

## Glycemic Thresholds for Diabetes-Specific Retinopathy: Implications for Diagnostic Criteria for Diabetes

The DETECT-2 Collaboration

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*Objective:* To re-evaluate the relationship between glycemia and diabetic retinopathy.

*Research design and methods:* We conducted a data pooling analysis of nine studies from five countries with 44623 participants aged 20 to 79 years with gradable retinal photographs. The relationship between diabetes-specific retinopathy (defined as moderate or more severe retinopathy) and three glycemic measures: fasting plasma glucose (FPG; n=41411), 2-hour post oral glucose load plasma glucose (2-h PG; n=21334), and glycated hemoglobin (HbA1c; n=28010), was examined.

*Results:* When diabetes-specific retinopathy was plotted against continuous glycemic measures, a curvilinear relationship was observed for FPG and HbA1c. Diabetes-specific retinopathy prevalence was low for FPG < 6.0 mmol/L and HbA1c < 6.0% but increased above these levels. Based on vigintile (20 groups with equal numbers) distributions, glycemic thresholds for diabetes-specific retinopathy were observed over the range 6.4-6.8 mmol/L for FPG, 9.8-10.6 mmol/L for 2-h PG, and 6.3-6.7% for HbA1c. Thresholds for diabetes-specific retinopathy from receiver operating characteristic curve analyses were 6.6 mmol/L for FPG, 13.0 mmol/L for 2-h PG, and 6.4% for HbA1c.

*Conclusion:* This study broadens the evidence-base on diabetes diagnostic criteria. A narrow threshold range for diabetes-specific retinopathy was identified for FPG and HbA1c but not for 2-h PG. The combined analyses suggest that the current diabetes diagnostic level for FPG could be lowered to 6.5 mmol/L and that an HbA1c of 6.5% is a suitable alternative diagnostic criterion.

The current diagnostic cut-points for diabetes (fasting plasma glucose [FPG] of 7.0 mmol/L and 2-hour post oral glucose load plasma glucose [2-h PG] of 11.1 mmol/L) are largely based on glycemic levels associated with a substantially increased risk of diabetes-associated microvascular complications, particularly retinopathy, above these levels (1-2). These cut-points were derived from cross-sectional epidemiological studies which examined retinopathy across a range of glycemic levels. The datasets used for this purpose were from Pima Indians, an Egyptian study, and unpublished data from the 3<sup>rd</sup> National Health and Nutrition Examination Survey (NHANES) (2).

Other studies have also examined this relationship, but the results have been inconsistent (3-5). All studies reported to date have had limited statistical power to examine

this relationship in detail and have adopted a very broad definition of retinopathy that included many cases of mild retinopathy, now known to have causes other than hyperglycemia (6). A more clinically relevant endpoint is diabetes-specific retinopathy (moderate or more severe levels of retinopathy) that is invariably due to hyperglycemia. Also different statistical methods have been used in previous studies which has an important effect on derived cut-points (5,7).

Several new datasets with retinopathy data have become available since the original studies used to derive current diabetes diagnostic cut-points (1-2). The DETECT-2 collaboration has pooled these datasets to examine and re-evaluate the relationship between retinopathy and three glycemic measures, FPG, 2-h PG, and glycated

hemoglobin (HbA1c). The size of the DETECT-2 dataset has allowed us to focus on the relationship between measures of glycemia and diabetes-specific retinopathy (i.e. moderate or more severe levels of retinopathy). These analyses were designed to inform current deliberations on possible revisions to the diagnostic criteria for diabetes.

## RESEARCH DESIGNS AND METHODS

The DETECT-2 project is an international data pooling collaboration. The primary objective of the collaboration was to examine aspects of screening for type 2 diabetes and impaired glucose tolerance across various populations and ethnic groups. Details of the collaboration are reported elsewhere (8-9). For the current analysis, studies included in the DETECT-2 database where retinopathy data had been collected were invited to provide these data for this analysis. Additional studies with retinopathy data identified by co-investigators through personal contact or literature search were also invited to contribute datasets. Retinopathy data were available from 12 studies in eight countries (4-5,7,10-18). This analysis focuses on the nine studies from five countries which had retinopathy data by grading. Participants aged 20 to 79 years, including those with known diabetes, with gradable retinal photographs and at least one measure of glycemia, were included. All studies were approved by respective institutional review boards and were conducted according to the Declaration of Helsinki.

