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Familial Aggregation and Determinants of Post Challenge Blood Glucose in Four Ethnic Populations

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Summary

We determine the familial aggregation and determinants of post challenge blood glucose (BG) in four ethnic populations. A national health survey was conducted in Malaysia in 1996. 18,372 subjects aged 30 years or older had post challenge BG measurements and another 846 subjects were pre-diagnosed to have diabetes on drug treatment. We imputed the BG of diagnosed diabetics by randomly selecting a value from the BG distribution of undiagnosed diabetics. Covariates of interest include ethnicity, gender, age, urban-rural residence, body mass index (BMI), physical activity, education, and household income. Ethnic and gender differences in mean BG persisted after adjustment for other covariates. Age and BMI were the only two factors with strong, positive and consistent effects on mean BG in all ethnic-sex groups. Family resemblance for BG as measured by intraclass correlation was small and homogenous across all ethnic groups and did not differ from resemblance in BG between spouses. In conclusion, BMI was the only consistent modifiable predictor of BG in all ethnic-sex groups. Environmental factors are probably more important than genetic factors as determinant of BG in the four ethnic populations studied.

Key Words: *Diabetes, Blood glucose, Risk factor, Familial aggregation, Family study, Cross-sectional population survey*

Introduction

Variation in blood glucose in a given population is the expression of various combinations of biological and environmental determinants. Environmental risk factors that had been studied include obesity, physical inactivity, diet, socio-economic status, urbanisation and modern lifestyle[1-3]. The effects of these factors are not always consistent in all studies. There are also well known differences in the prevalence of Type 2 diabetes mellitus (Type 2 DM) among ethnic groups [4]. This is attributable in part to differences in the genetic susceptibility to diabetes between populations. Further, it has been shown that the effect of environmental risk factors differs in different ethnic populations. For example, obesity has been described as the most powerful risk factor for Type 2 DM. Yet, among the five ethnic groups in South Africa[5], the two most obese groups- Bantu and Europid, had the lowest prevalence of diabetes. In another study of risk factors for diabetes in three Pacific populations[6], overweight was associated with diabetes in all females and Micronesian males but not in Melanesian and Indian males.

Family resemblance for blood glucose, due to shared gene or common environment or both, has also been investigated in several studies[7-10]. Given the known ethnic differences in the prevalence of diabetes presumably due in part to differences in genetic susceptibility, one might expect to observe differences in family resemblance for blood glucose between populations. To address this question would require a

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study on a random sample of families from several ethnic populations with known differences in the prevalence of diabetes in the same physical environment. A recent national health survey which was conducted in Malaysia presented us with this opportunity to examine the question. The health survey had used a two-stage cluster sampling design, the ultimate cluster was household. The vast majority of households not surprisingly consisted of family members, all of whom were sampled in the survey and most had blood glucose measurements taken. The adult population of Malaysia consists of four major ethnic groups - mainly Malay, Chinese, Indian and the indigenous people of Sabah and Sarawak on the island of Borneo. Previous study has shown marked differences in the prevalence of diabetes among them. The prevalence of diabetes varied from 13.9% in Indian, 7.7% in Chinese, 6.4% in Malay to 3.4% in the indigenous people of Sabah and Sarawak[23]. Type 1 diabetes mellitus (Type 1 DM) is rare in developing countries[4], including Malaysia[11]. We may reasonably assume that the diabetes ascertained in the survey is exclusively Type 2 DM.

The objective of this study is to describe the factors related to post challenge blood glucose concentration in the four ethnic populations in Malaysia. We further compare the family resemblance for post challenge blood glucose among the four ethnic groups.

Materials and Methods

Sample

A national health survey was conducted in Malaysia in 1996 to describe the health status, health related behaviour and health services utilisation for a representative sample of the population of Malaysia. An up to date and representative sampling frame for this population was provided by the frame used by the annual Labour Force survey conducted by the Department of Statistics[12]. The sampling frame was stratified by state and urban/rural residence. A stratified two-stage cluster sampling design with self-weighting sample was used to draw a sample of 17,995 households. However, only 13,025 (87%) of the households were contactable or responded. All residents of sampled households were included and yielded a sample size of 59903 individuals. For the survey component on blood glucose, 22,093 individuals aged 30 years or older from the four major ethnic groups were found to be eligible. 19,218 (87%) of them agreed to have their measurements taken or had evaluable measurements. For assessment of familial resemblance for blood glucose, we identify a sub-sample of 14,617 individuals from familial household. A familial household is defined as a household with two or more occupants who are related to one another. There were 6,525 familial households with a total of 14,617 individuals.

Survey procedure

During a home visit, the first hour was devoted to completing a questionnaire administered by an interviewer. The questionnaire included the following diabetes related items:

1. Have you ever been told by a doctor or other health personnel that you had high blood sugar (colloquially sweet urine disease)?
2. Have you ever been on medication (oral drug or insulin injection) for treatment of high blood sugar?
3. Are you still taking the medication now?

