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Bemnete Eyob Tadesse Date

Differential association of family history of diabetes and subtypes of prediabetes

By

Bemnete Eyob Tadesse
MPH

Global Epidemiology

_____

K.M. Venkat Narayan, MD, MSc, MBA
Committee Chair

_____

Lisa R. Staimez, MPH, PhD
Committee Chair

Differential association of family history of diabetes and subtypes of prediabetes

By

Bemnete Eyob Tadesse

Bachelor of Science
Wilson College
2010

Thesis Committee Chairs:
K.M. Venkat Narayan, MD, MSc, MBA
Lisa R. Staimez, MPH, PhD

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Abstract

Differential association of family history of diabetes and subtypes of prediabetes
By Bemnete Eyob Tadesse

Objective: Subtypes of prediabetes, isolated impaired glucose tolerance [iIGT] and isolated impaired fasting glucose [iIFG], are associated with different physiologic dysfunctions. The aim of the present analysis was to examine family history of type 2 diabetes (T2DM) as a risk factor for iIGT and iIFG among Asian Indians, a population that has innate susceptibility to reduced β-cell function.

Methods: We studied a population of 1,635 men and women from the Diabetes Community Lifestyle Improvement Program (D-CLIP) in Chennai, India. Family history was defined as a first-degree relatives including parents and siblings with T2DM. All subjects were given a 75g oral glucose tolerance test after an overnight fast. Fasting, 30-minute and 120-minute glucose and insulin were measured. Multinomial polytomous regression was used with glycemic status (normoglycemia [NGT], iIFG, iIGT, combined IFG and IGT, and T2DM) as the dependent variable according to American Diabetes Association guidelines. β-cell function was estimated using oral disposition index (DI_O) and insulin resistance was estimated by homeostasis model assessment (HOMA-IR).

Results: There were 341 individuals who had NGT, 200 iIFG, 202 iIGT, 268 IFG/IGT and 252 individuals had T2DM. A positive family history was reported by 745 (59%) of the participants. The mean age was 44 years (SD 9.3), mean BMI 27.4 kg/m^2 (SD 3.8) with 803 (63.6%) male participants. A positive family history was not statistically associated with iIFG [odds ratio, OR, 1.28, 95% confidence interval (CI) 0.89 – 1.84] and iIGT (OR 1.18, CI 0.82 – 1.68) in an age-, sex-, BMI- adjusted model when compared to normoglycemia. When stratified across mean age (44 years), family history of diabetes was significantly associated with iIFG (OR 1.79, CI 1.02 - 3.17) but not iIGT (OR 0.98, CI 0.59 – 1.62) adjusted for sex, BMI and HOMA-IR. DIo explained a large component of the relationship of family history and iIFG in young adults but not HOMA-IR.

Conclusions: These results demonstrate that family history of T2DM is an important risk factor for Asian Indian young adults who develop the iIFG subtype of prediabetes. Future longitudinal studies are needed to explore the role of poor β-cell function in the early development of prediabetes, particularly iIFG.

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Contents

INTRODUCTION

Type 2 diabetes mellitus (T2DM), one of the most common chronic diseases, affects over 418 million people globally, a number that is predicted to steeply rise to 642 million in the next 25 years [1]. Micro- and macro-vascular diabetic complications such as nephropathy, retinopathy, neuropathy, heart disease and atherosclerosis result in reduced life expectancy by as much as 10 years [2-5]. Complications can develop silently, without any obvious symptoms in individuals with hyperglycemia, even during the precursor state of diabetes, prediabetes [1]. Over 318 million people have prediabetes globally and are at high risk of developing T2DM [1].