**Classification of retinopathy.** The retinal photograph grading was performed by individual study centers. Retinopathy was classified as present or absent for initial analysis. Where data were available, those with retinopathy were further classified as minimal non-proliferative diabetic retinopathy (NPDR), mild NPDR, moderate NPDR, severe NPDR, or proliferative diabetic

retinopathy (PDR) based on the information provided by individual studies using the modified Airlie House classification levels (19), modified Early Treatment Diabetic Retinopathy Study (ETDRS) levels (20), or the Fukuda standard (21). Levels 14 to 20 indicate minimal NPDR; Levels 30 to 35 or Fukuda standard A1 indicate mild NPDR; Levels 40 to 47 or Fukuda standard A2 indicate moderate NPDR; Levels 50 to 53 or Fukuda standard A3 indicate severe NPDR; levels 60 to 90 or Fukuda standards A4 and B1 to B4 indicate PDR. The final retinopathy grading for each participant was based on the diagnosis in the more severely affected eye. The primary outcome used in this study was diabetes-specific retinopathy, which we defined as moderate or more severe levels of retinopathy.

All nine studies measured plasma glucose and the six studies which measured HbA1c used high performance liquid chromatography of which five used a DCCT-aligned assay (5,12,14-15,18).

**Statistical analysis.** Prevalence of diabetes-specific retinopathy was examined by: 1) 0.5 unit intervals of glycemic measures, and 2) vigintiles (dividing participants into 20 equally sized groups) of the distribution for each measure of glycemia. Logistic regression models were applied to test the relationships between diabetes-specific retinopathy and glycemia by 0.5 unit intervals and by vigintiles of each glycemic measure, with the lowest range as the reference. The analyses were repeated after adjusting for study center. The discriminatory power of each measure of glycemia for retinopathy was assessed as the area under the receiver operating characteristic (ROC) curve (AUC). An AUC of 1 indicates perfect discriminatory power and an AUC of 0.5 indicates that the discrimination is no better than chance. ROC curve analyses were used to examine thresholds based on optimizing sensitivity and specificity. The impact of various thresholds

on the prevalence of diabetes was examined by applying these values to the 16381 participants without known diabetes who had all three measures of glycemia.

Sensitivity analysis was performed on studies which 1) used a DCCT-aligned assay for HbA1c (AusDiab, CURES, MESA, NHANES III, SiMES), 2) one of the authors (T.Y.W) was personally involved in the grading of retinopathy using modified ETDRS (ARIC, AusDiab, BMES, MESA, SiMES), 3) participants were predominantly Caucasian (ARIC, AusDiab, BMES, MESA, NHANES III), 4) participants were Asian (CURES, Hiroshima study, SiMES), and 5) participants had all three measures of glycemia.

All statistical analyses were performed using SAS 9.1 for Windows (SAS Institute, Inc., Cary, NC, USA) and SPSS 16.0 for Windows (SPSS, Inc., Chicago, IL, USA).

## RESULTS

**Study participants.** In total, 44623 participants had information on both the presence and severity of retinopathy (Table 1): 1589 had minimal NPDR, 762 had mild NPDR, 430 had moderate NPDR, 50 had severe NPDR, and 171 had PDR. The number of participants available for each measure of glycemia was 41334 for FPG, 21334 for 2-h PG, and 27933 for HbA1c. Of these, 27445 participants had at least two measures and 18533 participants had all three measures. The characteristics of participants by study are shown in Supplementary Table 1 in the online appendix available at <http://care.diabetesjournals.org>.

**Prevalence of retinopathy.** The overall prevalence of any retinopathy was 6.7% and 1.5% for diabetes-specific retinopathy. In people with known diabetes, the prevalence of diabetes-specific retinopathy was 9.4%, in newly diagnosed diabetes 1.0%, in impaired glucose tolerance (1) 0.1%, in impaired fasting glucose (1) 0.1%, and with normal glucose tolerance 0.1%.

Figure 1 shows the prevalence of retinopathy by 0.5 unit intervals for each measure of glycemia for diabetes-specific retinopathy. These plots suggest a curvilinear relationship for FPG and HbA1c and retinopathy. Diabetes-specific retinopathy was virtually absent (prevalence < 0.4%) at low levels for each glycemic measure but began to increase from the FPG category of 6.0-6.4 mmol/L and from the HbA1c category of 6.0-6.4%. The curve for 2-h PG was flatter than for FPG and HbA1c and no definite interval of increase for 2-h PG was obvious.