Other questionnaire information collected include number of years of formal education completed, household income, leisure and occupational activity.

After the interview, the respondent's weight was measured in light indoor clothing without shoes using a bathroom spring balance. Height was measured without shoes using a measuring tape attached to a rigid wall. Blood glucose was measured by a trained nurse using reflectance photometer (Accutrend, Boehringer Mannheim). All subjects without a medical history of diabetes (negative response to question 1 above) were approached for blood glucose measurement. Only a sub-sample of known diabetic patients had blood glucose measurement taken too. The procedure was explained and verbal permission obtained from the respondent prior to the examination. Seventy-five gram of glucose monohydrate powder was mixed with a glass of plain water and ingested by the respondent. The respondent then fast for 2 hours (only plain water allowed) before blood sample was obtained by finger prick for blood glucose (BG) measurement. All nurses attended centralised training on the standardised protocol for BG measurement. During the field survey, supervisors conducted a weekly check on the compliance with BG measurement protocol. The precision of the reflectance photometer was deemed satisfactory for survey use. Within-run coefficient of variation was 2-4% and correlation with measurements on plasma using conventional laboratory method varied between 0.98 and 0.99 (unpublished data).

Definition and classification

A known diabetic is defined as a subject with medical history of diabetes and is currently on anti-diabetic medication (answered positively to questions 1 to 3 above). Twenty-five subjects with diagnosed diabetes had BG measurement; the mean (minimum, maximum) was 18.3 mmol/L(11.3, 31.2). In comparison, the mean (minimum, maximum) of rest of the sample (n=18,372) without history of diabetes was 5.3 mmol/L (1.2, 31.5). This provides evidence for the validity of self-reported diabetes. The diagnostic criteria recommended by WHO[13] based on 2 hour post loading blood glucose value are used to classify subjects without medical history of diabetes as diabetic, impaired glucose tolerance (IGT) or normal. The WHO criteria for diabetes requires the 2 hour post loading capillary blood glucose (BG) to be $\geq$ 11.1 mmol/L, for IGT the BG should be <11.1 and $\geq$ 7.8 mol/L, and to be normal BG should be < 7.8 mmol/L. The body mass index (BMI) is defined as weight/height^2 (kg/m^2). Physical activity was graded active if a person engaged in a sporting activity at least three times a week, each lasting at least 15 minutes or a person's daily activity including occupational activity was sufficiently rigorous to cause sweating. Otherwise, physical activity was graded inactive. Residence in a gazetted area with population exceeding 10,000 people is defined as urban, otherwise the residence is rural [12].

Statistical methods

By design of the survey, the vast majority of known diabetic patients had no BG measurements taken, and in principle their true blood glucose concentrations prior to diagnosis and unmodified by treatment are unknowable. We therefore imputed their BG values by randomly selecting a value from the BG distribution of undiagnosed diabetic patients in the sample for each subject known to have diabetes without BG measurement. The method successfully preserved the BG distribution of the original sample. Blood glucose values were log transformed for analysis.

A multiple linear regression model was used to estimate the effects of covariates on the mean log(BG). The base model included only age and ethic-gender group (eg. Malay-male). Interaction between ethnicity and gender was expected based on a previous descriptive study in this population[10]. Subsequent modelling added BMI, physical activity (active/inactive), urban/rural residence, household income and education in that order of importance, based on the literature findings[4]. An additional quadratic term for a continuous covariate (age and BMI) was included only if it significantly improved model fit. To better assess the impact of the adjustment on ethnic and gender differences, the eight ethnic-gender groups were coded such that their regression coefficients have interpretation as deviation from the overall average BG. Persistent ethnic and gender differences in mean BG were observed after adjustment. Moreover, interaction between ethnicity, gender and the other covariates can be expected based on literature findings[4]. The regression analyses were therefore repeated separately for each ethnic-sex group.

To account for the cluster sampling, we obtained robust variance estimates using the Huber's[14] or sandwich estimator. Probability weighted estimation were used to account for differential sampling probability. The sampling weights were adjusted for household non-response[15] using adjustment cells formed by the state and urban/rural residence. Post stratification[15] was further used to adjust the weighted sample totals to known population totals for age, gender and ethnicity based on 1996 census for population projection.

The true BG values of known diabetic patients in the sample are not of course missing; they are more properly regarded as right-censored at 11.1 mmol/L. Hence, instead of imputation, we repeated the analyses by assuming the log transformed BG values are distributed as right-censored Normal. We did not find significant departure from the normality using the test described by Chesher and Irish[16]. Censored normal linear regression model[17] was used to estimate the effects of covariates on log (BG). Covariates included were as above for linear regression model. Results were similar to those obtained from linear regression analysis and did not change the conclusion drawn. The reason for not using censored regression model as the primary method of analysis is because the procedure cannot produce residuals required for assessment of family resemblance (see below).