Prediabetes consists of three major subtypes; isolated impaired fasting glucose (iIFG), isolated impaired glucose tolerance (iIGT), and a group that has both IFG and IGT combined (IFG/IGT) [4, 6, 7]. While both IFG and IGT are measures used to assess risk of diabetes, the two measures may reflect different physiological mechanisms of development [6, 7]. Isolated impaired fasting glucose may be primarily associated with impairments in hepatic insulin sensitivity and pancreatic β-cell function, whereas iIGT is associated with whole body insulin resistance [6-9]. The two groups are also different in patterns of impaired insulin secretion [9]. While IGT subjects have both early- and late-phase defects in insulin secretory response, iIFG subjects have decreased first phase insulin secretory response [9]. Thus, hepatic insulin resistance and impairment in insulin secretion lead to increased fasting hepatic glucose secretion resulting in fasting hyperglycemia in iIFG subject [7]. Late impaired insulin secretion in iIGT in combination with whole body insulin resistance result in prolonged hyperglycemia [7]. Individuals with the combined IFG/IGT demonstrate both hepatic and muscle insulin

resistance [7, 9]. This evidence suggests that iIFG is a problem related to impairments in insulin secretion that may be innate, inherited, or acquired in earlier phases of life compared to average phases or time points, whereas iIGT is associated with pronounced insulin resistance as commonly seen over time, supported by the physiology related to obesity and aging [2, 10, 11].

South Asians experience the highest burden of T2DM with an estimated increase of the disease by 150% between the years 2000 and 2035 [12-14]. Strikingly, they develop T2DM at lower body mass indices (BMIs) and younger ages when compared to Caucasians and other ethnic groups [15-17]. They also show reduced β-cell function early, even with mild hyperglycemic status [18-20]. These studies highlight that there is an inherent susceptibility for β-cell dysfunction in this population even in the absence of commonly recognized risk factors such as obesity, physical inactivity and peripheral insulin resistance [14, 19, 21, 22]. A recent 10 year follow-up study among Asian Indians reported incidence rates of diabetes and prediabetes as high as 22.2 and 29.5 per 1,000 person years respectively [22]. The study further reported a 59% conversion rate from prediabetes to diabetes after 9 years of follow-up [22]. Furthermore, the population has unusually high proportion of iIFG (17%) compared to other high-risk populations (5% iIFG in Pima Indians) and lower proportion of iIGT (4%) [23]. Indeed, across studies examining the prevalence of iIFG and iIGT, various populations have largely noted a greater prevalence of iIGT [21, 24]. Thus, Asian Indians have a strong disease susceptibility with a different pathophysiology from commonly studied ethnicities, evident by early β-cell dysfunction and a higher proportions of iIFG.

Family history of diabetes is a strong, easily assessed, independent risk factor that increases the risk of T2DM between two and six fold [25-27]. Only a fraction of the family history and T2DM association is explained by lifestyle, anthropometric and genetic risk factors [28]. In a study that investigated the mediation of risk factors across the association of family history of diabetes and incidence of type 2 diabetes, BMI, waist and hip circumference, smoking, diet, physical activity, education level and genetic risk score combined explained only 13% of the association [28]. In addition, family history of diabetes has a graded association with the prevalence of diabetes, strengthening with a greater number of family members with diabetes [26]. Due to the independence and ease of ascertainment, family history is included in various diabetes risk models in the US, Europe, and Australia as a method of identifying high-risk individuals for early detection [29].

Studies of disease progression and risk factors of diabetes often examine high-risk populations, including individuals with prediabetes. Across the vast majority of T2DM research, prediabetes is largely defined by IGT criteria [30-34], and thus, existing research lacks examination of the iIFG subtype. Given the differences in physiological mechanisms of diabetes development across iIFG and iIGT, associations of family history may vary across subtypes. Studies in Asian Indians reported family history of diabetes as a significant risk factor for the broad category of prediabetes (odds ratio, OR, 1.67, 95% Confidence Interval, CI, 1.42 - 1.97) [35-38], without analyzing subtypes like iIFG. This study examines the association of family history of diabetes with iIFG and iIGT in Asian Indian adults from Chennai, India.

