h insulin △AUC (uIU/mL/min)	141.6 ± 61.6[c,d,e]	134.9 ± 28.5	.38	89.7 ± 42.0[b]	97.8 ± 69.2	.14
HbA1c (%)	6.4 ± 0.7[c,d,e]	6.7 ± 1.0	.51	5.8 ± 0.4[b,d]	5.8 ± 0.5	.59
HOMA-IR	3.4 ± 1.6[c,d,e]	2.6 ± 1.6	.17	1.8 ± 0.4[b]	2.1 ± 1.0	.010
HOMA-B	88.3 ± 51.1	95.5 ± 43.4	.16	90.5 ± 45.8	91.6 ± 56.1	.67
QUICKI	0.3 ± 0.0[c,d,e]	0.3 ± 0.0	.17	0.4 ± 0.0[b]	0.3 ± 0.0	.010

△AUC = area under the response curve after 75-g glucose loading in the OGTT; HbA1c = glycosylated hemoglobin; HOMA-IR = homeostatic model assessment for insulin resistance; HOMA-B = homeostatic model assessment for beta-cell function; QUICKI = quantitative insulin sensitivity check index.
[a]*P* value for the comparison between migraine and control groups after classifying the control group into undiagnosed DM, prediabetes and normal glucose subgroups.
[b]*P* < .05 when compared to the undiagnosed DM subgroup in control (n = 25).
[c]*P* < .05 when compared to the prediabetes subgroup in control (n = 46).
[d]*P* < .05 when compared to the normal glucose subgroup in control (n = 24).
[e]*P* < .05 when compared to the total migraine group (n = 86).

(n = 181)						
Normal glucose			Total			
Control (n = 24)	Migraine (n = 31)	*P* value	Control (n = 95)	Migraine (n = 86)	*P* value	[a]*P* value
16 (66.7)	25 (80.7)	.24	61 (64.2)	67 (77.9)	.043	.21
23 (95.8)	30 (96.8)	.85	93 (97.9)	84 (97.7)	.92	.80
		.99			.16	.47
17 (70.8)	22 (71.0)		69 (72.6)	54 (62.8)		
7 (29.2)	9 (29.0)		26 (27.4)	32 (37.2)		
		.24			.32	.53
5 (20.8)	5 (16.1)		19 (20.0)	18 (20.9)		
7 (29.2)	16 (51.6)		33 (34.7)	38 (44.2)		
12 (50.0)	10 (32.3)		43 (45.3)	30 (34.9)		
		.033			.33	.071
14 (58.3)	12 (38.7)		37 (39.0)	41 (47.7)		
3 (12.5)	14 (45.2)		31 (32.6)	28 (32.6)		
7 (29.2)	5 (16.1)		27 (28.4)	17 (19.7)		
3 (12.5)	4 (12.9)	.96	22 (23.2)	17 (19.7)	.58	.45
8 (33.3)	10 (32.3)	.93	32 (33.7)	24 (27.9)	.40	.73
7 (29.2)	5 (16.1)	.25	33 (34.7)	16 (18.6)	.014	.057
5 (20.8)	2 (6.45)	.11	16 (16.8)	5 (5.8)	.021	.085
46.0 ± 12.5	49.0 ± 8.0	.20	50.0 ± 11.0	51.0 ± 12.0	.12	.16
87.0 ± 11.5	84.0 ± 10.0	.52	90.0 ± 17.0	84.5 ± 15.0[b]	.007	.03
25.0 ± 4.72	23.4 ± 5.9	.45	25.0 ± 5.1	23.6 ± 5.0	.044	.24
120.0 ± 31.0[b]	120.0 ± 12.0	.79	130.0 ± 30.0	122.5 ± 10.0[b]	.010	< .001
81.5 ± 15.0	80.0 ± 20.0	.77	80.0 ± 10.0	80.0 ± 20.0[b]	.020	.016
4.8 ± 1.2[b]	5.2 ± 1.2	.11	5.0 ± 1.5	5.2 ± 1.1	.39	.018
0.9 ± 0.5[b]	1.3 ± 0.6	.10	1.2 ± 1.0	1.2 ± 0.6[b]	.81	.003
2.9 ± 0.9[b]	3.0 ± 1.1	.20	3.2 ± 1.2	3.0 ± 1.0[b]	.95	.007
1.4 ± 0.3	1.4 ± 0.3	.61	1.4 ± 0.3	1.4 ± 0.3	.044	.15
	10.0 ± 13.0			14.5 ± 12.0		
	4.0 ± 1.0			3.0 ± 2.0		
	6.0 ± 4.0			6.0 ± 5.0		