We use intraclass correlation coefficient (r) to measure the degree of family resemblance for blood glucose. This was calculated by an analysis of variance (ANOVA) for a one-way random effect model[18]. We first regressed log BG values on age, age^2, sex, ethnicity, urban/rural residence, physical activity, BMI, education and income to obtain the adjusted BG values (residuals). Both the unadjusted BG and residuals were used in the analysis. We obtained r for entire family and for spouses only. There were too few siblings and

parent-offspring pairs for analysis. This is because the survey design excluded individuals below 30 years of age for BG measurement, and few individuals above aged 30 years or older in the sample were living with their parents or with their sibs.

Statistical significance is accepted at 5% level. No attempt was made to adjust for multiple comparisons. The above methods were implemented using programs written in STATA software package [19].

Results

Table I shows the characteristics of the entire sample. Ethnic differences in distribution of urban-rural residence, education and income conform to known socio-economic differences among these populations. Indian and Malay women were more obese, while the indigenous people of Sabah and Sarawak and Chinese women were the leanest. Indian men and women had the highest mean BG, while other indigenous men and women had the lowest BG.

Table II shows the characteristics of the family sub-sample. Second generation members (parents and their siblings) constituted the largest proportion of family members. The proportion of third generation members (children and their cousins) was small because those aged less than 30 were excluded for BG measurements by the design of the survey.

Table III shows the geometric mean BG in relation to age, urban-rural residence, BMI, physical activity, education and household income in each ethnic-gender sub-group. In all sub-groups, mean BG rose with increasing age and BMI. Those of rural residence and those who were physically active had lower mean BG. Trends in the mean BG in relation to education and income were inconsistent; it was apparent in some sub-groups but not others.

Table IV shows the results of modelling log BG as a function of age, gender and ethnicity, urban-rural residence, BMI, physical activity, education and household income. Clearly ethnic and gender differences in mean BG persisted after adjustment for other covariates, though the differences were attenuated. Indian men and women were still the 2 sub-groups with the highest mean BG. Gender differences in the other ethnic groups persisted, with men having lower mean BG.

Table V shows the results of separate regression analyses in each ethnic-sex group. Age and BMI were the only two factors to show strong, positive and consistent effects on mean BG in all sub-groups. The effect of BMI on mean BG was uniformly linear, as illustrated in Figures 1 and 2. The effects of urban-rural residence and physical activity were less consistent. All groups showed an association of urban residence with higher BG, the association however was not statistically significant in Indian women and other indigenous men. Likewise all groups except Chinese women showed an effect of physical activity, with physical inactivity being associated with higher BG. The effect however was only statistically significant in Malay and Chinese men. The effects of education and income were the least consistent. A significant trend with education was observed in Malay, Chinese and Indian men only. Effect of income on BG was positive in Malay men and women, and other indigenous men, but not at all in Chinese. In all groups, the regression models accounted for only a modest amount of the variance in log BG, ranging from 5% to 12%.

Table VI shows the intraclass correlations as the measure of family resemblance for BG. When all family members were considered, the intraclass correlations for adjusted BG were significant but small in all ethnic groups. It ranged from 0.07 to 0.16. Spousal correlations for adjusted BG were also significant in all groups and did not differ from the correlations for all family members. The familial correlations calculated for unadjusted BG for families as well as spouses were uniformly higher than those for adjusted BG, but did not differ from the pattern observed in adjusted BG.

Table I: Characteristics of the sample by ethnic group and gender

	Malay		Chinese		Indian		Other indigenous*		All	
	Men	Women	Men	Women	Men	Women	Men	Women	Man	Women
	n=4282	n= 4992	n=2446	n=2929	n=638	n=743	n=1483	n=1705	n=8849	n=10369
Mean age (SD), years	47(13)	46(13)	48(12)	47(13)	45(12)	45(12)	46 (13)	45(13)	47 (13)	46(13)
urban residence	44%	45%	76%	78%	71%	72%	33%	31	53%	54%
BMI <25	71%	62%	67%	72%	67%	60%	76%	71%	70%	66%
25-29.9	24%	26%	28%	22%	28%	28%	21%	22%	25%	25%
≥30	5%	11%	5%	6%	5%	12%	3%	7%	5%	9%
physically active	52%	17%	45%	19%	44%	25%	63%	28%	52%	20%
Number of years of education										
0-3 years	19%	37%	18%	35%	16%	36%	36%	61%	21%	40%
4-10 years	49%	39%	51%	41%	54%	48%	43%	29%	49%	39%
>10 years	32%	24%	31%	24%	30%	16%	20%	10%	30%	21%
Household income :										
less than RM 1000**	52%	56%	24%	32%	31%	39%	63%	69%	44%	50%
RM 1-1999	29%	26%	28%	27%	33%	31%	21%	18%	28%	25%
≥RM 2000	19	18%	48%	41%	36%	30%	16%	13%	28%	24%
Mean BG (SD)	5.5 (3.5)	5.8(3.5)	6.0(3.6)	6.1(3.4)	7.0(4.8)	6.6(4.3)	4.9 (2.3)	5.4(3.0)	5.7 (3.5)	5.9(3.5)
diabetic	6.4%	6.8%	7.5%	7.8%	15.8%	11.8%	2.6%	4.2%	6.8%	7.0%

