HbA$_{1c}$ Values for Defining Diabetes and Impaired Fasting Glucose in Asian Indians

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Background

Glycated haemoglobin (HbA1c) serves as an established measure of glucose control in people with diabetes and is a measure of the degree of exposure to glucose over a cumulative period of time. As standardisation has improved [1], there is renewed interest in the potential to use HbA_{1c} to diagnose diabetes, and an international expert committee (IEC) in 2009 proposed a HbA_{1c} level of ≥6.5% for diagnosing diabetes and ≥6.0% for diagnosing impaired glycaemic states[2]. In the following year, 2010, American Diabetes Association (ADA) officially recognised HbA_{1c} as a diagnostic test recommending cut-points ≥6.5% for diabetes and 5.7% to 6.4% for high risk groups [3, 4].

However, there is considerable debate about the HbA_{1c} cut-points [5-8]. Studies in different population groups throughout the world to assess the appropriateness of the recommended HbA_{1c} values have suggested cut-points for diabetes ranging from ≥5.6% to ≥7.0% [5, 9-12]. Age, ethnicity, genetic make-up, erythrocyte life-span and erythrocyte environment all may contribute to inter-individual and inter-group variability of glycosylation of haemoglobin [2, 7, 9, 12-17] and thus to differences in the cut-points.

Three published regional studies from India, a country with very high and growing prevalence of diabetes, have suggested HbA_{1c} cut-points for Southern and Northern Indian populations. In a study conducted in 1998 by Snehalatha et.al, a HbA_{1c} cut-point of ≥6.0% was found to be highly sensitive and specific in detecting diabetes [18], whereas Mohan et.al. in the same city of Chennai found a cut-point of ≥6.4% to be more appropriate [19]. Another recently published study found a cut-point of ≥6.1% to be optimally sensitive and specific for detecting diabetes in a study population in Chandigarh in Northern India [20]. Given the geographical and ethnic diversity of India, clearly more data are needed to elucidate cut-points suitable for Indian populations. Utilising blood samples collected in a cohort study conducted in Northern (New Delhi) and Southern (Trivandrum) regions of India, we describe the normative distribution of HbA_{1c} and explore cut-points for defining diabetes and high-risk for diabetes.

Methods

Our study population was selected randomly from the India Health Study participants (IHS; n=4,000), conducted in three cities in India (New Delhi, Trivandrum and Mumbai) and completed in 2008. Details about the IHS is described elsewhere [21], briefly, the IHS was conducted between December 2006 and July 2008 with the primary objective of assessing the feasibility of establishing a prospective cohort in India to facilitate studies on incidence of cancer, cardiovascular diseases and other non-communicable diseases, and their risk factors; such as the patterns of eating and dietary habits in the Indian context. The sampling method was random and stratified by gender, religion and type of residence (urban/rural) and was powered to calculate the mean of various food and nutrient intake in each strata of the sample population. Pregnant women and people with previous history of cancer or cardiovascular event were not included in the study. The participants included mostly middle-class adults, aged 35 to 69 years who provided consent to participate and provide biological samples for the study. However, no biological samples were collected in Mumbai, due to inadequate laboratory resources and storage facilities in that area. HbA_{1c} measurements were conducted in a random sample of 525 individuals from the 3280 IHS participants in New Delhi and Trivandrum who provided fasting blood samples. The 525 participants included in this study were not statistically significantly different from the

remaining population in terms of their mean fasting plasma glucose, and were comparable in age and body mass index (BMI); however, those excluded from the study had a smaller waist and hip circumference compared to those included. Further, the sample excluded had a statistically significant higher prevalence of diabetes both known (13.9%) and Newly Diagnosed Diabetes (NDD) (12.8%) compared to those included (known diabetes=12.4% and NDD=10.2%), but comparatively lower prevalence of IFG (shown in Table-1). The comparatively lower prevalence of known diabetes and NDD in the sample population for this study, therefore, rules out the possibility of selection bias.

Definition and construct of the variable for glycaemic status

Based on subjective history, 64 people were classified as known diabetes. For the remaining 461, we used fasting plasma glucose (FPG) to classify participants as normal fasting glucose (NFG), impaired fasting glucose (IFG) and newly diagnosed diabetes (NDD) using both American Diabetes Association (ADA) and World Health Organization (WHO) criteria. As per ADA, normal was defined as FPG<100mg/dl (<5.6 mmol/l), IFG as FPG between 100 and 125mg/dl (5.6-7.0 mmol/l) and newly diagnosed diabetes (NDD) as FPG ≥126mg/dl (≥7.0mmol/l)[22]. Using the definition of WHO, participants with FPG <110mg/dl (<6.1mmol/l) were defined as normal, those having FPG between 110 and 125mg/dl (6.1-7.0mmol/l) as IFG and those with FPG ≥126mg/dl (≥7.0mmol/l) as NDD [23].

