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ORIGINAL ARTICLE

Variations in glycated haemoglobin with age among individuals with normal glucose tolerance: Implications for diagnosis and treatment—Results from the ICMR–INDIAB population-based study (INDIAB–12)

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Abstract

Aim To report on glycated haemoglobin (HbA1c) values among individuals with normal glucose tolerance (NGT) at different age groups, using data acquired from a large national survey in India.

Materials and methods Data on glycaemic parameters at different age groups were obtained from the Indian Council of Medical Research–INdia DIABetes (ICMR–INDIAB) study, in adults aged ≥ 20 years representing all parts of India. Age-wise distribution of HbA1c was assessed among individuals with NGT (n = 14,222) confirmed by an oral glucose tolerance test using the World Health Organization (WHO) criteria. Results were validated in another large epidemiological study (n = 1077) conducted in Chennai, India.

Results Among NGT individuals, HbA1c increased gradually with age from 5.16 ± 0.71% (33 mmol/mol) in the age group of 20–29 years to 5.49 ± 0.69% (37 mmol/mol) in those aged 70 + years. In the validation study, conducted in another study population, HbA1c was 5.35 ± 0.43% (35 mmol/mol) in age group of 20–29 years and 5.74 ± 0.50% (39 mmol/mol) in those aged 70 and above. In the INDIAB study, for every decadal increase in age, there is a 0.08% increase in HbA1c and this increase was more significant in females (females: 0.10% vs. males: 0.06%) and in urban (urban: 0.10% vs. rural: 0.08%) population.

Conclusions HbA1c levels increase steadily with age. This suggests that age-specific cutoffs be used while utilizing HbA1c to diagnose diabetes and prediabetes, so as to minimize the risk of overdiagnosis and unnecessary initiation of treatment in elderly people who could have physiological increase in HbA1c levels.

Keywords Glycated haemoglobin · Normative data · Diabetes · Prediabetes · Normal glucose tolerance · Age · Elderly · Asian Indians

Introduction

Advancing age is associated with increased prevalence of many chronic diseases, including type 2 diabetes (T2D). However, one needs to be careful while diagnosing T2D in the elderly, as many of these individuals may have physiological changes in their ability to regulate blood glucose, implying that abnormal results on diagnostic tests for diabetes need not always be indicative of pathology in this population. Glycated haemoglobin (HbA1c), one of the widely recommended diagnostic tests for diabetes, is also subject

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to such physiological variation [1, 2]. This is particularly relevant in some populations where the high prevalence of iron-deficiency anaemia and haemoglobinopathies makes diagnosis of diabetes using HbA1c challenging even in the younger population [3]. There are few data from South Asia on HbA1c levels among those with normal glucose tolerance to see the normative values of this parameter at different ages. The present study reports on the values of HbA1c among individuals with normal glucose tolerance at different age groups, using data acquired from a large nationally representative survey conducted in India and validation was done in another large epidemiological study in Chennai.

Materials and methods

Sampling and study population

The data on glycaemic parameters at different age groups were obtained from participants included in the national study on diabetes in India, the Indian Council of Medical Research–INdia DIABetes (ICMR–INDIAB) study, conducted in a nationally representative sample of the Asian Indian population [4–7]. The ICMR–INDIAB study was a cross-sectional, community-based survey of adults aged 20 years and above. The methodological details of the study have been published elsewhere [4]. In brief, the study sampled rural and urban residents of 30 States/Union Territories (UTs) of the country such that the sample was representative of India. A stratified multistage sampling design was used [4], wherein a three-level stratification based on geography, population size, and socioeconomic status (SES) of each state was done in order to obtain a truly representative sample of the population.

Biochemical assessment

Fasting capillary blood glucose [CBG] was determined using a glucose meter (One Touch Ultra, Lifescan Johnson & Johnson, Milpitas, California) after ensuring at least 8 h of overnight fasting. An oral glucose tolerance test [OGTT] was done using 82.5 g oral glucose load [equivalent to 75 g of anhydrous glucose] and the 2-h post-load CBG was estimated. In subjects with self-reported diabetes, only the fasting glucose was measured. Similar equipment was used throughout the study as a measure of quality assurance. In every fifth individual and all individuals with diabetes, a venous sample was drawn for assessment of HbA1c. Samples were centrifuged within 1 h at the survey site, and serum was transferred to separate labelled vials and temporarily stored in −20 °C freezers until they were transferred in cold chain to the central laboratory at the Madras Diabetes Research Foundation, Chennai, India. HbA1c assays were carried out by the same team of laboratory technicians using the same method throughout the study period. HbA1c was estimated by high-pressure liquid chromatography using the Variant™ II Turbo machine (Bio-Rad, Hercules, CA), which is certified by the National Glycohaemoglobin Standardization Program as having documented traceability to the Diabetes Control and Complications Trial reference method [8]. The intra- and inter-assay coefficients of variation for the assays ranged from 3.1 to 7.6%.