Logistic regression adjusted for study center showed that the first interval where the odds ratio (OR) for diabetes-specific retinopathy was significantly different from the reference FPG level of 4.0-4.4 mmol/L was 6.5-6.9 mmol/L (OR [95% confidence intervals, CI] 6.0 [2.1-17.1],  $p < 0.01$ ). The corresponding result for HbA1c was 6.5-6.9% (16.8 [2.3-123.7],  $p = 0.01$ ) compared with an HbA1c of 4.0-4.4.

Figure 2 shows the prevalence of diabetes-specific retinopathy by vigintiles of the glycemic distributions. The prevalence of diabetes-specific retinopathy was very low until the 15<sup>th</sup> vigintile for 2-h PG (vigintile range 9.8-10.6 mmol/L), and until the 17<sup>th</sup> vigintile for FPG (6.4-6.8 mmol/L) and for HbA1c (6.1-6.2%).

Logistic regression models adjusted for study center confirmed a statistically significant difference in the OR for diabetes-specific retinopathy compared with the 1<sup>st</sup> vigintile occurred from the 15<sup>th</sup> vigintile for 2-h PG (vigintile range 9.8-10.6 mmol/L; OR [95% CI] 10.1 [1.3-79.4],  $p = 0.03$ ), from the 17<sup>th</sup> vigintile for FPG (6.4-6.8 mmol/L; 2.5 [1.2-5.2],  $p = 0.01$ ), and from the 18<sup>th</sup> vigintile for HbA1c (6.3-6.7%; 4.5 [1.4-15.2],  $p = 0.01$ ).

Supplementary Table 2 in the online appendix shows the ROC curve analyses. The overall discriminatory power determined by AUCs was uniformly high for diabetes-specific retinopathy for each measure of glycemia –

0.87 (95% CI 0.85-0.89) for FPG, 0.89 (0.87-0.91) for 2-h PG, and 0.90 (0.88-0.92) for HbA1c. The overlapping of CIs suggests no statistical difference between the three measures of glycemia. The performance of a wide range of thresholds was examined, with particular attention to those that overlapped from the continuous and vigintile distribution plots. The thresholds which optimized sensitivity and specificity were 6.6 mmol/L for FPG, 13.0 mmol/L for 2-h PG and 6.4% for HbA1c (Table 2). These thresholds gave similar values for positive and negative predictive values. If these thresholds were used for diagnosing diabetes, the prevalence of newly-diagnosed diabetes would be 11.9%, 8.0%, and 6.3% according to FPG, 2-h PG, and HbA1c, respectively. The differences in performance based on ROC curve statistics for the three measures of glycemia were minor for threshold values around the above values (Supplementary Table 2).

Sensitivity analyses showed that the five studies which T.Y.W used the same retinopathy grading system or the five studies which used DCCT-aligned assays for HbA1c measurements provided similar results to the overall study. The optimal threshold for FPG was 6.4-6.5 mmol/L, 6.4-6.5% for HbA1c and 10.1-11.2 mmol/L for 2-h PG.

## **CONCLUSIONS**

The current diagnostic criteria for diabetes were derived from analyses of the relationship between retinopathy and measures of glycemia (1). Our study is the largest to examine this association using data from approximately 45000 participants from five countries, and provides the statistical power for a more detailed and precise examination of glycemic thresholds for diabetes-specific retinopathy (moderate non-proliferative and more severe retinopathy). Previous studies have only reported the association of glycemic measures with any retinopathy, which is less specific for hyperglycemia and

is very frequently detected in people without diabetes (7,16).

The association between glycemic measures and retinopathy has traditionally been investigated by plotting the prevalence of retinopathy against the decile distribution (the population divided into 10 equal groups) of each glycemic measure (1-2). Our large dataset allows analysis using vigintile distributions (the population divided into 20 equal groups) which narrows the glycemic range of each group. Based on logistic regression analysis of these vigintile distributions, glycemic thresholds for diabetes-specific retinopathy were observed in the range of 6.4-6.8 mmol/L for FPG, 9.8-10.6 mmol/L for 2-h PG, and 6.3-6.7% for HbA1c (Table 2).