* other indigenous refers to indigenous people of Sabah and Sarawak on island of Borneo

§ RM is Ringgit Malaysia, the local currency.

Table II: Characteristics of family sub-sample by ethnic group

	Malay n (%)	Chinese n (%)	Indian n (%)	Other indigenous n (%)
Sample size	7202 (49.3%)	4083 (27.9%)	1094 (7.5%)	2238 (15.3%)
Families	3329 (51.0%)	1749 (26.8%)	466 (7.1%)	981 (15.0%)
Spousal pairs	2927 (52.5%)	1432 (25.7%)	380 (6.8%)	831 (14.9%)
First generation members*	260 (4%)	275 (7%)	112 (10%)	149 (7%)
Second generation members §	6455 (90%)	3422 (84%)	893 (82%)	1920 (86%
Third generation members #	487 (7%)	386 (9%)	89 (8%)	169 (7%)
Male	3457 48%	1919 47%	503 46%	1052 47%
Diabetic	468 6.5%	314 7.7%	153 14.0%	76 3.4%
Mean age (SD)	46 (12)	48 (13)	45 (12)	46 (13)
Mean BMI (SD)	23.8 (4.3)	23.5 (3.9)	24.4 (4.5)	22.9 (4.1)
Mean BG (SD)	5.6 (3.4)	6.0 (3.5)	6.8 (4.6)	5.2 (2.6)

* first generation members refer to grandparents
§ second generation members refer to parents and their siblings
# third generation members refer to children and their cousins

Table III: Geometric mean BG (mmol/L) in relation to socio-demographic variables stratified by ethnicity and gender.

		Malay				Chinese				Indian				Other indigenous			
		Male		Female		Male		Female		Male		Female		Male		Female	
		Mean	(SE)	Mean	(SE)	Mean	(SE)	Mean	(SE)	Mean	(SE)	Mean	(SE)	Mean	(SE)	Mean	(SE)
Age group	30-39	4.6	-1	4.9	-1	4.8	-1	4.9	-1	5.2	-1	5.1	-1	4.4	-1	4.7	-1
	40-49	4.9	-1	5.2	-1	5.3	-1	5.4	-1	6.2	-1	5.7	-1	4.6	-1	5.1	-1
	50-59	5	-1	5.6	-1	5.6	-1	5.8	-1	7.4	-1.1	6.8	-1.1	4.7	-1	5	-1
	60-69	5.6	-1	5.9	-1	6.1	-1	6.8	-1	7.4	-1.1	6.5	-1.1	4.9	-1	5.5	-1
	≥ 70	5.2	-1	5.7	-1	6.4	-1.1	6.5	-1	5.7	-1.1	7.4	-1.1	5	-1	5.4	-1.1
Residence	urban	5.2	-1	5.3	-1	5.3	-1	5.6	1	6.1	-1	5.8	1	4.8	-1	5.1	-1
	rural	4.7	-1	5.1	-1	5.2	-1	5.4	1	5.8	-1	5.4	1	4.5	-1	4.9	-1
BMI	<25	4.7	-1	5	-1	5.1	-1	5.3	-1	5.9	-1	5.4	-1	4.5	-1	4.8	1
	25-29.9	5.4	-1	5.5	-1	5.5	-1	5.9	-1	6.3	-1	5.8	-1	4.9	-1	5.2	1
	≥ 30	6	-1	5.8	-1	6.3	-1.1	6.6	-1	6.8	-1.1	7.4	-1.1	5.2	-1.1	5.8	1
Physical	inactive	5.2	-1	5.3	-1	5.5	-1	5.5	-1	6.3	-1	5.9	-1	4.8	-1	5	1
activity	active	4.7	-1	5	-1	5.1	-1	5.6	-1	5.7	-1	5.2	-1	4.4	-1	4.8	1
Education	0-3 years	4.7	-1	5.4	-1	5.4	-1	5.9	-1	5.7	-1.1	6.1	-1	4.5	-1	5	-1
	4-10 years	4.9	-1	5.2	-1	5.2	-1	5.4	-1	6.3	-1	5.7	-1	4.5	-1	5	-1
	>10 years	5	-1	5	-1	5.3	-1	5.1	-1	5.7	-1	5.1	-1	4.8	-1	4.7	-1
Household	<RM1000	4.7	-1	5.1	-1	5.5	-1	5.6	-1	5.8	-1	5.5	-1	4.4	-1	4.9	-1
Income	RM1-1999	5	-1	5.4	-1	5.2	-1	5.4	-1	6.3	-1	5.9	-1	4.7	-1	5	-1
	≥ RM2000	5.3	-1	5.2	-1	5.3	-1	5.5	-1	6	-1	5.8	-1	5.1	-1	4.9	-1

