DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2010; **26**: 245–253.
Published online 15 April 2010 in Wiley InterScience (www.interscience.wiley.com) **DOI:** 10.1002/dmrr.1078

RESEARCH ARTICLE

Does abnormal insulin action or insulin secretion explain the increase in prevalence of impaired glucose metabolism with age in populations of different ethnicities?

F. Ning[1]* Q. Qiao[1,2] J. Tuomilehto[1,2] N. Hammar[3,4] S. Y. Ho[5] S. Söderberg[6,7] P. Z. Zimmet[6] J. E. Shaw[6] T. Nakagami[8] V. Mohan[9] A. Ramachandran[10] T. H. Lam[5] S. W. Andersson[3,11] E. D. Janus[5,12] E. J. Boyko[13] W. Y. Fujimoto[13] Z. C. Pang[14] for the DECODA Study Group

[1]*Department of Public Health, University of Helsinki, Helsinki, Finland* [2]*Diabetes Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland* [3]*Department of Epidemiology, AstraZeneca R&D, Mölndal, Sweden* [4]*Department of Epidemiology, Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden* [5]*Department of Community Medicine, University of Hong Kong, Hong Kong SAR, China* [6]*Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia* [7]*Department of Public Health and Clinical Medicine, Cardiology, Umeå University Hospital, Umeå, Sweden* [8]*Diabetes Center, Tokyo Women's Medical University School of Medicine, Tokyo, Japan* [9]*Madras Diabetes Research Foundation, Dr Mohan's Diabetes Specialities Centre, Chennai, India* [10]*India Diabetes Research Foundation, Dr A. Ramachandran's Diabetes Hospitals, Chennai, India* [11]*Department of Clinical Nutrition, Sahlgrenska Academy at Göteborg University, Göteborg, Sweden* [12]*Department of Medicine, University of Melbourne, Western Hospital, Victoria, Australia* [13]*Department of Medicine, University of Washington, Seattle, WA, USA* [14]*Qingdao Centers for Disease Control and Prevention, Qingdao, China*
*Correspondence to: F. Ning, Department of Public Health, University of Helsinki, Mannerheimintie 172, PL41, FI-00014 Helsinki, Finland. E-mail: feng.ning@helsinki.fi

Received: 4 June 2009
Revised: 5 March 2010
Accepted: 13 March 2010

Abstract

Background Age is associated with both impaired glucose and insulin metabolism. To what extent the age-related changes in insulin resistance (IR) and β-cell function contribute to the increase in prevalence of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) is less known, and this is investigated in this study.

Methods This study included 6610 men and 7664 women of different ethnic groups aged 30-69 years. IR and β-cell function were examined by the homeostasis model assessment of insulin resistance (HOMA-IR) and homeostasis model assessment of β-cell function (HOMA-B). Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated using logistic regression analysis adjusting for body mass index and study.

Results In Chinese men, the ORs (95% CIs) for IFG were 2.69 (1.70, 4.26), 2.51 (1.49, 4.21) and 2.89 (1.68, 4.97), respectively, in age groups of 40–49, 50–59 and 60–69 years compared with 30–39 years ($p < 0.001$ for trend); the corresponding figures for IGT were 1.73 (1.25, 2.38), 2.54 (1.78, 3.63) and 3.57 (2.46, 5.19) ($p < 0.001$ for trend). Similar trends for IGT were observed also in Chinese women and other ethnic groups, but not for IFG in Mauritius Indian and Creole men. Adjustment for HOMA-IR and HOMA-B reduced the ORs in all age groups of all ethnicities for both IFG and IGT, but the risk gradient between age groups remained particularly for the IGT.

Conclusions The age-related increase in glucose intolerance may not be fully explained by the defect in HOMA-IR and HOMA-B. As HOMA-IR and HOMA-B are only surrogate measures of insulin sensitivity and insulin secretion, the results need to be further investigated. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords age; insulin resistance; β-cell function; impaired fasting glucose; impaired glucose tolerance

Introduction

The prevalence of type 2 diabetes and impaired glucose tolerance (IGT) increases with age [1]. Several risk factors for type 2 diabetes, including ageing, increased adiposity and physical inactivity, predispose elderly people to develop glucose intolerance and insulin resistance (IR). The progression from normal glucose tolerance to IGT and type 2 diabetes is characterized by progressive defect in β-cell function or impaired β-cell compensation for IR [2]. Different opinions exist, however, on whether IR increases with age as does

IGT [3,4]. Similarly, a positive correlation of fasting plasma glucose (FPG) with age has been reported from some studies [5,6] but not in others [7,8]. The ageing of populations may further increase the burden of type 2 diabetes and pre-diabetes [impaired fasting glucose (IFG)/IGT] on health care systems worldwide [9]. Knowledge of the impact of age on IR together with β-cell function and glucose metabolism may have clinical implications in intervention and management of pre-diabetes and diabetes in elderly populations.

In this study, we aim to examine to what extent the age-related IR and β-cell dysfunction contribute to the increase in the prevalence of IFG and IGT based on the cross-sectional data of the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Asia (DECODA) study.

Materials and methods

Study populations

The DECODA study is based on collaborative analysis of existing databases of different study populations of Asian origin and Creole [10]. The Creole ethnic group is comprised of African and Malagasy ancestry with some European admixture [11]. Researchers who had carried out population-based cross-sectional or large occupational surveys on diabetes were invited to join the DECODA collaboration. Data on history of diabetes, FPG, 2-h plasma glucose (2hPG), fasting insulin, body mass index (BMI) and other variables were sent to the Diabetes Prevention Unit, Department of Chronic Disease Prevention of National Institute for Health and Welfare in Helsinki, Finland for collaborative data analysis. In this study, data from 11 studies including 6610 men and 7664 women aged 30–69 years were analysed. Informed consent of participants complying with the Declaration of Helsinki or other ethical standards was obtained in all studies.

To study glucose metabolism and insulin function in pre-diabetic status, subjects with diabetes previously diagnosed or detected on screening with FPG $\geq$7.0 mmol/L and/or 2hPG $\geq$11.1 mmol/L were excluded from this data analysis. Individuals with FPG of 6.1–6.9 mmol/L were categorized as IFG and those with 2hPG of 7.8–11.0 mmol/L were categorized as having IGT [12]. Fasting insulin assays differed among the 11 studies: 5 used conventional radioimmunoassays (RIA) that measured immunoreactive insulin and cross-react with proinsulin and its split products, whereas others used either an enzyme-linked immunosorbent assay (ELISA) or a chemiluminescence immunoassay for intact insulin (Table S1, supplementary information). Homeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-B) were calculated based on FPG and fasting insulin. HOMA-IR = (fasting insulin $\times$ FPG)/22.5, and HOMA-B = 20 $\times$ fasting insulin/(FPG $-$ 3.5) [13]. Fasting insulin concentration was measured in picomoles per litre and FPG concentration in millimoles per litre.