STATISTICAL METHODS

Study participants

The individuals from this study are participants in the baseline testing of the Diabetes Community Lifestyle Improvement Program (D-CLIP). The design of D-CLIP is described elsewhere [39]. In brief, D-CLIP is a lifestyle intervention randomized trial for the prevention of T2DM in Chennai, India [18, 39, 40]. A total of 19,377 individuals were screened from the community using a short survey, anthropometric measurements, and a random capillary blood glucose test [18, 39, 40]. Overweight men and women between the ages of 20 – 65 with random capillary glucose of ≥ 6.1 mmol/L (110 mg/dL) were eligible for baseline testing [18, 39, 40]. Exclusion criteria for D-CLIP participation included: pregnancy or breast-feeding, diagnosed diabetes, heart disease, serious illness or conditions which hindered physical activity [18, 39, 40]. Between 2008 and 2011 a total of 1,285 eligible participants completed baseline testing and were included in the present study.

Study procedures

Study procedures have been described elsewhere [39]. Briefly, a 75 g oral glucose tolerance test (OGTT) was administered after an overnight fast (at least 8 hears). Blood samples were collected at fasting, 30 minutes and then 120 minutes after consumption of glucose bolus [18, 39, 40]. In addition anthropometrics such as weight, height, body fat and waist circumference were collected [18, 39, 40].

Key Measures

Abnormal glucose regulation was defined as follows according to the American Diabetes Association criteria [41]: diabetes as fasting plasma glucose ≥7.0 mmol/L (126

mg/dL) or 2 hours postload glucose ≥ 11.1 mmol/L (200mg/dL) or both; iIFG as fasting plasma glucose 5.6 – 6.9 mmol/L (100 – 125 mg/dL) and 2-h postload glucose < 7.8 mmol/L (140 mg/dL) iIGT as 2 hours postload glucose 7.8 – 11.0 mmol/L (140 – 199 mg/dL) and fasting plasma glucose < 5.6 mmol/L (100 mg/dL); normoglycemia (NGT) as fasting plasma glucose 5.6 mmol/L (100 mg/dL) and 2-h postload glucose < 7.8 mmol/L (140 mg/dL) and combined IFG and IGT as fasting plasma glucose 5.6 – 6.9 mmol/L (100 – 125 mg/dL) and 2-h postload glucose 7.8 – 11.0 mmol/L (140-199 mg/dL).

The primary predictor variable was family history of diabetes measured as a dichotomous variable. As part of the baseline testing, participants filled out a questionnaire where they identified all first degree-relatives in addition to other family members with T2DM. For this study, family history of diabetes was defined as having at least one first-degree relative with T2DM specifically a mother, father, brother, or sister.

Covariates

Age, sex, body mass index (BMI) education, marital status, income, exercise, smoking and hypertension were defined from the administered questionnaire. To get sufficient number of subjects in the five glycemic groups, age was dichotomized into either "younger" or "older" using the mean age of the participants (44 years) for stratified analysis. Education was dichotomized as less than graduate-level (less than high school, high school higher secondary, technical education and undergraduate) vs. graduate-level (post graduate or above). Income was dichotomized as less than 25,000 Rupees (R) vs. greater than 25,000 R. Smoking was defined as being a current smoker and past and never smokers were combined. Hypertension was defined as systolic blood pressure of ≥

140 mmHg or diastolic blood pressure of ≥ 90mmHg or based on medical history use of medications. Out of the 1,285 participants who underwent baseline testing, subjects were excluded if they lacked any family history data, for missing glucose values and for having glucose or insulin variables that are considered biologically implausible (where 30 minutes insulin is less than fasting insulin or 30 minute glucose is less than fasting glucose). The final sample size was 1,635 for all analyses.