Table IV: Regression coefficients from linear models predicting mean log(blood glucose, mmol/L) :

		Base model		All covariates model	
		$\beta x10^{-2}$	(95% CI $x10^{-2}$)	$\beta x10^{-2}$	(95% CI $x10^{-2}$)
n		19218		19218	
Age		1.8	(1.5 - 2.2)	1.7	(1.3 - 2.1)
age^2		-0.01	(-0.02 - -0.008)	-0.009	(-0.013 - -0.005)
Other indigenous	men	-13.4		-7.6	
	Women	-5.7	(-7.7 - -3.7)	-1.3	(-3.3 - 0.8)
Malay	men	-6.8	(-8.3 - -5.2)	-5.3	(-6.8 - -3.7)
	women	-0.7	(-2.1 - 0.8)	-1.5	(-3.0 - -0.03)
Chinese	Men	-0.1	(-2.1 - 1.8)	-2.3	(-4.3 - -0.4)
	Women	3.9	(2.2 - 5.6)	1.6	(-0.2 - 3.3)
Indian	Men	14.0	(10.2 - 17.7)	11.3	(7.6 - 15.0)
	Women	8.8	(5.6 - 12.1)	5.3	(2.1 - 8.4)
BMI				1.7	(1.5 - 1.9)
Physically active	no (ref)			0	
	yes			-4.2	(-5.8 - -2.7)
Residence	urban (ref)			0	
	rural			-5.6	(-7.3 - -4.0)
Household income	< RM1000 (ref)			0	
	RM1-1999			3.1	(1.3 - 4.9)
	≥ RM2000			2.7	(0.7 - 4.8)
Number of years of education	0-3 years (ref)			0	
	4-10 years			3.0	(1.1 - 4.9)
	>10 years			4.7	(2.4 - 7.0)
R^2		5.4%		9.4%	

Table 5: Regression coefficients from linear models predicting mean log(blood glucose, mmol/L) in 4 ethnic populations stratified by sex.

	Malay		Chinese		Indian		Other indigenous	
	$\beta x10^{-2}$	(95% CI $x10^{-2}$)	$\beta x10^{-2}$	(95% CI $x10^{-2}$)	$\beta x10^{-2}$	(95% CI $x10^{-2}$)	$\beta x10^{-2}$	(95% CI $x10^{-2}$)
Men								
n	4282		2446		638		8849	
age	0.64	(0.50 - 0.78)	0.91	(0.73 - 1.1)	5.81	(3.49 - 8.13)	0.51	(0.32 - 0.69)
age^2	.	. .	.	. .	-0.0048	(-0.00696 - -0.00264)	.	. .
Residence								
Urban (ref*)	0		0		0		0	
Rural	-8.25	(-11.40 - -5.13)	-2.73	(-7.28 - 1.82)	-0.64	(-10.40 - 9.10)	-3.80	(-8.68 - 1.08)
BMI	2.06	(1.69 - 2.44)	1.90	(1.36 - 2.45)	1.60	(0.54 - 2.65)	1.03	(0.45 - 1.62)
Physically active								
No (ref*)	0		0		0		0	
Yes	-4.03	(-6.93 - -1.13)	-5.88	(-9.73 - -2.03)	-7.99	(-16.80 - 0.87)	-3.14	(-7.98 - 1.70)
Number of years of education								
0-3 years (ref)	0		0		0		0	
4-10 years	5.30	(1.25 - 9.35)	6.79	(0.78 - 12.80)	13.3	(0.20 - 26.50)	3.78	(-1.59 - 9.15)
>10 years	7.13	(2.05 - 12.20)	8.90	(2.19 - 15.60)	6.60	(-7.57 - 20.80)	4.92	(-2.66 - 12.50)
Household income								
< RM1000 (ref)	0		0		0		0	
RM1-1999	3.77	(0.37 - 7.18)	-1.88	(-7.50 - 3.73)	7.81	(-2.51 - 18.10)	2.64	(-2.61 - 7.89)
≥RM2000	5.66	(1.35 - 9.97)	-0.77	(-6.18 - 4.65)	5.67	(-5.52 - 16.90)	9.25	(1.55 - 16.90)
R^2	8.60	. .	8.31	. .	10.4	. .	4.94	. .