Migraine and Control Groups						
Normal glucose			Total			
Control (n = 24)	Migraine (n = 31)	*P* value	Control (n = 95)	Migraine (n = 86)	*P* value	[a]*P* value
5.1 ± 0.4[b,c,e]	5.1 ± 0.6	.93	5.4 ± 1.0	5.3 ± 0.6[b,d]	.20	< .001
7.6 ± 2.5[b]	7.7 ± 1.7	.54	9.3 ± 3.3	8.2 ± 2.0[b]	.016	< .001
6.9 ± 3.5[b,c]	7.2 ± 2.7	.70	10.2 ± 5.6	7.8 ± 3.1[b]	.003	< .001
5.7 ± 1.1[b,c,e]	5.8 ± 1.1	.88	7.3 ± 4.3	6.4 ± 2.3[b,d]	.012	< .001
15.2 ± 4.1[b,c,e]	15.9 ± 3.3	.93	21.1 ± 10.4	17.7 ± 4.8[b,d]	.006	< .001
7.0 ± 3.5[b,e]	7.2 ± 2.4	.42	8.3 ± 4.1	8.5 ± 4.6[b,d]	.85	< .001
31.7 ± 20.3[b]	37.5 ± 23.9	.57	39.1 ± 24.1	43.1 ± 27.2	.47	.014
43.9 ± 43.2[b]	42.1 ± 39.1	.91	52.9 ± 38.0	46.1 ± 36.0[b]	.46	.006
21.7 ± 26.4[b]	23.5 ± 11.1	.69	34.0 ± 32.6	31.1 ± 34.4[b]	.86	< .001
67.3 ± 54.6[b,e]	81.0 ± 35.5	.43	99.3 ± 68.5	90.8 ± 52.9[b,d]	.87	< .001
5.4 ± 0.4[b,c,e]	5.4 ± 0.4	.68	5.8 ± 0.6	5.6 ± 0.5[b,d]	.14	< .001
1.6 ± 0.80	1.7 ± 0.5	.48	1.9 ± 1.0	2.0 ± 1.2[b,d]	.83	< .001
94.5 ± 42.3	103.1 ± 41.5	.77	90.2 ± 41.0	93.3 ± 46.8	.17	.15
0.4 ± 0.0[b,e]	0.4 ± 0.0	.48	0.4 ± 0.0	0.3 ± 0.0[b,d]	.83	< .001

Table 3 Difference in Indicators of Glucose and Insulin Metabolism and Insulin Resistance Between Migraine and Control Groups After Excluding Undiagnosed Diabetes Mellitus Subgroup (n = 147)

	Control					
	Total (n = 70)	Prediabetes (n = 46)	Normal glucose (n = 24)	Migraine (n = 77)	[a]*P* value	[b]*P* value
Glucose level (mmol/L)						
0 min	5.2 ± 0.6	5.4 ± 0.7[d]	5.1 ± 0.4[c,e]	5.3 ± 0.6[d]	.54	.020
30 min	8.4 ± 2.2	8.7 ± 2.5	7.6 ± 2.5	8.2 ± 2.0	.76	.23
60 min	7.8 ± 4.6	10.0 ± 5.2[d,e]	6.9 ± 3.5[c]	7.4 ± 2.9[c]	.23	.005
120 min	6.4 ± 2.4	7.0 ± 2.7[d]	5.7 ± 1.1[c]	6.2 ± 1.6	.48	.008
2-h glucose △AUC (mmol/L/min)	18.0 ± 7.4	19.4 ± 8.5[d]	15.2 ± 4.1[c]	17.4 ± 4.5	.38	.003
Insulin level (uIU/ml)						
0 min	7.5 ± 2.4	7.8 ± 2.2	7.0 ± 3.5	8.3 ± 3.5	.085	.10
30 min	32.8 ± 20.9	36.4 ± 19.6	31.7 ± 20.3	43.6 ± 27.5	.056	.11
60 min	51.1 ± 34.2	52.8 ± 32.5	43.9 ± 43.2	43.8 ± 32.6	.77	.50
120 min	28.6 ± 23.6	33.1 ± 18.6	21.7 ± 26.4	28.7 ± 25.0	.44	.17
2-h insulin △AUC (uIU/mL/min)	85.3 ± 47.8	89.7 ± 42.0	67.3 ± 54.6	87.5 ± 53.3	.26	.091
HbA1c (%)	5.6 ± 0.5	5.8 ± 0.5[d]	5.4 ± 0.4[c,e]	5.6 ± 0.4[d]	.85	< .001
HOMA-IR	1.8 ± 0.5	1.8 ± 0.4[d]	1.6 ± 0.80[c,e]	1.9 ± 0.9[d]	.070	.035
HOMA-B	91.4 ± 42.6	90.5 ± 45.8	94.5 ± 42.3	92.3 ± 46.8	.55	.50
QUICKI	0.4 ± 0.0	0.4 ± 0.0[d]	0.4 ± 0.0[c,e]	0.4 ± 0.0[d]	.070	.035