Laboratory methods

Blood samples (15 ml) from the participants were collected after an overnight fast. Fasting plasma glucose (FPG) was estimated by the glucose oxidase / peroxidase method [24] (Delhi: GOD-PAP; Randox Laboratories Ltd., Antrim, UK; Trivandrum: GOD-POD; Autospan; Span Diagnostics Ltd., Surat, India). HbA_{1c} was measured on SYNCHRON CX 5 using reagents from BECKMAN COULTER. The system uses two cartridges, one for haemoglobin and one for A_{1c}. Haemoglobin reagent is used to measure total haemoglobin concentration by a colorimetric method. One part of sample is mixed with 8.6 parts of reagent automatically. Change in absorbance which is directly proportional to concentration of total haemoglobin is measured at 410 nm. A_{1c} reagent is used to measure the haemoglobin A_{1c} concentration by a turbidimetric immune-inhibition method. In the reaction, HbA_{1c} antibodies combine with HbA_{1c} from sample to form soluble antigen antibody complexes. Polyhaptens from the reagent then bind with the excess antibodies and the resulting agglutinated complex is measured tubidimetrically at 340 nm. The final result is reported as percentage (%) HbA_{1c} automatically and is calculated as A_{1c} (g/dl) × 100/Hb (g/dl).

Statistical analysis

All statistical analyses were performed using STATA version 10.1. We described the study population in terms of their clinical, anthropometric and bio-chemical characteristics using means and standard errors (SE). Bivariate associations between continuous variables and the categories of glycaemic states were determined using ANOVA with Scheffe's multiple comparison tests. Pearson's correlation co-efficient was used to analyse the correlation between HbA_{1c} and FPG among unknown diabetes participants. All statistical associations were considered to be significant with a two-sided p-value less than 0.05. There were 64 participants with a history of diabetes and were on medication; hence, HbA_{1c} cut-points were calculated for NDD and IFG. Receiver Operating Characteristics curves (ROC) were used to identify the optimum sensitivity and specificity with 95% confidence interval (CI) for defining the HbA_{1c} cut-points against the FPG criteria using both the ADA and the WHO. The Area Under Curve (AUC) was constructed and the point closest to the upper-left corner with maximum sensitivity and specificity was selected as the optimal cut point [25]. Sensitivity was defined as the proportion of participants with IFG or diabetes who were

identified correctly by a HbA_{1c} value greater than or equal to the cut point. Specificity was defined as the proportion of participants without IFG and diabetes who were correctly identified by a HbA_{1c} value less than the cut point. Positive predictive value (PPV), negative predictive value (NPV) and accuracy for defining diabetes and IFG with their 95% CI were estimated for each cut-point of HbA_{1c}. We also estimated the proportion of subjects without known diabetes who would be classified as NFG, IFG and NDD at different cut-points of HbA_{1c}.

Results

The mean FPG was 105.1 (±1.37) mg/dl for participants without known history of diabetes. Based on ADA and WHO criteria respectively, 44.9% (95% CI 40.3%-49.6%) and 71.4% (95% CI 67.0%-75.5%) were NFG, and 44.7% (95% CI 40.1%-49.4%) and 18.2% (95% CI 14.8%-22.1) had IFG. Overall prevalence of diabetes (both known and NDD) in the study population was 21.3 (95% CI 17.9%-25.1%), 12.2% (95% CI 9.5%-15.3%) had a known history of diabetes and 10.4 % (95% CI 7.8%-13.6%) were NDD. Table-2 describes the study population characteristics stratified by their glycaemic states: 44.5% were males and 55.4% females. Mean HbA_{1c} was 5.4 (±0.04) %, 5.7 (±0.06) %, 5.8 (±0.09)%, 7.5 (±0.33) % and 8.4 (±0.32) % in participants with NFG, IFG (ADA), IFG(WHO), NDD and known diabetes respectively. The correlation (Pearson's correlation co-efficient) between HbA_{1c} and FPG for participants without known history of diabetes was 0.61 (p<0.001) (Fig-1), but varied across the different glycaemic strata. According to WHO criteria, the correlation between HbA_{1c} and NFG was 0.15 (p=0.006), IFG 0.27 (p=0.008) and NDD 0.61 (p<0.001), which was similar to the ADA criteria: NFG 0.10 (p=0.13), IFG 0.23 (p=0.001) and NDD 0.61 (p<0.001).