	Malay		Chinese		Indian		Other indigenous	
	$\beta x10^{-2}$	(95% CI $x10^{-2}$)	$\beta x10^{-2}$	(95% CI $x10^{-2}$)	$\beta x10^{-2}$	(95% CI $x10^{-2}$)	$\beta x10^{-2}$	(95% CI $x10^{-2}$)
Women								
n	4992	. .	2929	. .	743 .	.	1705 .	.
age	1.90	(1.17 - 2.63)	0.85	(0.69 - 1.02)	1.02	(0.65 - 1.38)	0.62	(0.43 - 0.81)
age^2	-0.0012	(-0.0017 - -0.000612) .		. .	. .	. .	.	.
Residence								
- urban (ref*)	0		0		0		0	
- rural	-5.35	(-8.09 - -2.62)	-4.28	(-8.29 - -0.27)	-5.25	(-14.30 - 3.85)	-5.01	(-9.82 - -0.20)
BMI	1.44	(1.16 - 1.73)	1.58	(1.13 - 2.03)	2.05	(1.32 - 2.78)	1.62	(1.09 - 2.15)
Physically active								
- no (ref)	0		0		0		0	
- yes	-3.26	(-6.70 - 0.19)	0.562	(-3.60 - 4.72)	-4.21	(-0.18 - 3.34)	-3.62	(-7.99 - 0.75)
Number of years of education								
0-3 years (ref)	0		0		0		0	
4-10 years	-0.37	(-4.08 - 3.35)	3.08	(-1.42 - 7.59)	1.83	(-6.60 - 10.30)	3.77	(-1.16 - 8.71)
>10 years	0.78	(-3.69 - 5.25)	3.35	(-2.05 - 8.74)	-4.25	(-14.90 - 6.44)	2.58	(-4.88 - 10.00)
Household income								
< RM1000 (ref)	0		0		0		0	
RM1-1999	5.34	(2.18 - 8.51)	0.29	(-4.29 - 4.87)	7.65	(-0.58 - 15.90)	-1.22	(-7.34 - 4.90)
≥RM2000	1.34	(-2.48 - 5.15)	2.77	(-1.52 - 7.07)	3.51	(-5.64 - 12.70)	-2.41	(-8.99 - 4.16)
R^2	6.87	. .	9.11	. .	12.2 .	.	5.91 .	.

* ref : reference category in regression analysis

Table VI: Intraclass correlations (r) for post challenge blood glucose

	Malay		Chinese		Indian		Other indigenous	
Families								
n*	3329		1749		466		981	
r_{adj} # (95% CI)	0.10	(0.07 - 0.13)	0.10	(0.06 - 0.13)	0.07	(0.01 - 0.15)	0.16	(0.11 - 0.21)
r_{unadj} ## (95% CI)	0.12	(0.09 - 0.15)	0.09	(0.06 - 0.13)	0.10	(0.03 - 0.17)	0.18	(0.13 - 0.23)
Spouses								
n §	2927		1432		380		831	
r_{adj}# (95% CI)	0.12	(0.08 - 0.15)	0.09	(0.04 - 0.14)	0.10	(0.01 - 0.20)	0.17	(0.10 - 0.23)
r_{unadj} ## (95% CI)	0.15	(0.11 - 0.18)	0.13	(0.08 - 0.18)	0.16	(0.07 - 0.26)	0.19	(0.13 - 0.25)

* n : number of families; § n : number of spousal pairs

r_{unadj} : unadjusted log BG

r_{adj} : log BG adjusted for age, sex, ethnicity, BMI, physical activity, urban-rural residence, education and income.