The large size of this dataset enables diabetes-specific retinopathy to be plotted against measures of glycemia as a continuous variable. A curvilinear relationship was observed, especially for FPG and HbA1c, as opposed to the linear association observed between blood pressure and cardiovascular disease. Diabetes-specific retinopathy was rare at low levels of glycemia but increased from a range of 6.0-6.4 mmol/L for FPG and 6.0-6.4% for HbA1c. A threshold for increasing retinopathy was less obvious for 2-h PG, probably related to the smaller number of study participants with this measure and diabetes-specific retinopathy. Change point analyses, which were used previously in two population-based studies (22), were applied to these curves in an attempt to identify statistically significant thresholds, but we were unable to demonstrate a clear threshold for any glycemic measure by this method. This could suggest that within the ranges of visually detected thresholds for the three measures, changes in the prevalence of diabetes-specific retinopathy remain somewhat linear.

The continuous and vigintile plots provided a similar range of threshold values for FPG and

HbA1c. ROC curve analyses were then used to compare performance in relation to optimizing sensitivity and specificity of glycemic values in the range around these thresholds. These analyses suggest thresholds of 6.6 mmol/L for FPG and 6.4% for HbA1c. The corresponding ROC value for 2-h PG was 13.0 mmol/L.

Combining the results derived from the vigintile distribution, continuous plots and ROC curve analyses, suggest cut-point values of 6.5 mmol/L for FPG and 6.5% for HbA1c which could be considered in deliberations on modifying the current diagnostic criteria for diabetes. The results for 2-h PG were too inconsistent to consider modifying the current diagnostic cut-point of 11.1 mmol/L.

It should be noted that these values do not result in equivalent estimates for prevalent diabetes. This has been an ongoing issue with the current diagnostic criteria whereby using FPG alone or an OGTT to diagnose diabetes, give different diabetes prevalence (23). From our data (Supplementary Table 2), lowering the FPG to 6.5 mmol/L would result in a diabetes prevalence of 13.0% based on FPG alone and 18.6% based on an OGTT using an FPG of 6.5 mmol/L or a 2-h PG of 11.1 mmol/L. The prevalence of diabetes defined by an HbA1c of 6.5% is considerably lower (5.7%). This discrepancy in prevalence may be problematic for epidemiological studies but is not necessarily a disadvantage for individual patient care. An HbA1c of 6.5% was associated with a higher sensitivity and specificity than an FPG of 6.5 mmol/L and a higher specificity than a 2-h PG of 11.1 mmol/L. In other words, fewer people would be identified as having diabetes, but this would not compromise the identification of people with diabetes-specific retinopathy. Whether this would have any deleterious ramifications in relation to identifying individuals at increased risk of other microvascular or macrovascular disease remains to be determined.

This study necessarily included populations from different countries with varying racial/ethnic backgrounds. There have been reports of differences in HbA1c levels independent of glucose between black, white and South Asian populations (24-25). In our study, subgroup analysis by Asian and predominantly Caucasian populations showed no difference in the optimal HbA1c threshold (6.4% for both). However, our study was not designed and did not have sufficient numbers to examine potential black-white difference.

Strengths of this study include its large sample size drawn from populations across different countries and racial/ethnic groups, the ability to focus on diabetes-specific retinopathy, and availability of data to examine three glycemic measures. Our study has some limitations. First, this study was based on cross-sectional data, whereas diagnostic thresholds would ideally be informed by incidence data of diabetes complications. Second, the methods used to assess and classify retinopathy differed between studies and it was not possible to independently review the grading of all photographs. Nevertheless, inter- and intra-observer consistency for retinopathy in the different studies was of the order of 80-98% (3,10,15) and mis-classification, especially for moderate or more severe forms of retinopathy, is likely to be minimal although cannot be entirely eliminated. Furthermore, analysis of the studies which T.Y.W was involved in the standardized grading of retinal photographs showed cut-points for FPG and HbA1c similar to our entire study cohort. Third, no quality assurance of measures of glycemia could be applied across the studies. Nevertheless, all studies measured HbA1c using high performance liquid chromatography and analysis of the five studies which used a DCCT-aligned assay showed an HbA1c cut-point of 6.4-6.5%. Fourth, the Hiroshima study with large sample size and the Pima Indian study with