Table-3 shows the ROC results for HbA_{1c} cut-points evaluated against FPG criteria (both ADA and WHO) for participants with unknown diabetes. The optimal HbA_{1c} cut-point for NDD using FPG≥126mg/dl was 5.8% with a sensitivity of 75%, specificity of 75.4% and an area under curve (AUC) of 0.819. For IFG (ADA criteria) a cut-point of 5.5% had the optimum sensitivity (59.7%) and specificity (59.9%) with an AUC of 0.627. For IFG (WHO criteria) a cut-point of 5.6% was found to have the optimum sensitivity (60.7%) and specificity (65.1%) with an AUC of 0.671. The HbA_{1c} cut-point of ≥5.5% would correctly identify 70.2 and 59.7% of the participants with IFG using WHO and ADA criteria, respectively (Table-4). The cut-point of ≥5.8% would correctly identify 75% of participants with diabetes, however 42.9% and 33.5% of participants with IFG (using WHO and ADA criteria, respectively), and 19.8% and 15.5% of normal participants (using WHO and ADA criteria respectively) will also be included (Table-4). Although using the currently recommended HbA_{1c} level of ≥6.5% decreases the proportion of false positives, the proportion with diabetes identified correctly (true positives) decreases by 21% in absolute terms (Table-4).

Discussion

There was a high prevalence of diabetes (FPG ≥126 mg/dl) in the study population with 10.4% being newly diagnosed. The optimal HbA_{1c} cut-points for NDD (≥5.8%) and IFG (≥5.5% / ≥5.6%) was considerably lower than those recommended by the IEC (≥6.5 % for diabetes and ≥6.0% for IFG) [2] and the ADA (≥6.5 % for diabetes and ≥5.7% for high risk groups) [3, 4]. Our results, however, are consistent with other studies conducted across the world, which have found values lower than the recommended levels for diabetes: 5.8% in the Dutch population [9], 6.1%, 5.6% and 6.3% in Chinese population [5, 11, 26], 5.7% in the US population [10], ≥5.6% in Japanese population (Funagata study) [27] and ≥6.0% in an American population in Pittsburgh and Memphis [13]. We found a low sensitivity and

specificity, and low AUC for HbA_{1c} cut-point for IFG using FPG criterion. However several studies suggest that HbA_{1c} is not sensitive for screening of IFG [2, 5]. A systematic review of nine studies (six European and three Asian) published between 1998 and 2004 found $HbA_{1c} \geq 6.1\%$ and $\geq 6.2\%$ to be optimal for the detection of diabetes, but sensitivity of HbA_{1c} for detecting impaired glycaemic states was in general low across the studies [28].

In the context of India, our study cut-point of $\geq 5.8\%$ for diabetes is lower than those of Snehalatha et.al. (study conducted in 1998) and Kumar et.al (study conducted in 2008-09) who found a HbA_{1c} cut-point of $\geq 6.0\%$ and $\geq 6.1\%$ to be optimally sensitive and specific for detecting NDD in South Indian and North Indian population groups respectively [18, 20]. However, our study results compare and contrast the findings of the study by Mohan et.al. While the HbA_{1c} cut-point for IFG using FPG criterion was the same (5.6%), we found a much lower cut-point for NDD (5.8%) compared to Mohan et.al. (6.4%) using the same FPG$\geq$126mg/dl criterion [19], but the AUC in general were lower in our study. The demographic and biochemical characteristics of the study participants were different from that of the participants in Mohan et.al's Chennai Urban Rural Epidemiological Study (CURES). Our study participants were older and had a higher body mass index (BMI) compared to CURES. The laboratory analysis method for HbA_{1c} used in CURES was High Performance Liquid Chromatography (HPLC) and that used in the IHS was Immuno-turbidimetry [19] and both instruments are NGSP (National Glycohaemoglobin Standardisation Programme) certified.