Statistical analysis

The 10-year age-specific prevalence of IFG and IGT was calculated for each study. Differences in proportions were evaluated by Chi-square test. Considering the difference in laboratory assays of fasting insulin and FPG between studies, Z score ($Z = [\chi - \mu]/\sigma$) transformation for HOMA-IR, HOMA-B and glucose concentrations was made for each study before the studies of the same ethnic group were pooled together. Logistic regression analysis was used to estimate age-specific odds ratios (ORs) and 95% confidence intervals (95% CIs) for IFG and IGT in each ethnic group subsequently adjusting for BMI, study, HOMA-IR and HOMA-B. All analyses were performed using SPSS for Windows (Version 15.0; SPSS Inc., Chicago, IL, USA). A probability (p) less than 0.05 (two tailed) was considered statistically significant.

Results

The characteristics of participants differed slightly among studies of the same ethnicity (Table 1). Among the three Chinese studies, the Qingdao study population was the oldest, and had the highest FPG, 2hPG and BMI ($p < 0.001$ for all). There was no difference between the two Hong Kong Chinese studies, except that mean of fasting insulin, HOMA-IR and HOMA-B were lower in the Hong Kong Cardiovascular Risk Factor Prevalence Study (HK-cvrfps) than in the Hong Kong Workforce Survey on Cardiovascular Risk Factors (HK-wcvdrf). Asian Indians from the Chennai Urban Rural Epidemiology Study (CURES) in Chennai, India, in 2001 had higher FPG, 2hPG, fasting insulin and HOMA-IR than the Chennai Urban Population Study in 1997 (CUPS1997) ($p < 0.001$ for all).

In all ethnic groups, the mean Z scores of FPG and 2hPG increased with age among men and women, whereas HOMA-B declined with age, although in some populations this decline did not reach statistical significance. However, no consistent trend was observed for mean HOMA-IR across age groups (Figure 1). The prevalence of IFG (Table 2) and IGT (Table 3) increased significantly with age in men and women of all ethnic groups (p for trends <0.05 for all) except for IFG in Mauritian Indians and Creole men. The increase was more prominent for IGT than for IFG in both men and women, and the association of age with IFG and IGT was not altered after adjusting for BMI and studies. Adjustment for hypertension did not change the results (data for hypertension not shown).

Further adjustment for either HOMA-IR or HOMA-B or both simultaneously reduced the OR for IFG and IGT in all age groups of all ethnic groups (Tables 2 and 3). The reduction was slightly larger in the middle and old age

DOI: 10.1002/dmrr

Table 1. Characteristics of the studies at baseline

Ethnicity/ country	Studies	Age (years) mean (range)	*N* (% men)	BMI (kg/m^2)	FPG (mmol/L)	2hPG (mmol/L)	Fasting insulin (pmol/L)	HOMA-IR	HOMA-B	Year of screening
Chinese/China	HK-wscvdrf	41 (30–66)	1065 (58.5)	23.8 (0.11)	4.94 (0.02)	5.75 (0.05)	61.5 (1.05)	13.9 (0.27)	940.0 (17.66)	1991
	HK-cvrfps	45 (30–69)	1896 (48.7)	24.0 (0.08)	5.10 (0.01)	6.16 (0.04)	40.5 (0.77)	9.4 (0.20)	525.5 (12.91)	1995–1996
	Qingdao2006	48 (30–69)	2162 (41.7)	25.4 (0.07)	5.29 (0.01)	6.32 (0.03)	45.3 (0.73)	10.8 (0.19)	604.8 (12.28)	2006
	All	45 (30–69)	5123 (47.8)	24.5 (0.06)	5.15 (0.01)	6.16 (0.02)	46.8 (0.62)	11.0 (0.15)	639.0 (18.98)	
Creole/Mauritius	Mauritius1987	45 (30–69)	889 (46.7)	24.1 (0.16)	5.39 (0.02)	6.39 (0.06)	47.1 (1.62)	11.6 (0.42)	535.3 (18.72)	1987
	Mauritius1992	47 (30–69)	557 (43.3)	25.5 (0.20)	5.49 (0.02)	6.28 (0.07)	78.1 (2.05)	19.3 (0.53)	811.8 (23.73)	1992
	Mauritius1998	40 (30–68)	271 (43.2)	25.0 (0.29)	5.32 (0.04)	6.17 (0.10)	64.5 (2.98)	15.3 (0.77)	773.1 (34.41)	1998
	All	45 (30–69)	1717 (45.0)	24.7 (0.10)	5.42 (0.01)	6.33 (0.04)	59.8 (1.07)	14.6 (0.27)	655.1 (32.73)	
Indian/India	CUPS1997	44 (30–69)	665 (40.5)	22.9 (0.16)	4.38 (0.02)	5.60 (0.06)	48.5 (1.74)	10.0 (0.39)	1093.0 (45.29)	1996–1998
	CURES	42 (30–69)	1326 (45.1)	23.3 (0.11)	4.81 (0.02)	6.11 (0.04)	59.6 (1.22)	12.9 (0.27)	1050.6 (31.76)	2001
	All	43 (30–69)	1991 (43.5)	23.2 (0.09)	4.70 (0.01)	6.00 (0.04)	55.5 (1.00)	11.9 (0.25)	1041.7 (15.53)	
Indian/Mauritius	Mauritius1987	43 (30–69)	2196 (46.3)	23.4 (0.09)	5.17 (0.01)	6.39 (0.03)	52.5 (1.07)	12.3 (0.27)	652.4 (12.61)	1987
	Mauritius1992	46 (30–69)	1110 (47.8)	24.9 (0.13)	5.40 (0.02)	6.57 (0.05)	78.3 (1.51)	19.2 (0.39)	858.4 (17.82)	1992
	Mauritius1998	41 (30–68)	618 (43.0)	24.4 (0.18)	5.33 (0.01)	6.40 (0.07)	71.6 (2.02)	17.1 (0.52)	822.2 (23.88)	1998
	All	44 (30–69)	3924 (46.2)	24.1 (0.06)	5.29 (0.01)	6.51 (0.03)	62.4 (0.71)	15.0 (0.18)	718.0 (21.80)	
Japanese/Brazil and America	San Paulo1992	55 (37–69)	365 (48.5)	24.5 (0.18)	5.16 (0.03)	6.01 (0.09)	38.4 (2.47)	8.9 (0.63)	506.1 (39.70)	1992–1993
	San Paulo1999	52 (31–69)	696 (42.5)	24.0 (0.13)	6.13 (0.02)	7.29 (0.06)	54.8 (1.78)	15.2 (0.45)	426.9 (28.56)	1999–2000
	Seattle	51 (34–69)	458 (51.3)	24.1 (0.16)	5.27 (0.03)	7.35 (0.07)	93.7 (2.20)	22.3 (0.56)	1212.5 (35.35)	2001
	All	52 (31–69)	1519 (46.5)	24.3 (0.10)	5.63 (0.02)	7.01 (0.04)	63.6 (1.16)	15.8 (0.29)	731.0 (35.40)	

Data are age-adjusted mean (SE) unless otherwise stated.
BMI, body mass index; FPG, fasting plasma glucose; 2hPG, 2-h plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-B, homeostasis model assessment of β-cell function; HK-cvrfps, Hong Kong Cardiovascular Risk Factor Prevalence Study; HK-wscvdrf, Hong Kong Workforce Survey on Cardiovascular Risk Factors; CUPS1997, Chennai Urban Population Study in 1997; CURES, Chennai Urban Rural Epidemiology Study.