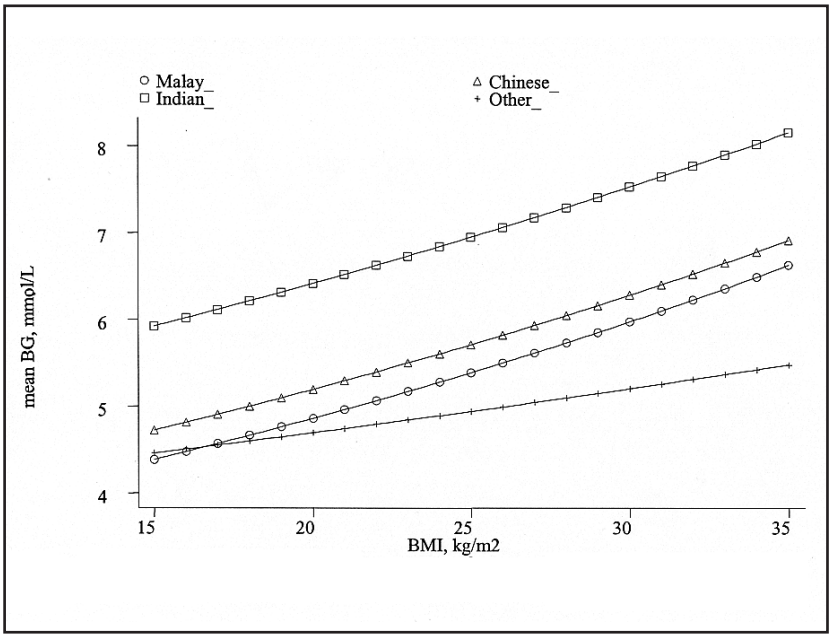

Figure I: Predicted geometric mean BG for men by ethnic group

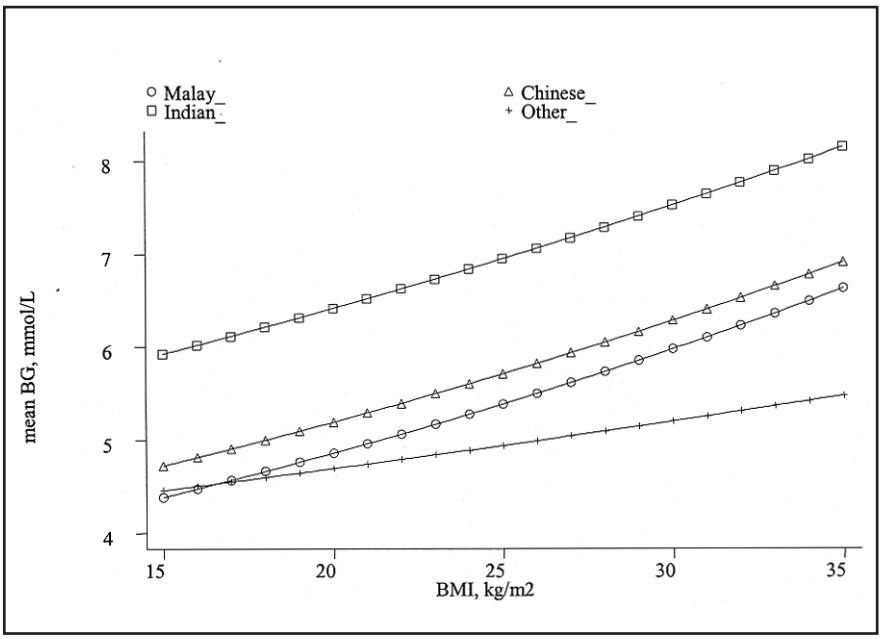

Figure II: Predicted geometric mean BG for women by ethnic group

Discussion

Caution is warranted in interpreting the results of this study. Firstly, this is a cross-sectional study. One cannot be certain that factors related to hyperglycaemia actually preceded the rise in BG. For example, subjects diagnosed with diabetes may move to the city to access better medical care, thus producing spurious association between urban residence and BG. This however is unlikely, and is mitigated by the high proportion (37%) of diabetic patients who were undiagnosed in the sample. On the other hand, diabetes can cause weight loss[20], or diabetic patients may be encouraged to exercise and to lose weight. This will lead to attenuation of the relation between BMI and BG, as well as between physical activity and BG. Secondly, there may be doubt about the validity of the results based on the analyses of imputed BG data. The BG values of diagnosed diabetic patients can be regarded as right censored at 11.1 mmol/L. Results of analyses using censored regression model were similar to those obtained using imputed BG values for diagnosed diabetic patients. Even had BG measurements been taken from diagnosed diabetic patients, their BG values certainly would not represent their true BG values prior to diagnosis and unmodified by treatment. Results of analyses based on such measurements would be biased. BG values drawn from the distribution of undiagnosed diabetics in the sample is the best guess of the true BG values of diagnosed diabetics prior to diagnosis. If anything, this is conservative as diagnosed diabetic patients may have greater degree of hyperglycaemia than undiagnosed diabetic patients. Thirdly, a potential selection bias that could cause the low familial correlations observed in the study is selective non-availability of diabetic family members. This affects all family studies that actually examined available family members rather than based on family history recall. For example, premature mortality of diabetic parent or grandparent is almost certain to occur. We repeated the analyses excluding all single parents and grandparents from the sample. The results were similar. Arguably, diabetic parents, siblings or even children could have selectively left their family household, typically because of employment or marriage. We think this is unlikely, if anything the opposite is more likely to be true. Finally, this study is based on secondary analyses of data collected for other purpose. We regard the study as purely exploratory and any conclusion drawn is at best preliminary.