△AUC = area under the response curve after 75-g glucose loading in the OGTT; HbA1c = glycosylated hemoglobin; HOMA-IR = homeostatic model assessment for insulin resistance; HOMA-B = homeostatic model assessment for beta-cell function; QUICKI = quantitative insulin sensitivity check index.
[a]*P* value for the comparison between subjects with migraine and the total control group .
[b]*P* value for the comparison between migraine and control group after classifying the control group into prediabetes and healthy controls.
[c]*P* < .05 when compared to the prediabetes subgroup in control.
[d]*P* < .05 when compared to the normal glucose subgroup in control.
[e]*P* < .05 when compared to the total migraine group.

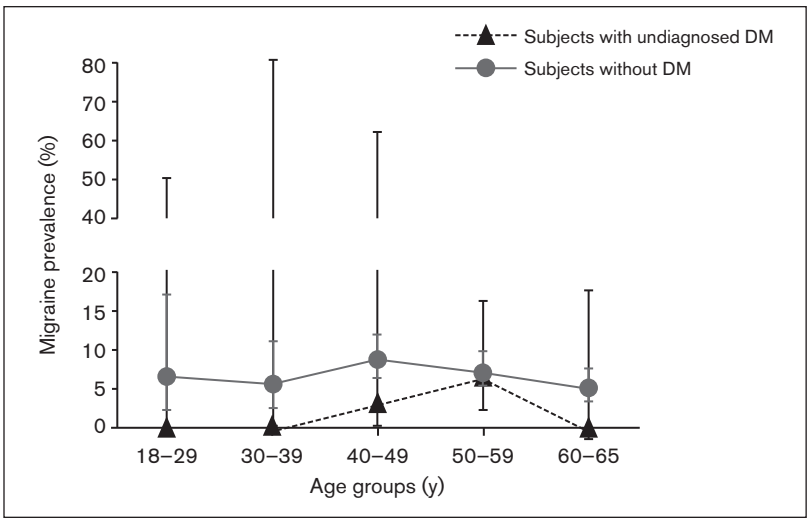

Fig 4 Migraine prevalence (%) and the 95% confidence interval (95% CI) related to age in those with and without undiagnosed DM. All of the 1,832 participants were grouped by fasting blood glucose (FBG) of ADA criteria and stratified into participants with DM (FBG ≥ 7.0 mmol/L) and those without DM (FBG < 7.0 mmol/L). Additionally, the participants were stratified by six age groups to investigate the migraine distribution between participants with and without DM.

Association between DM and Migraine

When participants were diagnosed by FBG in accordance with ADA criteria,[26] the prevalence of migraine in subjects with undiagnosed DM was lower than in those without DM; however, the association between DM and migraine was not statistically significant in all 1,832 participants (Fig 4, Table 4). In the participants of the OGTT, DM was negatively associated with migraine when diagnosed with FBG only and remained negatively associated when diagnosed with the FBG, HbA1c, and 2-hour blood glucose in OGTT.