DOI: 10.1002/dmrr

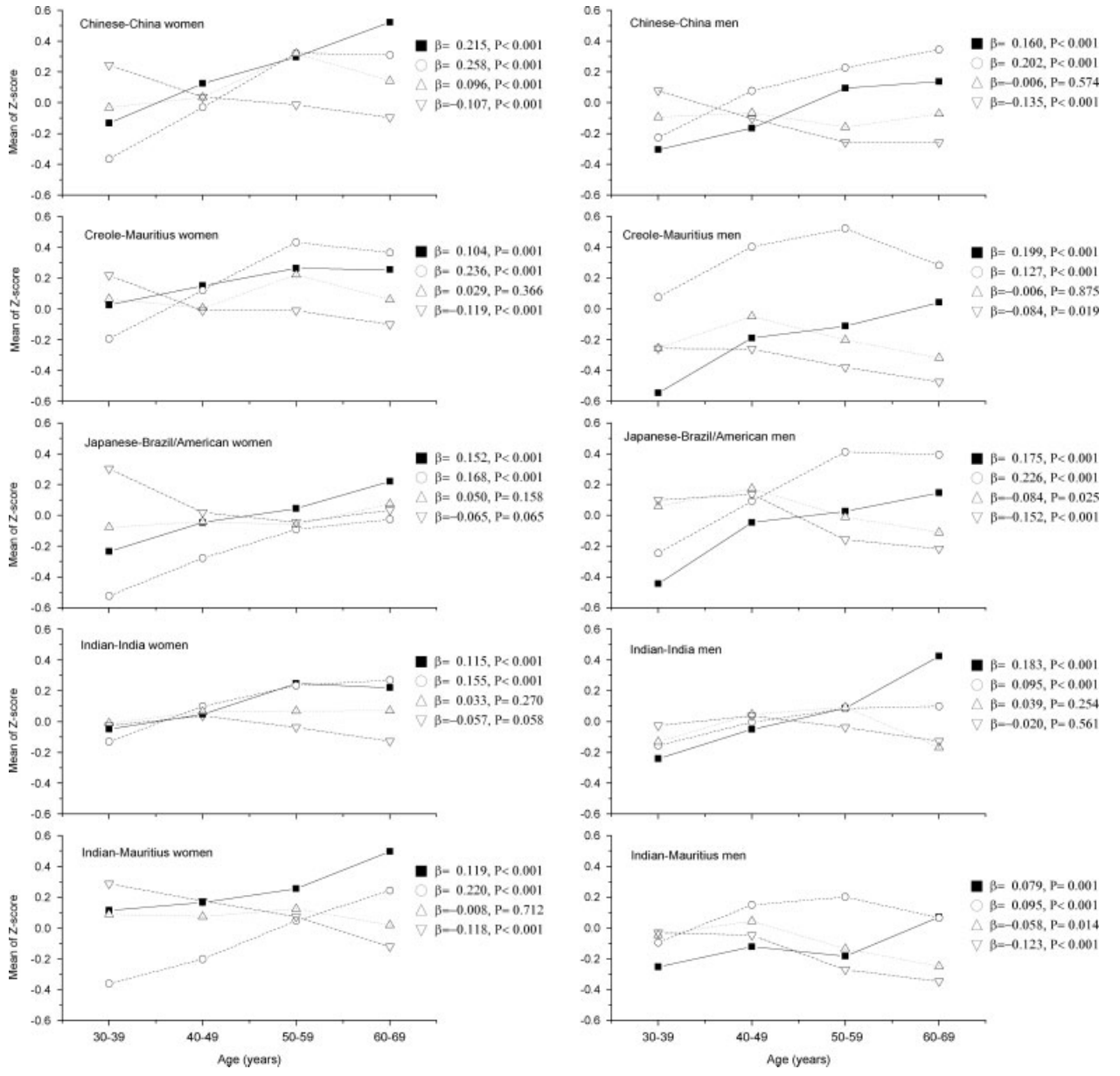

Figure 1. Age-specific mean of *Z* score of fasting plasma glucose (■), 2-h plasma glucose (○), HOMA-IR (△), and HOMA-B(▽) for women and men in five ethnic groups. Standardized β-coefficients of correlations between these variables and age are also shown. HOMA-IR: homeostasis model assessment of insulin resistance, HOMA-B: homeostasis model assessments of β-cell function

groups than in the young age group for IFG in some ethnic groups but not in others. The results based on pooled data analysis of all ethnic groups showed that the OR for IGT was reduced when both HOMA-IR and HOMA-B appeared simultaneously in the model, but the risk gradient for IGT across age groups still remained (Table 3), indicating an independent effect of age. The age-related increase in IFG also remained after the multivariate adjustment for HOMA-IR and HOMA-B although decreased substantially.

Discussion

We found that the prevalence of IFG and IGT, particularly the prevalence of IGT, increased with age even after the adjustment for HOMA-IR and HOMA-B. The mean of HOMA-IR did not increase with age in most studies, except for Asian Indian and Chinese, Creole and Japanese-Brazil/American women, whereas β-cell function declined with age in almost all studies. The age-related decline in β-cell function and the IR may contribute to the presence of glucose intolerance across age groups, not only in the elderly population. As HOMA-IR and HOMA-B were only surrogate measures of insulin sensitivity and insulin secretion, further investigations are warranted.