Calculations

Insulin resistance was estimated using homeostasis model assessment of insulin resistance (HOMA-IR) using the following formula: HOMAI-IR = [fasting insulin × fasting glucose] / 22.5[42]. β-cell function was estimated by the oral disposition index (DI_O) as a function of the insulinogenic index (IGI) using the formula $DI_O = ([\Delta I_{0-30}] / [\Delta G_{0-30}] \times [1/\text{fasting insulin}])$ [43]. Whole body insulin sensitivity was estimated using the modified Matsuda index which is calculated as: Modified Matsuda = (10,000/square root of [fasting glucose × fasting insulin] × [mean glucose × mean insulin]) [44, 45].

Statistical Analysis

Continuous variables were presented as mean (standard deviation) and categorical variables as proportions (%). The baseline characteristics of subjects were assessed by family history of diabetes status using student's t-test for continuous variables and chi-squared test for categorical variables. Non-normally distributed continuous variables were log transformed to achieve a normal distribution and presented as geometric mean (standard deviation). A multivariate polytomous logistic regression was performed to evaluate the contribution of family history of diabetes to iIFG, iIGT, IFG/IGT and T2DM using NGT as the reference group. The variables age, sex, BMI, HOMA-IR and DI_O were

added step by step to create the final models. We further examined the interaction of FHD with age (continuous, categorical using textiles and categorical using mean), sex and BMI (continuous) through backward elimination using the Wald chi-squared test statistics. The regression models are presented as odds ratios (ORs) and the 95% confidence intervals. SAS Version 9.3 statistical software was used for all statistical analyses (SAS Institute, Cary, NC). A two-side probability was used for all tests of statistical significance. A $p < 0.05$ was considered statistically significant

RESULTS

The basic characteristics of the study sample by family history of diabetes are shown in Table 1 (unadjusted). More than half (n = 745, 59%) of the study participants reported family history of diabetes. Those with a positive family history of diabetes were significantly younger when compared to those without family history of diabetes with the mean age of 43 years (SD 9.3) vs. 46 (SD 8.8), ($p < 0.0001$). Participants with a family history of diabetes also had significantly higher BMI when compared to those without family history of diabetes with a mean BMI 28 kg/m^2 (SD 3.8) vs. 27 (SD 3.9) ($p = 0.0004$). In addition, participants with positive family history of diabetes were better educated (graduate-level 61% vs 49%, $p < 0.01$), earned more money (monthly household income > 25,000 Rs 35% vs 27%, $p < 0.01$), and had a higher percent body fat (29% vs. 28%, $p = 0.08$) compared to those without family history of diabetes. Waist circumference, exercise, smoking, and hypertension were not different between the two groups. Participants' values for HbA1c as well as 0, 30, and 120 minute glucose and insulin were also similar between those with a family history of diabetes compared to those without. Participants with a family history of diabetes had a significantly higher HOMA-IR ($p = 0.03$) and significantly lower DI_O ($p = 0.003$) while the IGI ($p = 0.2$) and modified matsuda index ($p = 0.1$) were comparable between the two groups. Overall, 341 (27%) had NGT, 252 (20%) had T2DM, 200 (16%) iIFG, 202 (16%) iIGT and 268 (21%) had IFG/IGT.

Table 2 shows the association of family history of diabetes with glycemic status. In a bivariate analysis (Model 1), family history of diabetes increased the odds of iIFG by 20% ($p = 0.3$), iIGT by 14% ($p = 0.5$), IFG/IGT, 41% ($p = 0.03$) and diabetes by 20% (p

= 0.3) compared to NGT. In a multivariable model (Model 4) adjusted for age, sex and BMI, family history of diabetes was associated more highly with both iIFG and with iIGT compared to NGT, although associations remained not statistically significant. The additional adjustment of the model with HOMA-IR did not change the relative associations; ORs were reduced approximately 3% across all prediabetes and diabetes categories. However, the adjustment of the model for the DI_O attenuated up to 35% (Models 6, 7).