Results of two studies from different population groups in China, Hong Kong Chinese and Chinese Han in Shanghai, have found different cut-points of HbA_{1c} for diabetes 5.5% [29] and 6.1% respectively[5]. Two other recent studies in China, in Shanghai (2007-08) and Qingdao (2006), suggested cut-points of $\geq 6.3\%$ and $\geq 5.6\%$ to have optimal sensitivity and specificity for detecting NDD [11, 26]. This is plausible considering the inter-individual variability in the amount of glycosylation and the diversity in population characteristics. This suggests that apart from inter-nation variability in the distribution of normative HbA_{1c} levels, the intra-nation variability found by studies on different population groups within countries like India and China could further add to the complexity of identifying a common HbA_{1c} cut-point.

Recently, a number of studies across the world that have examined the concordance between glucose-based criteria (FPG, Oral Glucose Tolerance Test-OGTT) and HbA_{1c} criterion for screening of diabetes, suggests that there is significant discordance between glucose-based and the recommended HbA_{1c} (≥ 6.5 %) criteria which is further accentuated by age, gender and race [13, 30-34]. An editorial by Cohen et.al. summaries the existing empirical evidence of this inter-individual variability and in the light of these, further reiterates the need for studies in composite population groups representative of the prevailing diversities for effective utilization of HbA_{1c} [35].

The correlation between HbA_{1c} and FPG was fairly high (0.61) in the study population which may be attributed to the high prevalence of diabetes. Our results are, however, comparable to results reported by Snehalatha et.al. in Southern India (r=0.82) [18], a retrospective analysis of data of type-II diabetes patients living in Oman (r=0.62) [36], and the Atherosclerosis Risk in Communities (ARIC) study (r=0.73) [37] conducted in the U. S. African Americans have also reported remarkably similar correlations. Conversely, a study conducted on Dutch population comprising of participants from the New Hoorn Study [9] showed only a moderate correlation (r=0.46).

Given the limitations of HbA_{1c} as a screening test in non-diabetes individuals, researchers have attempted to identify methods to improve its efficacy. A study using the NHANES

1999-2004 data showed that HbA_{1c} as a screening test may have higher predictive validity in subjects who are stratified according to their risk factors for diabetes [38]. A Swedish population-based study showed that the combination of HbA_{1c}, FPG and BMI is more sensitive and specific than HbA_{1c} alone and has a high PPV for screening of type 2 diabetes [39]. Again studies among Korean and Chinese adults suggest that a combination of HbA_{1c} and FPG can detect a greater proportion of NDD compared to each of these tests alone [30, 40]. Other studies suggest that performing a test for FPG followed by HbA_{1c} estimation in selected patients who are at risk of developing diabetes can minimize the requirement of OGTT, which can be both time consuming and inconvenient to patients [41-45]. UK department of Health recommends a coupled algorithm of HbA_{1c} and OGTT for screening of diabetes. Individuals who are found to have HbA_{1c} between 6% and 6.4% undergo OGTT to confirm the presence of diabetes [46].

In the IHS study two hour plasma glucose (2-hPG) test was not done, hence the glycaemic states and HbA_{1c} for the study population was based on the FPG criteria alone. It is thus possible that we might have missed a group with normal FPG but elevated 2-hPG. Moreover, apart from being a single test, the results of FPG are more reproducible than 2-hPG and considered to be as good a predictor of glycaemic status for unknown diabetes as 2-hPG [5, 47, 48].

Conclusion

Our findings contribute to the debate on appropriate international cut-points for HbA_{1c} and its potential value as a screening tool. The possible roles of age, race, genetic make-up, erythrocyte life-span and erythrocyte environment which contribute to the inter-individual variability of glycosylation of haemoglobin [2, 9, 13, 14, 16] may be more heterogeneous in the Indian sub-continent. We found a lower HbA_{1c} cut-point for diabetes than that reported in the three studies conducted in South and North Indian population groups and than is currently recommended by IEC and ADA [2, 3]. There is a need for larger population-based studies comprised of composite population groups from different regions of the country in order to draw a consensus on the normative value of HbA_{1c} for Asian Indians. Further, Asian Indians being a highly heterogeneous community will provide a greater scope for researchers to understand the determinants of HbA_{1c} responsible for inter-individual glycation of haemoglobin and thereby, the different observed relationships between HbA_{1c} and glycaemia.