IR and decreased insulin secretion are the major factors contributing to the deterioration of glucose metabolism [14,15]. Elderly individuals are apparently able to maintain normal glucose tolerance by secreting more insulin to overcome the IR [16]. This compensatory response can be maintained, despite the presence of subtle defect in the ability of elderly individuals to increase their

DOI: 10.1002/dmrr

Table 2. Prevalence (number of events) in each age group,odds ratios (ORs) and 95% confidence intervals (95% CIs) for impaired fasting glucose in older age groups compared with age group of 30–39 years

Ethnicity	Age (years) 30–39 ORs (95% CIs)	40–49 ORs (95% CIs)	50–59 ORs (95% CIs)	60–69 ORs (95% CIs)	*p* for trend
Men					
Chinese-China % (N)	3.1 (27)	10.0 (84)	10.0 (42)	11.1 (35)	–
Model 1	1	2.69 (1.70, 4.26)	2.51 (1.49, 4.21)	2.89 (1.68, 4.97)	<0.001
Model 2: 1 + HOMA-IR	1	2.76 (1.70, 4.46)	2.72 (1.59, 4.68)	3.06 (1.73, 5.42)	<0.001
Model 3: 1 + HOMA-B	1	2.39 (1.50, 3.80)	2.02 (1.19, 3.40)	2.34 (1.35, 4.06)	0.012
Model 4: 1 + HOMA-IR + HOMA-B	1	2.06 (0.85, 5.02)	1.37 (0.53, 3.54)	1.42 (0.51, 3.94)	0.977
Creole–Mauritius % (N)	11.1 (37)	17.8 (33)	22.2 (36)	11.7 (11)	–
Model 1	1	1.64 (0.98, 2.73)	2.11 (1.27, 3.51)	1.02 (0.50, 2.10)	0.140
Model 2: 1 + HOMA-IR	1	1.58 (0.93, 2.70)	2.28 (1.34, 3.87)	1.01 (0.47, 2.15)	0.117
Model 3: 1 + HOMA-B	1	1.59 (0.95, 2.67)	1.99 (1.19, 3.33)	0.98 (0.47, 2.01)	0.212
Model 4: 1 + HOMA-IR + HOMA-B	1	1.01 (0.36, 2.85)	1.51 (0.54, 4.18)	0.27 (0.05, 1.43)	0.497
Indian-India % (N)	2.1 (8)	1.6 (4)	5.4 (8)	7.5 (6)	–
Model 1	1	0.76 (0.23, 2.55)	2.70 (0.99, 7.34)	4.28 (1.40, 13.07)	0.004
Model 2: 1 + HOMA-IR	1	0.62 (0.18, 2.13)	2.09 (0.73, 5.99)	4.17 (1.35, 12.87)	0.009
Model 3: 1 + HOMA-B	1	0.86 (0.25, 2.91)	2.92 (1.06, 8.04)	4.64 (1.49, 14.42)	0.003
Model 4: 1 + HOMA-IR + HOMA-B	1	0.68 (0.16, 2.88)	1.09 (0.28, 4.22)	4.78 (1.24, 18.39)	0.056
Indian–Mauritius % (N)	8.3 (67)	13.1 (64)	15.7 (52)	6.7 (12)	–
Model 1	1	1.49 (1.03, 2.15)	1.89 (1.27, 2.81)	0.78 (0.41, 1.49)	0.193
Model 2: 1 + HOMA-IR	1	1.57 (1.07, 2.29)	2.02 (1.34, 3.05)	0.86 (0.45, 1.65)	0.107
Model 3: 1 + HOMA-B	1	1.42 (0.98, 2.06)	1.73 (1.16, 2.58)	0.71 (0.37, 1.36)	0.429
Model 4: 1 + HOMA-IR + HOMA-B	1	1.17 (0.55, 2.46)	1.25 (0.58, 2.71)	0.68 (0.24, 1.91)	0.768
Japanese-Brazil/America % (N)	23.1 (27)	28.5 (55)	41.8 (79)	34.5 (71)	–
Model 1	1	1.33 (0.71, 2.48)	3.12 (1.67, 5.85)	2.25 (1.22, 4.16)	0.001
Model 2: 1 + HOMA-IR	1	1.35 (0.72, 2.52)	3.29 (1.75, 6.20)	2.35 (1.27, 4.34)	0.001
Model 3: 1 + HOMA-B	1	1.24 (0.65, 2.37)	2.74 (1.44, 5.20)	1.98 (1.06, 3.70)	0.006
Model 4: 1 + HOMA-IR + HOMA-B	1	1.06 (0.51, 2.22)	2.76 (1.32, 5.75)	1.98 (0.96, 4.08)	0.008
Total % (N)	6.6 (166)	12.2 (240)	17.3 (217)	15.4 (135)	–
Model 1	1	1.66 (1.33, 2.07)	2.26 (1.79, 2.86)	1.74 (1.32, 2.28)	<0.001
Model 2: 1 + HOMA-IR	1	1.67 (1.33, 2.10)	2.41 (1.90, 3.07)	1.83 (1.38, 2.42)	<0.001
Model 3: 1 + HOMA-B	1	1.58 (1.26, 1.98)	2.02 (1.59, 2.56)	1.54 (1.17, 2.03)	<0.001
Model 4: 1 + HOMA-IR + HOMA-B	1	1.26 (0.94, 1.69)	1.54 (1.14, 2.08)	1.19 (0.84, 1.70)	0.086
Women					
Chinese-China % (N)	4.1 (34)	6.3 (65)	16.2 (90)	13.4 (35)	–
Model 1	1	1.20 (0.78, 1.86)	2.58 (1.68, 3.98)	2.61 (1.55, 4.39)	<0.001
Model 2: 1 + HOMA-IR	1	1.29 (0.82, 2.02)	2.45 (1.57, 3.84)	2.69 (1.58, 4.60)	<0.001
Model 3: 1 + HOMA-B	1	1.03 (0.66, 1.60)	2.06 (1.33, 3.21)	2.04 (1.20, 3.48)	<0.001
Model 4: 1 + HOMA-IR + HOMA-B	1	1.24 (0.55, 2.81)	1.77 (0.79, 3.99)	1.88 (0.72, 4.96)	0.107
Creole–Mauritius % (N)	5.5 (21)	11.5 (24)	19.0 (40)	19.3 (28)	–
Model 1	1	2.04 (1.10, 3.79)	3.32 (1.87, 5.90)	3.60 (1.95, 6.62)	<0.001
Model 2: 1 + HOMA-IR	1	2.36 (1.25, 4.46)	3.63 (2.01, 6.55)	4.17 (2.22, 7.85)	<0.001
Model 3: 1 + HOMA-B	1	1.76 (0.94, 3.28)	2.83 (1.57, 5.07)	2.94 (1.58, 5.49)	<0.001
Model 4: 1 + HOMA-IR + HOMA-B	1	1.71 (0.36, 8.18)	2.48 (0.57, 10.75)	4.01 (0.81, 19.94)	0.076
Indian-India % (N)	0.6 (3)	2.5 (9)	1.7 (3)	5.2 (5)	–
Model 1	1	4.26 (1.14, 15.94)	3.11 (0.61, 15.81)	11.04 (2.49, 45.98)	0.003
Model 2: 1 + HOMA-IR	1	4.59 (1.18, 17.87)	3.33 (0.64, 17.49)	12.45 (2.66, 58.32)	0.003
Model 3: 1 + HOMA-B	1	3.88 (1.03, 14.57)	2.96 (0.58, 15.09)	9.96 (2.25, 44.08)	0.005
Model 4: 1 + HOMA-IR + HOMA-B	1	3.21 (0.69, 14.99)	3.14 (0.51, 19.23)	11.77 (2.18, 63.52)	0.006
Indian–Mauritius % (N)	3.5 (33)	6.7 (37)	10.7 (41)	14.1 (31)	–
Model 1	1	1.65 (1.01, 2.69)	2.77 (1.71, 4.50)	4.21 (2.49, 7.10)	<0.001
Model 2: 1 + HOMA-IR	1	1.90 (1.15, 3.16)	3.11 (1.88, 5.14)	4.97 (2.89, 8.56)	<0.001
Model 3: 1 + HOMA-B	1	1.45 (0.88, 2.38)	2.29 (1.40, 3.76)	3.37 (1.98, 5.74)	<0.001
Model 4: 1 + HOMA-IR + HOMA-B	1	0.86 (0.20, 3.71)	2.34 (0.66, 8.26)	1.29 (0.32, 5.21)	0.396
Japanese-Brazil/America % (N)	14.7 (17)	24.3 (52)	32.5 (80)	24.7 (57)	–
Model 1	1	1.90 (0.97, 3.73)	2.43 (1.27, 4.68)	2.42 (1.23, 4.77)	0.013
Model 2: 1 + HOMA-IR	1	1.87 (0.95, 3.69)	2.56 (1.32, 4.93)	2.37 (1.20, 4.67)	0.014
Model 3: 1 + HOMA-B	1	1.92 (0.97, 3.81)	2.32 (1.20, 4.49)	2.46 (1.24, 4.89)	0.015
Model 4: 1 + HOMA-IR + HOMA-B	1	1.72 (0.71, 4.15)	2.47 (1.05, 5.80)	2.42 (1.01, 5.83)	0.040
Total % (N)	3.9 (108)	7.9 (187)	16.2 (255)	16.4 (157)	–
Model 1	1	1.66 (1.28, 2.14)	2.86 (2.22, 3.68)	3.30 (2.49, 4.36)	<0.001
Model 2: 1 + HOMA-IR	1	1.82 (1.40, 2.37)	3.03 (2.34, 3.92)	3.57 (2.68, 4.76)	<0.001
Model 3: 1 + HOMA-B	1	1.49 (1.15, 1.93)	2.42 (1.87, 3.13)	2.80 (2.11, 3.72)	<0.001
Model 4: 1 + HOMA-IR+ HOMA-B	1	1.35 (0.96, 1.90)	1.73 (1.24, 2.41)	2.04 (1.41, 2.93)	<0.001