high prevalence of diabetes-specific retinopathy may have influenced the results. However, sensitivity analyses which excluded these two studies did not alter the overall results. Finally not all included studies were randomly sampled populations (e.g. MESA) and some (e.g. AusDiab) oversampled people with diabetes and/or pre-diabetes. Common to all such analyses is the issue of whether or not to include people with previously diagnosed diabetes. If people with known diabetes currently receiving blood glucose lowering treatment are included, the population-based characteristics of the study sample are maintained but a bias associated with treatment-induced effects on glycemia is introduced and the level of glycemia assessed in each study may be lower than that which led to retinopathy. Excluding people with treated diabetes from the analyses eliminates this bias but changes the characteristics of the population by eliminating many individuals with retinopathy making it much more difficult to identify a threshold (2,7). Large incidence studies are needed to resolve these issues and determine the optimal levels of glycemia that predict the development of diabetes-specific retinopathy.

In summary, this pooled analysis of glycemia and diabetes-specific retinopathy among close to 45000 participants, substantially broadens the evidence-base on glucose-specific and HbA1c diabetes diagnostic thresholds. Our results demonstrate narrow glycemic threshold ranges for the presence of diabetes-specific retinopathy, and suggest that the current diabetes diagnostic level for FPG should be lowered to 6.5 mmol/L and that an HbA1c of 6.5% is a suitable alternative diagnostic criterion.

**Author contribution.** *Study concept and design:* S.C., K.B-J., J.S. *Acquisition of data:* S.C., K.B-J., T.W. *Drafting of the*

*manuscript:* S.C., C.L. *Analysis and interpretation of data and critical revision of the manuscript for important intellectual content:* S.C., C.L., T.W., B.B., J.S., K.B-J. *Statistical analysis:* C.L.

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**Table 1: Summary of studies included in these analyses**

<b>Name of study</b>	<b>Country</b>	<b>Year</b>	<b>Age range</b>	<b>N*</b>	<b>Measures available</b>
ARIC (10)	USA	1993-1995 (Visit 3)	49-73	10873	FPG
AusDiab (5)	Australia	1999-2000	25-90	2052	FPG, 2-h PG, HbA1c
BMES (11)	Australia	1992-1994	45-97	2915	FPG
CURES (12)	India	2002-2004 (Phase III)	20-85	2200	FPG, 2-h PG, HbA1c
Hiroshima study (4)	Japan	1990-2004	17-99	12873	FPG, 2-h PG, HbA1c
MESA (14)	USA	2002-2004 (2 <sup>nd</sup> examination)	45-85	5920	FPG, HbA1c
NHANES III (15)	USA	1988-1994	40-74	2869	FPG, 2-h PG, HbA1c
Pima Indian study (17)	USA	1982 (1 <sup>st</sup> examination)	15-85	1829	FPG, 2-h PG
SiMES (18)	Singapore	2004	40-79	3170	HbA1c

\*Number of participants aged 20-79 years included in the analysis.

ARIC = The Atherosclerosis Risk In Communities Study; AusDiab = Australian Diabetes Obesity and Lifestyle study; BMES = Blue Mountains Eye Study; CURES = Chennai Urban Rural Epidemiology Study; MESA = Multi-ethnic Study of Atherosclerosis; NHANES III = 3<sup>rd</sup> National Health and Nutrition Examination Survey; SiMES = Singapore Malay Eye Study; FPG = fasting plasma glucose; 2-h PG = 2 hour post load plasma glucose; HbA1c = glycated hemoglobin

**Table 2: Threshold ranges for diabetes-specific retinopathy (moderate NPDR or more severe retinopathy) derived from logistic regression models (adjusted for center) of the glycemic measures by continuous distribution and vigintile distribution, and ROC curve analysis**

	<b>FPG (mmol/L)</b>	<b>2-h PG (mmol/L)</b>	<b>HbA1c (%)</b>
<b>Logistic regression</b>			
Continuous distribution	6.5-6.9	No threshold	6.5-6.9
Vigintile distribution	6.4-6.8	9.8-10.6	6.3-6.7
<b>ROC curve analysis</b>			
	6.6	13.0	6.4

FPG = fasting plasma glucose; 2-h PG = 2 hour post oral glucose load plasma glucose; HbA1c = glycosylated hemoglobin.