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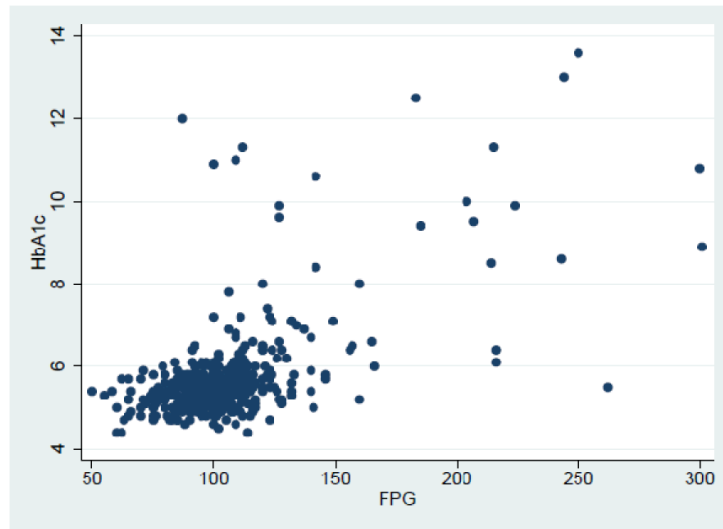
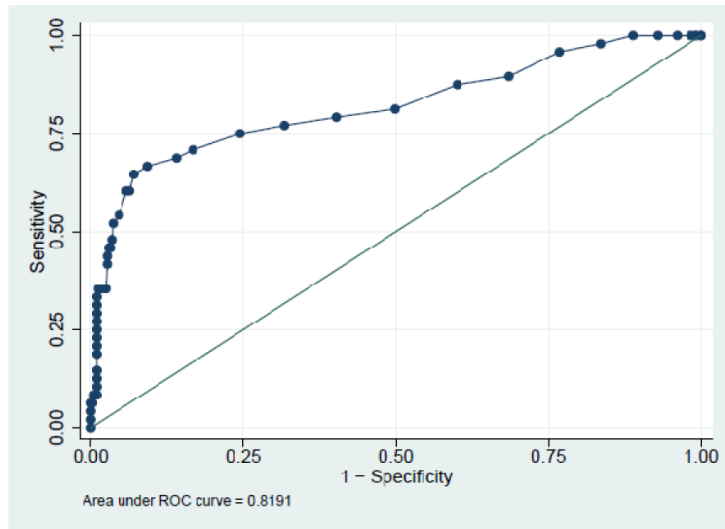**Figure-1. Correlation between HbA$_{1c}$ and FPG (Pearson's correlation)**

Figure – 2. Receiver Operating Characteristic Curve for diabetes using FPG≥126mg/dl criterion

Table-1

Comparison of characteristics of population included in the study (for whom HbA$_{1c}$ results were available) with those excluded from the study (for whom HbA$_{1c}$ results were not available)

Characteristics	Overall (n=3280)	Mean (SE)		P-Value^f
		Included (525)	Excluded (2755)	
Age	47.6 (0.43)	47.5 (0.42)	48.7 (0.19)	0.01
BMI (kg/m^2)	25.9 (0.22)	25.9 (0.22)	25.3 (0.10)	0.01
Waist circumference (cms)	92.5 (0.53)	92.8 (0.54)	87.4 (0.24)	<0.001
Hip circumference (cms)	96.3 (0.48)	96.4 (0.48)	91.9 (0.23)	<0.001
Fasting Plasma Glucose (FPG)	115.3 (1.13)	113.3 (1.94)	115.8 (1.32)	0.38
Proportions (%)				P-Value$^#$
Known diabetes	17.4	12.4	13.9	<0.001
IFG (ADA)	36.5	44.8	26.2	<0.001
IFG (WHO)	14.4	18.3	10.2	<0.001
NDD	15.4	10.2	12.8	<0.001

SE-Standard Error; BMI-Body Mass Index (derived from height and weight and expressed as kg/m^2); IFG-Impaired Fasting Glucose; NDD-Newly Diagnosed Diabetes

^{f}Statistically significant difference between the two groups of participants by ttest