Model 1 adjusted for body mass index and studies.

insulin secretion rate in response to a given increment in plasma glucose concentration revealed by the graded glucose infusion study [17]. Studies [18–21] have also shown that insulin sensitivity does not decrease with age and the decline in insulin sensitivity is most likely secondary to changes in body composition and physical

DOI: 10.1002/dmrr

Table 3. Prevalence (number of events) in each age group,odds ratios (ORs) and 95% confidence intervals (95% CIs) for impaired glucose tolerance in older age groups compared with age group of 30–39 years

	Age (years)				
Ethnicity	30–39 ORs (95% CIs)	40–49 ORs (95% CIs)	50–59 ORs (95% CIs)	60–69 ORs (95% CIs)	*p* for trend
Men					
Chinese-China % (N)	8.2 (71)	13.7 (115)	18.5 (78)	24.4 (77)	–
Model 1	1	1.73 (1.25, 2.38)	2.54 (1.78, 3.63)	3.57 (2.46, 5.19)	<0.001
Model 2: 1 + HOMA-IR	1	1.72 (1.25, 2.38)	2.61 (1.82, 3.74)	3.58 (2.45, 5.22)	<0.001
Model 3 : 1 + HOMA-B	1	1.67 (1.21, 2.30)	2.40 (1.67, 3.44)	3.39 (2.32, 4.93)	<0.001
Model 4: 1 +HOMA-IR + HOMA-B	1	1.53 (1.10, 2.12)	2.15 (1.49, 3.10)	2.97 (2.02, 4.35)	<0.001
Creole–Mauritius % (N)	12.3 (41)	16.2 (30)	21.0 (34)	25.5 (24)	–
Model 1	1	1.31 (0.78, 2.18)	1.83 (1.10, 3.04)	2.59 (1.45, 4.62)	0.001
Model 2: 1 + HOMA-IR	1	1.25 (0.74, 2.11)	1.88 (1.12, 3.16)	2.64 (1.46, 4.74)	<0.001
Model 3: 1 + HOMA-B	1	1.30 (0.78, 2.18)	1.82 (1.09, 3.03)	2.58 (1.44, 4.61)	0.001
Model 4: 1 + HOMA-IR + HOMA-B	1	1.04 (0.61, 1.79)	1.58 (0.93, 2.69)	2.29 (1.26, 4.18)	0.004
Indian-India % (N)	7.0 (27)	13.7 (35)	20.1 (30)	21.3 (17)	–
Model 1	1	2.22 (1.30, 3.81)	3.56 (2.01, 6.29)	4.78 (2.40, 9.54)	<0.001
Model 2: 1 + HOMA-IR	1	2.06 (1.20, 3.56)	3.27 (1.83, 5.84)	4.58 (2.28, 9.20)	<0.001
Model 3: 1 + HOMA-B	1	2.27 (1.33, 3.90)	3.61 (2.04, 6.39)	4.84 (2.42, 9.66)	<0.001
Model 4: 1 + HOMA-IR + HOMA-B	1	2.07 (1.19, 3.61)	3.15 (1.74, 5.70)	4.50 (2.22, 9.12)	<0.001
Indian–Mauritius % (N)	11.9 (97)	18.4 (90)	18.7 (62)	20.0 (36)	–
Model 1	1	1.54 (1.12, 2.12)	1.75 (1.22, 2.49)	2.07 (1.35, 3.20)	<0.001
Model 2: 1 + HOMA-IR	1	1.57 (1.14, 2.17)	1.80 (1.25, 2.59)	2.20 (1.42, 3.40)	<0.001
Model 3: 1 + HOMA-B	1	1.56 (1.14, 2.15)	1.79 (1.25, 2.56)	2.13 (1.38, 3.29)	<0.001
Model 4: 1 + HOMA-IR + HOMA-B	1	1.50 (1.08, 2.08)	1.63 (1.12, 2.35)	2.00 (1.29, 3.11)	<0.001
Japanese-Brazil/America % (N)	17.9 (21)	26.9 (52)	36.0 (68)	38.9 (81)	–
Model 1	1	2.13 (1.17, 3.90)	3.62 (2.00, 6.56)	4.05 (2.29, 7.17)	<0.001
Model 2: 1 + HOMA-IR	1	2.19 (1.19, 4.04)	3.93 (2.15, 7.18)	4.37 (2.45, 7.82)	<0.001
Model 3: 1 + HOMA-B	1	2.14 (1.17, 3.90)	3.65 (2.00, 6.63)	4.07 (2.29, 7.24)	<0.001
Model 4: 1 + HOMA-IR + HOMA-B	1	2.17 (1.15, 4.07)	3.46 (1.86, 6.43)	3.95 (2.17, 7.19)	<0.001
Total % (N)	10.2 (257)	16.4 (322)	21.7 (272)	26.8 (235)	–
Model 1	1	1.65 (1.38, 1.98)	2.33 (1.92, 2.83)	3.04 (2.46, 3.76)	<0.001
Model 2: 1 + HOMA-IR	1	1.64 (1.36, 1.97)	2.39 (1.97, 2.91)	3.11 (2.51, 3.85)	<0.001
Model 3: 1 + HOMA-B	1	1.64 (1.37, 1.97)	2.30 (1.90, 2.80)	3.01 (2.43, 3.72)	<0.001
Model 4: 1 + HOMA-IR + HOMA-B	1	1.52 (1.26, 1.83)	2.07 (1.70, 2.53)	2.73 (2.20, 3.39)	<0.001
Women					
Chinese-China % (N)	9.2 (76)	17.2 (177)	22.2 (123)	35.1 (92)	–
Model 1	1	1.72 (1.29, 2.31)	1.92 (1.39, 2.66)	3.84 (2.68, 5.47)	<0.001
Model 2: 1 + HOMA-IR	1	1.80 (1.34, 2.42)	1.84 (1.32, 2.56)	3.93 (2.74, 5.64)	<0.001
Model 3: 1 + HOMA-B	1	1.71 (1.27, 2.29)	1.89 (1.36, 2.63)	3.77 (2.63, 5.41)	<0.001