Given the significant differences in age, BMI, and sex between those with family history of diabetes and those without, we assessed effect modification of age, sex, and BMI on the association of family history of diabetes and glycemic status. Age as a continuous variable in a family history interaction term was borderline significant (p = 0.07) while sex, and continuous BMI were not statistically significant. Upon stratification by age, family history diabetes was significantly associated with iIFG (n = 90) but not iIGT (n = 103), specifically in the younger group (Table 3). Adjusted for sex and BMI, the odds of iIFG in the younger group was significantly greater than having NGT (Model 1, OR = 1.84, 95% CI = 1.05 – 3.23, p = 0.03). This association was not detected in the older group (Model 1, OR = 1.00, 95% CI = 0.60 – 1.64, p = 0.8). These differential findings across prediabetes groups in the younger age stratum were maintained after further adjustment for HOMA-IR (Model 2 OR iIFG = 1.79, 95% CI = 1.02 – 3.17, p = 0.04), but not DIo (Model 3, OR iIFG = 1.53, 95% CI = 0.85 – 2.74, p = 0.2). DIo attenuated associations, regardless of whether HOMA-IR was in the model; thus DIo explained a significant proportion of the association between family history of diabetes and iIFG.

DISCUSSION

This study examined the differences in family history of diabetes between iIFG and iIGT, two states of prediabetes that develop under different physiologic and metabolic conditions. The results of the present study suggest that: (1) family history of disease was significantly associated with greater iIFG but not iIGT, specifically among young adults less than 44 years in age and (2) poor β-cell function explains a large component of the relationship of family history and iIFG in young adults but not HOMA-IR.

Other studies in different populations also found that family history is associated with general prediabetes, however, most did not differentiate between iIFG and iIGT in their results [22, 36, 38, 46]. However, a cross sectional study on 8,106 individuals of European origins from the German Center for Diabetes Research, reported after adjusting for sex, age and BMI that family history of diabetes increased the risk for iIFG by 26% while the association with iIGT was not significant [47]. Moreover, another cross-sectional study in Mexico determined the association of family history of diabetes and IFG in 3,863 children and adolescents aged 7 – 15. Results of the present study showed an independent association of family history with IFG after adjusting for age, sex and BMI [48].

As previous studies have reported, there is an underlying innate susceptibility in Asian Indians for glucose intolerance evident by early β-cell dysfunction, with β-cell dysfunction more highly associated with glycemic status than insulin resistance [17, 19]. According to a meta-analysis, beta cell function, along with lower BMIs and the prediabetes subtype of iIFG are all associated with family history of diabetes [47]. In another meta-analysis that includes various ethnicities, the estimated conversion rates to

T2DM within a year was higher for iIFG (sevenfold) than iIGT (fivefold) [49] further suggesting individuals with iIFG may have a unique predisposition to diabetes development. The notion that iIFG is a condition of innate or inherited reductions of insulin secretion is further support by our study with the increased association of family history with iIFG.

This study has several strengths. Participants for the baseline study were selected from a large-scale community screening of 19,377 individuals. The study included participants who were iIGT or iIFG, allowing comparison across these distinct prediabetes groups. Furthermore, the study examined the association among a population that has an understudied phenotype of high levels of diabetes but low levels of obesity. Another strength of the study is that participation was limited to previously undiagnosed T2DM subjects. Since participants are unaware of their diabetes status during the questionnaire, recall bias is minimized when answering family history and other lifestyle related questions. Furthermore, our definition of family history of diabetes was comprehensive including mother, father, brother, and sister.

There are several potential limitations to this study. The study population may not be representative of all Asian Indians due to convenience sampling. Since family history of diabetes was self-reported, some study participants may have reported no family history, even if their family history status was unknown to them. Due to the cross-sectional nature of the study and the age dependency of T2DM, young participants were likely to have healthy first-degree relatives that could acquire T2DM over the years which could be a misclassification of family history. Furthermore, this study relied on data from individuals who were overweight. However, low BMIs were included in the

sample due to the South Asian BMI cut-points set to a lower threshold for overweight and also due to the overweight criteria of the D-CLIP study being sufficiently fulfilled by waist criteria, irrespective of BMI. The age stratified analysis only compared two age strata due to sample size.