This study has its strength. The sample studied is a probability sample that is representative of the target population. Response rate was high, and standard procedures were used to correct for possible non-response bias. The sample of families studied is also a representative random sample of families from the community. Most family studies have typically recruited volunteer families or families ascertained through diabetic probands in hospital. Such samples may contain disproportionate large number of families with multiply affected members because having a family member with diagnosed diabetes should improve the diagnostic opportunity for remaining undiagnosed diabetics in a family. Secondly, we have used BG rather than diabetic status as the dependent variable. Apart from allowing us to measure the degree of family resemblance, use of BG can be justified because people with BG in the impaired glucose tolerance range have higher risk of macrovascular diseases. The risk is probably graded throughout the entire range of BG, analogous to those for blood pressure and blood cholesterol. Hence, with respect to risk of cardiovascular disease, any choice of cut-off value to define diabetes is arbitrary. The varying age of onset of diabetes is known to cause difficulty in family study of diabetes. Using BG obviates this problem since the degree of an individual's hyperglycaemia is measured relative to the expected level for his age, sex, ethnicity and other covariates, rather than defined using a fixed arbitrary level that applies for all individuals. Age adjustment alone has been shown to enhance the power of a study to detect familial clustering of diabetes[21]. Hence, use of BG as a continuous dependent variable rather than the binary diabetes status variable makes for more powerful analysis not just in determining factors associated with high BG but also in assessing family resemblance.

This study has demonstrated that BMI is the only consistent and major modifiable determinant of BG in both sexes and all ethnic groups. Other studies have found the effect of BMI may differ between populations [5,6]. We did not find such heterogeneity of effect. This serves to emphasize the important potential role of prevention and treatment of obesity as a strategy to reduce BG levels. This study has also demonstrated that observed differences in mean BG and thus of prevalence of diabetes between the two sexes and among ethnic groups cannot be explained by differential distribution of established determinants like age, BMI, physical activity, urbanization and socio-economic status. Clearly ethnic populations differ in

their susceptibility to high BG. It is tempting to attribute the differences in susceptibility to genetic factor. However, the findings of this study on family resemblance for BG among ethnic groups do not support this.

Family resemblance for a trait is due to shared gene or common family environment or both. Family environment is difficult to measure. We have however adjusted BG for age, sex, ethnicity, BMI, physical activity, urban-rural residence, education and income to account for their possible influence on family resemblance. Of course, subtle socio-cultural differences among ethnic groups must still exist in spite of the adjustment. The four ethnic populations studied differ considerably in prevalence of diabetes. They are likely to have different genetic make-up, and cultural-environmental influences are also likely to differ among them. In all ethnic groups, we have found presence of family resemblance for BG. That is, individuals who share genes and common family environment, tend to be more alike in their BG values. However, we have found little heterogeneity in familial correlation across ethnic groups. This is surprising. A previous study in Jerusalem[8] comparing familial correlation for fasting BG across 4 origin groups, European, Asian, North African and mixed origin, have found similar homogeneity of familial correlation. The authors had attributed the unexpected finding partly to the use of fasting BG, a weak marker for glucose intolerance. We have used post-challenge BG and yet the findings were similar. Another explanation offered by the authors of the Jerusalem study was the homogeneity of lifestyle across origin groups as a result of rapid and increasing Westernisation of the economy and socio-cultural environment in Israel. This applies in Malaysia too, which has witnessed rapid socio-economic development during the last 30 years.

No less remarkable, the magnitude of the familial correlation was relatively low and similar to that for spousal correlation in all ethnic groups. Premature mortality of diabetic family members as well as non-availability of members below 30 years of age in the sample may tend to deflate the familial correlation. Repeat analysis excluding single parents or grandparents did not change the result at all. Nevertheless, one must still expect the magnitude of familial correlation to be greater than spousal correlation, if genetic influence is appreciable at all. This was not so. This suggests common familial environmental factors contribute to the observed familial resemblance for BG found in these populations rather than shared genes. Adjustment for covariates uniformly decreased the magnitude of both familial and spousal correlations, albeit slightly, suggesting these covariates did contribute to family resemblance for BG.

Taken together, these findings suggest that environmental factors are probably more important than genetic factors as determinant of BG in the four ethnic populations studied. This does not mean genetic factors have no role at all, only that they are not sufficient to explain the differences in BG among ethnic groups. A tentative interpretation of the results is this. Environmental factors common to all ethnic populations, related perhaps to a modernizing lifestyle and acting on underlying genetic susceptibility, are the major contributors to the variation in BG. Differential exposure to these environmental factors then explained the differences in observed BG distributions across ethnic populations. The rise of the modern epidemic of Type 2 DM in developing countries[22] is consistent with this interpretation. The putative environmental factors however remain largely undefined. In this study, the regression models accounted for only between 5 to 12% of the variance in BG. Covariates like urban-rural residence, income and education are no more than crude proxy measures for a modernising lifestyle. Clearer conceptual definition and, better and more reliable method for measuring the so-called modern lifestyle are urgently needed.

In conclusion, this study has found that BMI was the only consistent modifiable predictor of BG in both sexes and all ethnic groups. Familial aggregation in BG did occur, but its magnitude was small and homogenous across ethnic populations. Other environmental factors probably have greater influence on BG but they remain poorly defined. The results of this study however must be regarded as preliminary, further purpose design research is required to confirm or refute the findings.

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