Model 4: 1 + HOMA-IR + HOMA-B	1	1.61 (1.19, 2.17)	1.51 (1.07, 2.11)	3.22 (2.23, 4.65)	<0.001
Creole–Mauritius % (N)	17.8 (68)	22.1 (46)	27.6 (58)	26.9 (39)	–
Model 1	1	1.19 (0.78, 1.82)	1.45 (0.96, 2.20)	1.51 (0.95, 2.39)	0.039
Model 2: 1 + HOMA-IR	1	1.29 (0.84, 2.00)	1.49 (0.98, 2.28)	1.62 (1.01, 2.60)	0.023
Model 3: 1 + HOMA-B	1	1.23 (0.80, 1.89)	1.51 (0.99, 2.30)	1.57 (0.99, 2.51)	0.027
Model 4: 1 + HOMA-IR + HOMA-B	1	1.19 (0.77, 1.84)	1.24 (0.80, 1.92)	1.37 (0.85, 2.22)	0.178
Indian-India % (N)	8.8 (43)	11.6 (42)	17.6 (31)	16.7 (16)	–
Model 1	1	1.57 (0.99, 2.49)	3.03 (1.79, 5.11)	3.31 (1.72, 6.38)	<0.001
Model 2: 1 + HOMA-IR	1	1.50 (0.94, 2.40)	2.89 (1.70, 4.90)	3.16 (1.63, 6.12)	<0.001
Model 3: 1 + HOMA-B	1	1.54 (0.97, 2.45)	3.00 (1.77, 5.06)	3.24 (1.68, 6.26)	<0.001
Model 4: 1 + HOMA-IR + HOMA-B	1	1.38 (0.86, 2.22)	2.74 (1.61, 4.66)	2.87 (1.48, 5.58)	<0.001
Indian–Mauritius % (N)	19.6 (187)	22.6 (125)	27.4 (105)	35.5 (78)	–
Model 1	1	1.03 (0.79, 1.34)	1.37 (1.03, 1.82)	2.19 (1.57, 3.04)	<0.001
Model 2: 1 + HOMA-IR	1	1.12 (0.85, 1.47)	1.46 (1.08, 1.95)	2.40 (1.71, 3.37)	<0.001
Model 3: 1 + HOMA-B	1	1.05 (0.80, 1.37)	1.41 (1.05, 1.88)	2.28 (1.63, 3.19)	<0.001
Model 4: 1 + HOMA-IR + HOMA-B	1	1.04 (0.79, 1.37)	1.27 (0.94, 1.71)	1.98 (1.40, 2.80)	<0.001
Japanese-Brazil/America % (N)	24.1 (28)	28.2 (61)	33.5 (83)	41.4 (96)	–
Model 1	1	1.49 (0.87, 2.55)	2.01 (1.18, 3.42)	2.82 (1.67, 4.78)	<0.001
Model 2: 1 + HOMA-IR	1	1.50 (0.87, 2.58)	2.05 (1.20, 3.50)	2.79 (1.64, 4.75)	<0.001
Model 3: 1 + HOMA-B	1	1.49 (0.87, 2.56)	2.01 (1.18, 3.43)	2.83 (1.67, 4.80)	<0.001
Model 4: 1 + HOMA-IR + HOMA-B	1	1.42 (0.82, 2.47)	1.92 (1.12, 3.31)	2.60 (1.52, 4.46)	<0.001
Total % (N)	14.5 (402)	19.0 (451)	25.4 (400)	33.6 (321)	–
Model 1	1	1.31 (1.13, 1.53)	1.66 (1.41, 1.96)	2.48 (2.07, 2.98)	<0.001
Model 2: 1 + HOMA-IR	1	1.38 (1.18, 1.61)	1.67 (1.41, 1.97)	2.56 (2.13, 3.08)	<0.001
Model 3: 1 + HOMA-B	1	1.32 (1.13, 1.55)	1.68 (1.42, 1.98)	2.51 (2.09, 3.02)	<0.001
Model 4: 1 + HOMA-IR + HOMA-B	1	1.27 (1.08, 1.48)	1.45 (1.22, 1.71)	2.20 (1.83, 2.66)	<0.001

Model 1 adjusted for body mass index and studies.

fitness [22,23]. Obesity and physical inactivity are two major risk factors contributing to the deterioration of glucose intolerance. It is plausible that the effect of obesity and physical inactivity is mediated through IR, but IR could not fully explain the age-related increase in IGT and IFG in this study, and the association of age with IGT

DOI: 10.1002/dmrr

and IFG was also independent of body fat composition (measured as BMI). The same was also observed in our previous report on European population [3]. To further check whether such an association will be altered by central obesity measured by waist circumference, the data analysis was also performed in a subgroup of individuals who had the waist circumference measured at baseline (men = 6583, women = 7651). This did not change the results substantially, and the results are shown in Tables S2 and S3. A sensitivity analysis by including previously undiagnosed diabetes did not change the observations based on the non-diabetic population reported in this article. However, it should be kept in mind that the upper age limit of the present study is 69 years. Whether the impact of age on IR and glucose metabolism remains the same in people above 69 years needs to be further investigated.