In conclusion, family history of diabetes is associated with iIFG in young adults but not iIGT after adjusting sex, BMI and insulin resistance. β-cell function explained a large component of the relationship of family history and iIFG, suggesting the need to develop longitudinal studies that explore β-cell dysfunction in those with iIFG, particularly in the earlier stages of the life course. Identifying risk factors for early β-cell dysfunction may produce new and more effective strategies to reduce prediabetes in Asian Indians and other high-risk, lean populations, and subsequently, reduce the global burden of diabetes and its costly complications.

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TABLES

Table 1 - Selected socio-demographic and metabolic characteristics by family history of diabetes: The Diabetes Community Lifestyle Improvement Program (D-CLIP) trial baseline testing participants (N=1,263)

Characteristics	Overall (n=1,263)	FHD+ (n = 745)	FHD- (n =518)	*p*
Socio demographic characteristics				
Male sex, n (%)	803 (63.6)	454 (60.9)	349 (67.4)	0.02
Age (years)	44.2 ± 9.3	43.1 ± 8.8	45.9 ± 9.6	<0.0001
Education: graduate, n (%)	707 (56.2)	456 (61.4)	251 (48.6)	<0.0001
Married, n (%)	1,125 (89.1)	652 (87.5)	473 (91.3)	0.03
Household income >25,000 R n, (%)	358 (31.7)	230 (35.1)	128 (27.1)	0.004
Health Characteristics				
BMI (kg/m^2)	27.4 ± 3.8	27.7 ± 3.9	27.1 ± 3.6	0.004
Waist circumference (cm)	94 ± 9.4	94.1 ± 9.5	93.9 ± 9.3	0.8
Body fat (%)	28.7 ± 7.8	29 ± 7.9	28.2 ± 7.7	0.08
Exercise, n (%)	719 (56.9)	414 (55.6)	305 (58.9)	0.2
Smoke, n (%)	106 (8.4)	57 (7.7)	49 (9.5)	0.3
Hypertension, n (%)	163 (12.9)	90 (12.1)	73 (14.1)	0.3
Glycemic characteristics				
Fasting glucose (mmol/L)*	5.7 ± 1.2	5.7 ± 1.2	5.7 ± 1.2	0.6
30-min glucose (mmol/L)*	9.6 ± 1.2	9.7 ± 1.2	9.6 ± 1.2	0.4
2 h glucose (mmol/L)*	8.4 ± 1.4	8.4 ± 1.4	8.3 ± 1.4	0.3
Fasting insulin (µlU/mL)*	5.7 ± 1.2	5.7 ± 1.2	5.7 ± 1.2	0.6
30-min insulin (µlU/mL)*	9.6 ± 1.2	9.7 ± 1.2	9.6 ± 1.2	0.4
2-h insulin ((µlU/mL)*	625.8 ± 2	633.3 ± 2	615.1 ± 2	0.5
HbA1c (%)*	6.1 ± 1.1	6.1 ± 1.1	6.1 ± 1.1	0.4
1/fasting Insulin (L/pmol)*	0.01 ± 0.009	0.02 ± 0.009	0.01 ± 0.01	0.1
Insulinogenic Index ($pmol_{ins}$ /$mmol_{glu}$)	88.4 ± 2.3	86 ± 2.3	92 ± 2.3	0.2
HOMA-IR [$mmol_{glu}$× $pmol_{ins}/(L^2)$]	3.4 ± 2.1	3.4 ± 2.3	3.2 ± 2.0	0.03
Modified Matsuda [$(L^2)/mmol_{glu}$× $pmol_{ins}$]*	9.1 ± 1.7	8.9 ± 1.7	9.4 ± 1.7	0.1
Oral disposition Index ($L/mmol_{glu}$)*	1.3 ± 2.4	1.2 ± 2.3	1.4 ± 2.4	0.003
Glycemic Status				
NGT, n (%)	341 (27.0)	188 (25.2)	153 (29.5)	0.09
Isolated IFG, n (%)	200 (15.8)	119 (16.0)	81 (15.6)	0.9
Isolated IGT, n (%)	202 (16.0)	118 (15.8)	84 (16.2)	0.9
IFG/IGT, n (%)	268 (21.2)	170 (22.8)	98 (18.9)	0.1
Diabetes, n (%)	252 (20.0)	150 (20.1)	102 (19.7)	0.8