#### **FIGURE LEGENDS**

**Figure 1:** Prevalence of diabetes-specific retinopathy (moderate or more severe retinopathy) with 95% confidence intervals, number of retinopathy cases, and participants within each interval by 0.5 unit intervals for FPG and 2-h PG, and HbA1c.

**Figure 2:** Prevalence of diabetes-specific retinopathy (moderate or more severe retinopathy) by vigintiles of the distribution of FPG, 2-h PG, and HbA1c.

Figure 1

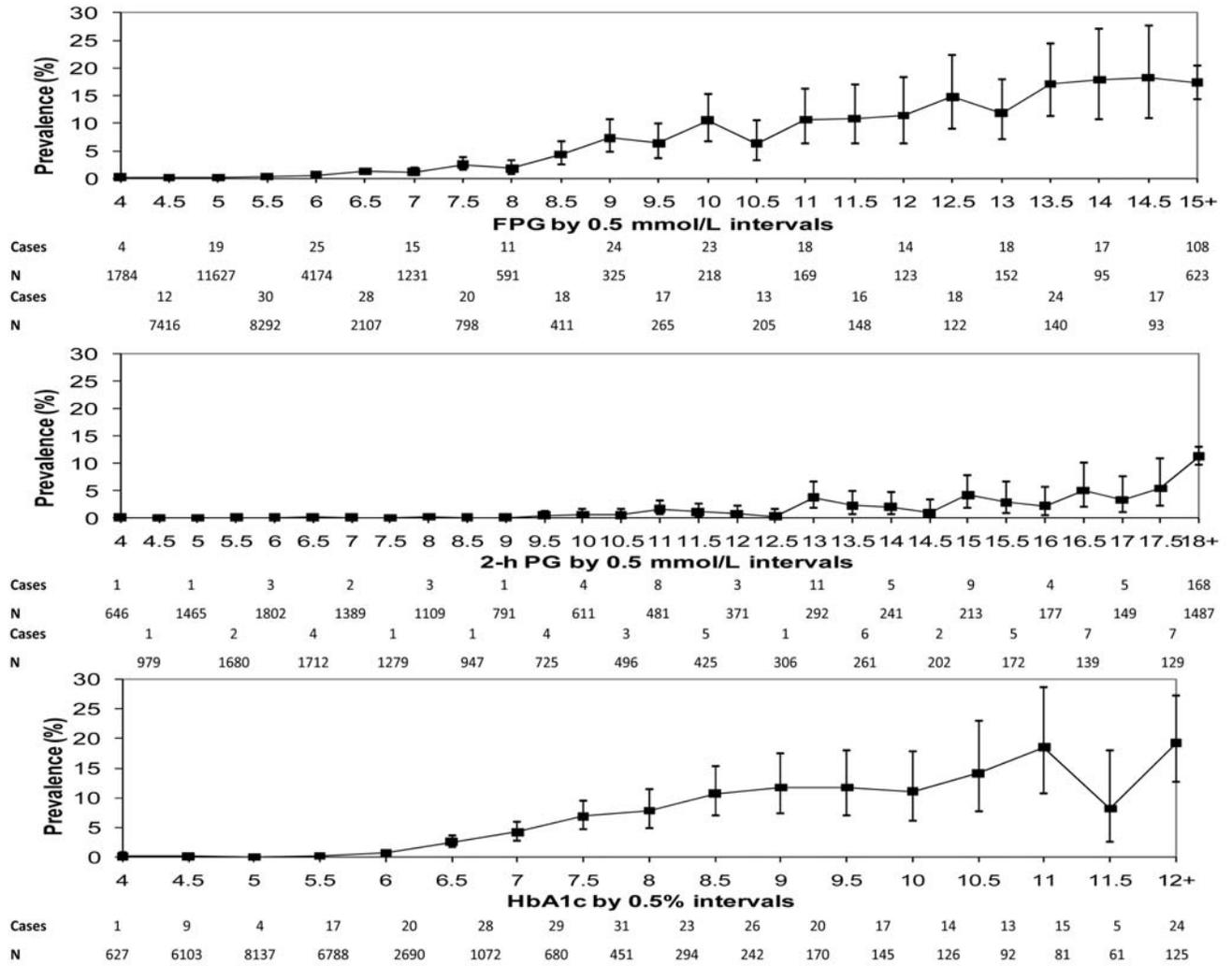


Figure 2