A negative impact of ageing on β-cell function has been shown in many studies [18,24,25]. It appears to be highly attributable to an impairment of proinsulin conversion to insulin [26]. Our study also revealed a slightly declining trend in HOMA-B with age, but this only partly explained the increase in IGT/IFG in older age groups. HOMA as a surrogate marker of β-cell function may underestimate the magnitude of the β-cell defect across declining glucose tolerance status, compared with a direct measure of insulin secretion [27]. However, both HOMA-IR and HOMA-B correlated reasonably well with clamp tests when used to assess the risk of type 2 diabetes in both cross-sectional and prospective studies [28–31]. On the other hand, hyperglycaemia may accelerate the loss of β-cell mass because β-cell from older individuals appears to be more sensitive to adverse effects of glucose-induced apoptosis [32]. Studies also showed that β-cell function declined in elderly population even though their glucose remained in the normal range [1,20]. To what extent ageing contributes to the deterioration of insulin action and insulin secretion observed in the elderly population remains uncertain. It will be of considerable interest to determine the effect of ageing on insulin secretion and IR and their relationship with the deterioration of glucose intolerance in the elderly population. It should also be noted that HOMA-IR is calculated based on fasting values and may reflect hepatic IR better than peripheral IR. The latter would require the evaluation of glucose and insulin values after a glucose load. It is therefore possible that this unmeasured component of IR contributes to the increase in IGT observed with age and was missed.

Evidence has shown that individuals with a family history of diabetes have lower insulin sensitivity and decreased β-cell compensation than those without; diabetes in first-degree relatives may increase IR that was independent of the degree of obesity [33]. Familial factors play an effect on the relationship between insulin sensitivity and glucose effectiveness, which may modulate the risk for the development of pre-diabetes and diabetes. It is well known that insulin is capable of preventing protein breakdown by increasing amino acid availability needed for protein synthesis in muscle tissue. Ageing is associated with impaired substrate utilization and IR, probably due to a sedentary lifestyle and elevated body fat causing impaired mitochondrial function. An age-related decline in physical activity may contribute to the decreased ability of muscle to metabolize and oxidize fat, which would lead to defects in muscle insulin sensitivity. Unfortunately, data on family history of diabetes and physical activity were not available in the current study, and their effect cannot be evaluated.

The main strengths of our study are: (1) the collaborative analysis was based on individual data rather than aggregate data; (2) all studies included are population-based except for HK-wcvdrf which is an occupational study; (3) a standard 2-h 75 g oral glucose tolerance test was used to classify individuals with diabetes, IFG and IGT; (4) data analysis has been carried out using standard methods for all ethnic groups. A limitation of our study was that all studies are cross-sectional, the direction of these associations cannot be conclusively determined and a causal relationship cannot be inferred. In addition, there are discrepancies in assays of fasting insulin, FPG and 2hPG between studies. To reduce the discrepancies study-specific Z scores were calculated and used in the data analyses. Both HOMA-IR and HOMA-B are only surrogate indicators of insulin sensitivity and β-cell function which are mainly based on glucose and insulin levels at the fasting status. They do not directly reflect the capacity of the β-cell to cope with the glucose challenge, and thus may be less associated with the IGT. The extent to which this has biased the present study needs to be further explored.

In conclusion, among the non-diabetic adult population included in this study, the deterioration in glucose metabolism with age may only be partly attributed to the defect in HOMA-IR and HOMA-B. Because HOMA-IR and HOMA-B are only surrogate measurement of insulin secretion and insulin sensitivity and have certain limitation, the study question needs to be further investigated.

Supporting information

Supporting information may be found in the online version of this article.

Acknowledgements

This study was supported by grants from Academy of Finland (118492, 129197) and Finnish Centre for International Mobility Fellowship (CIMO TM-08-5694); Unrestricted grants from AstraZeneca R&D, Mölndal, Sweden for data analysis are also acknowledged.

Conflict of interest

No potential conflicts of interest relevant to this article were declared.

DOI: 10.1002/dmrr

Appendix

Studies and investigators in this collaborative study are:

China

Hong Kong Cardiovascular Risk Factor Prevalence Study: T. H. Lam, S. Y. Ho, E. D. Janus, Department of Community Medicine, School of Public Health, University of Hong Kong, Hong Kong SAR, China.

Hong Kong Workforce Survey on Cardiovascular Diseases Risk Factors: G. T. C. Ko, J. C. N. Chan, C. S. Cockram, The Chinese University of Hong Kong, The Prince of Wales Hospital, Hong Kong SAR, China.

Qingdao Diabetes Survey 2006: Q. Qiao[1,2], Z. C. Pang[3], SH. J. Wang[3], for the Qingdao Diabetes Study Group 2006 (http://www.qddiabetes.org/Organize-6.asp), [1]Department of Public Health, University of Helsinki, Helsinki, Finland; [2]Diabetes Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland; [3]Qingdao Centers for Disease Control and Prevention, Qingdao, China.

India

The Chennai Urban Population Study 1997 (CUPS1997): V. Mohan, Madras Diabetes Research Foundation and Dr Mohan's Diabetes Specialties Centre, Chennai, India.

Chennai Urban Rural Epidemiological Study (CURES): V. Mohan, M. Deepa, Madras Diabetes Research Foundation and Dr Mohan's Diabetes Specialities Centre, Chennai, India.

Japanese Migrants Cohorts

Japanese American Community Diabetes Study: W. Y. Fujimoto, E. J. Boyko, M. McNeely, J. Shofer, D. Leonetti, University of Washington, Seattle, USA.

Japanese Brazilian Diabetes Study Group 1992, São Paulo, Brazil: S. R. G. Ferriera, L. Franco, A. Hirai, S. Gimeno, Preventive Medicine Department, Federal University of São Paulo, São Paulo, Brazil.

Japanese Brazilian Diabetes Study Group 1999, São Paulo, Brazil: S. R. G. Ferriera, L. Franco, A. Hirai, S. Gimeno, Preventive Medicine Department, Federal University of São Paulo, São Paulo, Brazil.

Mauritian Indian and Creole Cohorts

Mauritius Non-Communicable Disease Study: P. Zimmet[1], J Tuomilehto[2,3], J. Shaw[1], K. G. M. M. Alberti[4], S. Söderberg[1,5], Sudhir Knowlessur[6], [1]Baker IDI Heart and Diabetes Institute, Melbourne, Australia; [2]Department of Public Health, University of Helsinki, Helsinki, Finland; [3]Diabetes Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland; [4]Imperial College, Mint Wing, St Marys Hospital, London, UK; [5]Department of Public Health and Clinical Medicine, Cardiology, University of Umeå, Umeå, Sweden; [6]Ministry of Health, Port Louis, Mauritius.