Discussion

This was a community-based, case-control study conducted in Heihe City, Heilongjiang province of China. Results showed that the distributions of participants with newly diagnosed DM and prediabetes were similar between total participants and those with and without migraine who participated in the OGTT. Furthermore, there were no significant differences in demographic characteristics and body measurement indicators between these groups. Therefore, participants who un-

Table 4 Association Between Undiagnosed Diabetes Mellitus and Migraine

Items	Subjects with migraine (% of subjects in this group)	Subjects without migraine (% of subjects in this group)	Unadjusted ORs		[a]Adjusted ORs	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
Diagnosed by FBG in the general population						
Subjects without DM (n = 1,684) (Ref)	120 (7.1)	1,577 (92.9)	1.00	–	1.00	–
Subjects with DM (n = 128)	5 (3.7)	130 (96.3)	0.51 (0.20–1.26)	.14	0.66 (0.26–1.72)	.40
Diagnosed by FBG in subjects participating in OGTT						
Subjects without DM (n = 14) (Ref)	84 (50.3)	83 (49.7)	1.00	–	1.00	–
Subjects with DM (n = 167)	2 (14.3)	12 (85.7)	0.17 (0.04–0.76)	.021	0.13 (0.03–0.69)	.016
Diagnosed by FBG, 2-h blood glucose, and HbA1c in subjects participating in OGTT						
Subjects without DM (n = 34) (Ref)	77 (52.4)	70 (47.6)	1.00	–	1.00	–
Subjects with DM (n = 147)	9 (26.5)	25 (73.5)	0.33 (0.14–0.75)	.008	0.37 (0.15–0.93)	.035

OR = odds ratio; CI = confidence interval; DM = diabetes mellitus; FBG = fasting blood glucose; HbA1c = glycosylated hemoglobin; OGTT = oral glucose tolerance test; Ref = reference group.

[a]Adjusted by age, sex, nationality, body mass index, marital status, education level, household income, smoking intake, drinking intake, history of hypertension, and family history of diabetes mellitus.

derwent the OGTT presented a good representative sample for the total group of participants.

DM and prediabetes present impaired insulin sensitivity and are highly prevalent in the general population in China. In 2010, a national-based investigation suggested that in China, the prevalence of DM was 11.6% and of prediabetes was 50.1%.[16] Given these high prevalence rates, it is possible that hyperglycemia and impaired insulin sensitivity may exist to some extent in individuals with migraine and in control patients. Therefore, it is necessary to exclude those diagnosed with DM (due to the controlling of glucose levels by using drugs and other therapies) and to implement criteria for including subjects with impaired insulin sensitivity in both migraine and control groups to determine whether migraine is associated with impaired glucose and insulin metabolism. Accordingly, subgroup analyses were conducted in this study.

Previous studies have suggested subjects with migraine present higher HOMA-IR levels than controls.[30,31] However, the current results showed that insulin resistance only existed in the prediabetes subgroup in participants with migraine. The results also suggested that the phenomenon relating to those with migraine exhibiting higher HOMA-IR levels may be partly due to the higher proportion of prediabetes in the migraine group.

In addition, the results of this case-control study indicated that DM was negatively associated with migraine, regardless of diagnosis by FBG only or with the comprehensive indices including FBG, HbA1c, and 2-hour blood glucose in the OGTT, consistent with previous studies.[18,19] Furthermore, Blau and Pyke conducted a study of 36 participants with both diabetes and migraine and found that 5 of them expressed complete loss of migraine or marked reductions at the onset of diabetes, which further supports these results.[32] However, when participants were diagnosed by FBG only, the association between DM and migraine was not statistically significant in all 1,832 participants, which may be partly due to the high rate of underdiagnosis of DM by FBG only. Bao et al[33] suggested that when FBG is used as the only diagnostic criterion, the prevalence of DM would be underestimated by 26.0%, and undiagnosed DM would be underestimated by 40.0%. Moreover, the small sample size of the current study may also have played an important role in the insignificant association between DM and migraine.

This study compared the glucose and insulin metabolism indicators between migraine patients and different control subgroups including undiagnosed DM, prediabetes, and normal glucose control. To the best of the authors' knowledge, this is the first study to make this type of comparison. Results suggest that insulin resistance may only occur in the migraine subgroup with prediabetes. Further studies with larger sample sizes should be conducted to further confirm this conclusion. Although the sample size of the current study was larger than in previous related studies,[3,13,14,30] it was still relatively small, which partly limited statistical power for assessing the association between migraine and insulin resistance.

Also, it should be noted that this investigation was a case-control study, and so it could not infer a definite causal association between DM and migraine.

Conclusions

Insulin sensitivity seems to be impaired in individuals with migraine who also have prediabetes, and DM may be negatively associated with migraine. Additional studies with larger sample sizes are required to further confirm the associations between migraine and glucose and insulin metabolism, and between migraine and DM.

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