$^#$Chi-square test for significant difference between the groups

Table-2
Characteristics of the study population

Characteristics	Overall (n=525)	Mean (SE)^f				
		NFG	IFG (ADA)	IFG (WHO)	NDD	Known diabetes
Age	47.3 (.52)	46.1 (.54)	47.5 (.67)	48.2 (1.03)	50.1 (1.49)[***#]	51.8 (1.03)
BMI (kg/m^2)	26 (.25)	25.4 (.33)	26.4 (.37)	27.5 (0.61)[**]	25.8 (.47)	26.5 (0.58)
Waist circumference (cms)	92.7 (.54)	92 (.81)	93.3 (.90)	92.2 (1.52)[**]	90.3 (2.02)[#]	97.2 (1.58)
Hip circumference (cms)	96.5 (.49)	96 (.73)	97.6 (.78)	99.4 (1.35)[*]	93.7 (1.98)[#]	98.6 (1.34)
HbA$_{1c}$	5.9 (.08)	5.4 (.04)	5.7 (.06)[*]	5.8 (.09)[*]	7.5 (.34)[***###]	8.4 (0.32)[** ##]

SE-Standard Error; NFG-Normal Fasting Glucose; IFG-Impaired Fasting Glucose; BMI-Body Mass Index (derived from height and weight and expressed as kg/m^2); NDD – Newly Diagnosed Diabetes; ADA – American Diabetes Association; WHO – World Health Organisation

^{f}Statistical association (ANOVA Prob>F) between the categories of FPG (NFG, IFG, NDD) and the continuous variables (population characteristics):

[*] $P<0.05$,

[**] $P<0.01$ and

[***] $P<0.001$ (compared to NFG);

[#] $P<0.05$,

[##] $P<0.01$ and

[###] $P<0.001$ (compared to IFG)

Table-3

HbA$_{1c}$ cut-points in Asian Indians

Status		Criteria	Mean HbA$_{1c}$	Optimal HbA$_{1c}$ cut-point	Sensitivity	95% CI	Specificity	95% CI	PPV	95% CI	NPP	95% CI	AUC	Accuracy	95% CI
Pre-diabetes	IFG (WHO) n=84	FPG ≥ 110 mg/dl and <126 mg/dl	5.8 (±0.09)	5.6	60.7	49.5 – 71.2	65.1	59.6 – 70.2	25	19.2 – 31.5	83.3	78.1 – 87.6	0.671	64.2	59.3 – 68.8
	IFG (ADA) n=206	FPG ≥100 mg/dl and <126 mg/dl	5.7 (±0.06)	5.5	59.7	52.7 – 66.5	59.9	52.9 – 66.6	59.7	52.7 – 66.5	59.9	52.9 – 66.6	0.628	59.8	54.9 – 64.6
Newly Diagnosed Diabetes (NDD) (WHO & ADA) n=48		FPG ≥126 mg/dl	7.5 (±0.33)	5.8	75	60.4 – 86.4	75.5	71.1 – 79.6	26.3	19.1-34.5	96.3	93.6 – 98.1	0.819	75.5	71.3 – 79.3

IFG-Impaired Fasting Glucose; FPG-Fasting Plasma Glucose; CI-Confidence Interval; PPV-Positive Predictive Value; NPV-Negative Predictive Value; AUC-Area Under Curve

Table-4

Proportion of subjects with NFG, IFG and diabetes identified using different cut-points for HbA$_{1c}$

HbA$_{1c}$ cut-points	Normal fasting glucose (NFG)				Impaired fasting glucose (IFG)				Newly Diagnosed Diabetes (NDD)	
	WHO criteria n= 329		ADA criteria n= 207		WHO criteria n= 84		ADA criteria n= 206		Diabetes n= 48	
	count	%	count	%	count	%	count	%	count	%
≥ 4.5	327	99.4	205	99	83	98.8	205	99.5	48	100
≥5.0	289	87.8	179	86.5	78	92.9	188	91.3	48	100
≥5.5	147	44.7	83	40.1	59	70.2	123	59.7	39	81.3
≥5.6	115	35	66	31.9	51	60.7	100	48.5	38	79.2
≥5.7	89	27.1	47	22.7	42	50	84	40.8	37	77.1
≥5.8	65	19.8	32	15.5	36	42.9	69	33.5	36	75
≥5.9	41	12.5	16	7.7	28	33.3	53	25.7	34	70.8
≥6.0	33	10	14	6.8	25	29.8	44	21.4	33	68.8
≥6.1	19	5.8	7	3.4	19	22.6	31	15	32	66.7
≥6.2	12	3.6	3	1.4	17	20.2	26	12.6	31	64.6
≥6.3	11	3.3	3	1.4	15	17.9	23	11.2	29	60.4
≥6.4	10	3	3	1.4	14	16.7	21	10.2	29	60.4
≥6.5	9	2.7	2	1	10	11.9	17	8.3	26	54.2