References

1. Chang AM, Halter JB. Aging and insulin secretion. *Am J Physiol Endocrinol Metab* 2003; **284**(1): E7–E12.
2. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999; **104**(6): 787–794.
3. Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Heine R, Wareham NJ. DECODE Study Group. Are insulin resistance, impaired fasting glucose and impaired glucose tolerance all equally strongly related to age? *Diabet Med* 2005; **22**(11): 1476–1481.
4. Ferrannini E, Vichi S, Beck-Nielsen H, Laakso M, Paolisso G, Smith U. Insulin action and age. European group for the study of insulin resistance (EGIR). *Diabetes* 1996; **45**(7): 947–953.
5. Simon D, Senan C, Garnier P, Saint-Paul M, Papoz L. Epidemiological features of glycated haemoglobin A1c-distribution in a healthy population. The Telecom study. *Diabetologia* 1989; **32**(12): 864–869.
6. Wiener K, Roberts NB. Age does not influence levels of HbA1c in normal subject. *QJM* 1999; **92**(3): 169–173.
7. Kilpatrick ES, Dominiczak MH, Small M. The effects of ageing on glycation and the interpretation of glycaemic control in type 2 diabetes. *QJM* 1996; **89**(4): 307–312.
8. Kabadi UM. Glycosylation of proteins. Lack of influence of aging. *Diabetes Care* 1988; **11**(5): 429–432.
9. Szoke E, Shrayyef MZ, Messing S, *et al*. Effect of aging on glucose homeostasis: accelerated deterioration of beta-cell function in individuals with impaired glucose tolerance. *Diabetes Care* 2008; **31**(3): 539–543.
10. Qiao Q, Nakagami T, Tuomilehto J, *et al*. Comparison of the fasting and the 2-hour glucose criteria for diabetes in different Asian cohorts. *Diabetologia* 2000; **43**(12): 1470–1475.
11. Nyamdorj R, Qiao Q, Soderberg S, *et al*. BMI compared with central obesity indicators as a predictor of diabetes incidence in Mauritius. *Obesity (Silver Spring)* 2009; **17**(2): 342–348.
12. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; **15**(7): 539–553.
13. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**(7): 412–419.
14. Abdul-Ghani MA, Sabbah M, Kher J, Minuchin O, Vardi P, Raz L. Different contributions of insulin resistance and beta-cell dysfunction in overweight Israeli Arabs with IFG and IGT. *Diabetes Metab Res Rev* 2006; **22**(2): 126–130.
15. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes Care* 2006; **29**(5): 1130–1139.
16. Basu R, Dalla Man C, Campioni M, *et al*. Effects of age and sex on postprandial glucose metabolism: differences in glucose turnover, insulin secretion, insulin action, and hepatic insulin extraction. *Diabetes* 2006; **55**(7): 2001–2014.
17. Lillioja S, Mott DM, Spraul M, *et al*. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians. *N Engl J Med* 1993; **329**(27): 1988–1992.
18. Chiu KC, Lee NP, Cohan P, Chuang LM. Beta cell function declines with age in glucose tolerant Caucasians. *Clin Endocrinol (Oxf)* 2000; **53**(5): 569–575.
19. Chiu KC, Martinez DS, Chu A. Comparison of the relationship of age and beta cell function in three ethnic groups. *Clin Endocrinol (Oxf)* 2005; **62**(3): 296–302.
20. Basu R, Breda E, Oberg AL, *et al*. Mechanisms of the age-associated deterioration in glucose tolerance: contribution of alterations in insulin secretion, action, and clearance. *Diabetes* 2003; **52**(7): 1738–1748.
21. Elahi D, Muller DC, McAloon-Dyke M, Tobin JD, Andres R. The effect of age on insulin response and glucose utilization during four hyperglycemic plateaus. *Exp Gerontol* 1993; **28**(4–5): 393–409.
22. Rooyackers OE, Adey DB, Ades PA, Nair KS. Effect of age on in vivo rates of mitochondrial protein synthesis in human

skeletal muscle. *Proc Natl Acad Sci U S A* 1996; **93**(26): 15364–15369.
23. Toth MJ, Sites CK, Cefalu WT, Matthews DE, Poehlman ET. Determinants of insulin-stimulated glucose disposal in middle-aged, premenopausal women. *Am J Physiol Endocrinol Metab* 2001; **281**(1): E113–E121.
24. Roder ME, Schwartz RS, Prigeon RL, Kahn SE. Reduced pancreatic B cell compensation to the insulin resistance of aging: impact on proinsulin and insulin levels. *J Clin Endocrinol Metab* 2000; **85**(6): 2275–2280.
25. Iozzo P, Beck-Nielsen H, Laakso M, Smith U, Yki-järvinen H, Ferrannini E. Independent influence of age on basal insulin secretion in nondiabetic humans. European group for the study of insulin resistance. *J Clin Endocrinol Metab* 1999; **84**(3): 863–868.
26. Fritsche A, Madaus A, Stefan N, *et al*. Relationships among age, proinsulin conversion, and beta-cell function in nondiabetic humans. *Diabetes* 2002; **51**(Suppl 1): S234–S239.
27. Festa A, Williams K, Hanley AJ, Haffner SM. Beta-cell dysfunction in subjects with impaired glucose tolerance and early type 2 diabetes: comparison of surrogate markers with first-phase insulin secretion from an intravenous glucose tolerance test. *Diabetes* 2008; **57**(6): 1638–1644.
28. Bonora E, Targher G, Alberich M, *et al*. Homeostasis model assessment mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies on subjects with various degrees of glucose intolerance and insulin sensitivity. *Diabetes Care* 2000; **23**(1): 57–63.
29. Haffner SM, Miettinen M, Stern MP, The homeostasis model in the San Antonio Heart Study. *Diabetes Care* 1997; **20**(7): 1087–1092.
30. Haffner SM, Kennedy E, Gonzalez C, Stern MP, Miettinen H. A prospective analysis of the HOMA model: the Mexico City Diabetes Study. *Diabetes Care* 1996; **19**(10): 1138–1141.
31. Song Y, Manson JE, Tinker L, *et al*. Insulin sensitivity and insulin secretion determined by homeostasis model assessment and risk of diabetes in a multiethnic cohort of women: the Women's Health Initiative Observational Study. *Diabetes Care* 2007; **30**(7): 1747–1752.
32. Maedler K, Schumann DM, Schulthess F, *et al*. Aging correlates with decreased beta-cell proliferative capacity and enhanced sensitivity to apoptosis: a potential role for Fas and pancreatic duodenal homeobox-1. *Diabetes* 2006; **55**(9): 2455–2462.
33. Ishikawa M, Pruneda ML, Adams-Huet B, Raskin P. Obesity-independent hyperinsulinemia in nondiabetic first-degree relatives of individuals with type 2 diabetes. *Diabetes* 1998; **47**(5): 788–792.

DOI: 10.1002/dmrr