+FHD = with family history of diabetes, FHD- = without family history of diabetes BMI= body mass index, NGT = normoglycemia, iIFG = isolated impaired fasting glucose, iIGT = isolated impaired glucose tolerance, IFG/IGT = combined IFG and IG Data expressed as mean ± (SD) or n, (%) *Geometric mean ± (geometric SD)

Table 2 - Multinomial logistic regression models for the association between family history of diabetes and glucose tolerance categories: The Diabetes Community Lifestyle Improvement Program (D-CLIP) trial baseline testing participants (N=1,263)

Model		iIFG (n = 200)		iIGT(n = 202)		IFG/IGT (n = 268)		Diabetes (n =252)	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Model 1									
	FHD	1.20	0.84 - 1.70	1.14	0.80 - 1.63	1.41	1.02 - 1.96	1.20	0.86 - 1.66
Model 2									
	FHD	1.32	0.92 - 1.89	1.19	0.83 - 1.70	1.61	1.15 - 2.25	1.42	1.01 - 2.00
	Age	1.04	1.02 - 1.06	1.02	1.00 - 1.03	1.05	1.03 - 1.06	1.06	1.04 - 1.08
Model 3									
	FHD	1.31	0.91 - 1.88	1.20	0.84 - 1.72	1.61	1.15 - 2.25	1.46	1.04 - 2.06
	Age	1.04	1.02 - 1.06	1.02	1.00 - 1.04	1.05	1.03 - 1.06	1.06	1.04 - 1.08
	Male	0.92	0.64 - 1.32	1.23	0.85 - 1.77	1.07	0.77 - 1.50	1.48	1.04 - 2.11
Model 4									
	FHD	1.28	0.89 - 1.84	1.18	0.82 - 1.68	1.54	1.09 - 2.16	1.42	1.01 - 2.01
	Age	1.04	1.02 - 1.06	1.02	1.00 - 1.04	1.05	1.03 - 1.07	1.06	1.04 - 1.08
	Male	1.01	0.70 - 1.47	1.37	0.94 - 2.00	1.35	0.95 - 1.92	1.68	1.17 - 2.42
	BMI	1.06	1.01 - 1.11	1.07	1.01 - 1.12	1.13	1.08 - 1.18	1.07	1.02 - 1.13
Model 5									
	FHD	1.25	0.87 - 1.80	1.15	0.80 - 1.65	1.50	1.05 - 2.13	1.39	0.96 - 2.02
	Age	1.04	1.02 - 1.06	1.02	1.00 - 1.04	1.06	1.04 - 1.08	1.08	1.06 - 1.10
	Male	0.91	0.63 - 1.34	1.26	0.86 - 1.85	1.15	0.80 - 1.67	1.45	0.97 - 2.17
	BMI	1.00	0.95 - 1.06	1.01	0.96 - 1.07	1.02	0.97 - 1.07	0.91	0.86 - 0.97
	HOMA-IR	1.47	1.26 - 1.70	1.41	1.21 - 1.63	1.87	1.64 - 2.14	2.36	2.05 - 2.71
Model 6									
	FHD	1.07	0.73 - 1.57	1.00	0.69 - 1.46	1.14	0.77 - 1.68	1.03	0.65 - 1.65
	Age	1.04	1.02 - 1.06	1.05	1.00 - 1.04	1.05	1.03 - 1.07	1.07	1.04 - 1.10
	Male	1.01	0.69 - 1.48	1.37	0.93 - 2.01	1.36	0.91 - 2.02	1.69	1.04 - 2.75
	BMI	1.04	0.98 - 1.09	1.05	1.00 - 1.10	1.09	1.04 - 1.15	1.02	0.98 - 1.09
	$logDI_O$	0.30	0.22 - 0.41	0.38	0.28 - 0.51	0.08	0.06 - 0.12	0.02	0.01 - 0.02
Model 7									
	FHD	1.07	0.73 - 1.57	1.00	0.69 - 1.46	1.14	0.77 - 1.69	1.03	0.65 - 1.65
	Age	1.04	1.02 - 1.06	1.02	1.00 - 1.04	1.05	1.03 - 1.08	1.07	1.05 - 1.10
	Male	0.95	0.64 - 1.40	1.29	0.87 - 1.90	1.23	0.82 - 1.85	1.53	0.93 - 2.51
	BMI	1.01	0.95 - 1.07	1.02	0.97 - 1.08	1.04	0.98 - 1.10	0.96	0.89 - 1.03
	HOMA-IR	1.22	1.00 - 1.42	1.20	1.04 - 1.40	1.36	1.18 - 1.58	1.44	1.22 - 1.69
	$logDI_O$	0.33	0.24 - 0.47	0.42	0.30 - 0.57	0.10	0.07 - 0.15	0.02	0.01 - 0.03

FHD = family history of diabetes, BMI = body mass index, iIFG = isolated impaired fasting glucose, iIGT = isolated impaired glucose tolerance, IFG/IGT = combined IFG and IG, HOMA-IR = homeostasis model assessment of insulin resistance, logDIo = log Oral disposition Index, For all models normoglycemia is comparison group

Table 3 - Multinomial logistic regression models for the association between family history of diabetes and glucose tolerance categories, stratified by age category : The Diabetes Community Lifestyle Improvement Program (D-CLIP) trial baseline testing participants (N=1,263)

		Young (< 44 years)		Old (≥ 44 years)	
		OR	**95% CI**	**OR**	**95% CI**
Model 1: FHD, Sex, BMI					
	iIFG	1.84	1.05 - 3.23	1.00	0.60 - 1.64
	iIGT	0.94	0.58 - 1.54	1.48	0.89 - 2.49
	IFG/IGT	1.93	1.14 - 3.26	1.30	0.82 - 2.06
	T2DM	1.06	0.63 - 1.80	1.61	1.02 - 2.53
Model 2: FHD, Sex, BMI, HOMA-IR					
	iIFG	1.79	1.02 - 3.17	0.98	0.59 - 1.62
	iIGT	0.92	0.56 - 1.51	1.46	0.87 - 2.45
	IFG/IGT	1.86	1.08 - 3.22	1.28	0.80 - 2.06
	T2DM	1.05	0.58 - 1.88	1.57	0.97 - 2.55
Model 3: FHD, Sex, BMI, $logDI_O$					
	iIFG	1.53	0.85 - 2.74	0.83	0.49 - 1.40
	iIGT	0.80	0.48 - 1.34	1.28	0.75 - 2.18
	IFG/IGT	1.56	0.86 - 2.85	0.89	0.53 - 1.51
	T2DM	1.10	0.52 - 2.31	0.94	0.51 - 1.71
Model 4: FHD, Sex, BMI, HOMA-IR, $logDI_O$					
	iIFG	1.51	0.84 - 2.72	0.84	0.50 - 1.42
	iIGT	0.80	0.48 - 1.33	1.30	0.76 - 2.21
	IFG/IGT	1.53	0.83 - 2.80	0.92	0.54 - 1.56
	T2DM	1.07	0.51 - 2.27	0.96	0.52 - 1.77

44 years = mean age, FHD = family history of diabetes, BMI = body mass index, iIFG = isolated impaired fasting glucose, iIGT = isolated impaired glucose tolerance, IFG/IGT = combined IFG and IG, HOMA-IR = homeostasis model assessment of insulin resistance, logDIo = log Oral disposition Index, For all models normoglycemia is comparison group