For the current study, we included only those individuals who had normal glucose tolerance (NGT) which was defined as fasting capillary blood glucose (CBG) less than 100 mg/dl and 2-h post glucose CBG less than 160 mg/dl two hours after the intake of oral glucose as defined by the American Diabetes Association (ADA) and the World Health Organization (WHO) criteria, respectively [9, 10]. The 2-h post glucose < 160 mg/dl by CBG which is equivalent to < 140 mg/dl by venous plasma [10]. All individuals with diabetes and/or prediabetes, i.e. impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) by either ADA or WHO criteria, were excluded.

Validation study

Validation of the results was conducted in another population-based study, called Chennai urban rural epidemiology study (CURES) [11, 12]. CURES was conducted in phases. Phase I of CURES was a representative sample of 26,001 individuals in Chennai. Phase 2 involved those with self-reported diabetes. Phase 1 and Phase 2 are not discussed further in this paper. In Phase 3 of CURES, every tenth individual from Phase I was brought to our centre for standardized oral glucose tolerance tests (performed using venous plasma samples) and based on the results were classified as normal glucose tolerance [fasting plasma glucose < 100 mg/dl (< 5.6 mmol/l) and 2Hr plasma glucose values < 140 mg/dl (< 7.8 mmol/l)] or as prediabetes or diabetes. For the current study, only individuals with NGT were included. The venous blood sample was drawn in the fasting state after ensuring 8–12 h of overnight fasting. This was followed by an oral administration of 75 g of glucose in all individuals (except in individuals with self-reported diabetes who were excluded). All samples were analysed at the Madras Diabetes Research Foundation (MDRF) laboratory as stated earlier. This validation study included 1,077 individuals with NGT.

The approval of the Institutional Ethics Committee was obtained for the study and written informed consent was provided by all study participants.

Statistical analysis

Statistical analyses were performed using the SAS statistical package (version 9.2; SAS Institute, Inc., Cary, NC). Estimates were expressed as mean ± SD. Student's t test was used to compare groups for continuous variables. p value of < 0.05 was considered significant.

Results

Table 1 presents the age-wise distribution of HbA1c among individuals with NGT. In the overall study population (n = 14,222), the HbA1c increased gradually with age from 5.16 ± 0.71% (33 mmol/mol) in age group of 20–29 years to 5.51 ± 0.74% (37 mmol/mol) in those aged 70–79 years. A similar pattern is observed when stratified as urban or rural and gender. However, among males and in the urban population, it decreased after the age of 70 years. Urban residents had higher mean HbA1c compared to rural residents across all age groups, and males had higher mean HbA1c than females in all age groups, except in the age group of 50–59 years and 70 + years.

In the validation study, conducted in the CURES study using the venous plasma sample also, the HbA1c increased gradually from 5.35 ± 0.43% (35 mmol/mol) in age group of 20–29 years to 5.74 ± 0.50% (39 mmol/mol) in those aged 70 and above (Table 2).

While looking at the decadal increase in the HbA1c levels, it was observed that the HbA1c values increased at the rate of 0.08% per decade in the overall population, with a greater change observed among urban population (urban vs. rural: 0.10% vs 0.08% per decade) and in females (female vs. male: 0.10% vs. 0.06% per decade). In the validation study (CURES), the decadal increase in HbA1c was 0.11% per decade in the overall population.

Figure 1 presents the distribution plots of HbA1c (mean plus upper limit of one standard deviation) in the overall population showing a slight, but perceptible, rise with age in both the INDIAB (Fig. 1a) and CURES (Fig. 1b) population.

Figure 2 presents the density plots of HbA1c by different age groups in the overall population. There is an increasing skewness to the right in the HbA1c distributions among individuals in the advanced age groups in both populations, INDIAB (Fig. 2a) and CURES [Fig. 2b].

Discussion

The key findings of our study are (i) there is an increase in HbA1c with age in Asian Indians; (ii) for every decadal increase in age, there is a 0.08% increase in HbA1c; (iii) this decadal increase in HbA1c was more significant in females and in the urban population.

Currently, HbA1c has widely been used for decades as an index of average glycaemia, a measure to identify the risk of developing diabetes complications, and a measure of the quality of diabetes care, owing to its greater convenience (fasting not required), greater preanalytical stability, and less day-to-day perturbations during stress, diet, or illness [9]. More recently based on the recommendations of the ADA, HbA1c has been used as a single test to diagnose diabetes and prediabetes [13]. The normal HbA1c representing a state of normal glucose tolerance is defined as 5.6% (38 mmol/

Table 1 Age-wise distribution of HbA1c by gender and region among individuals with normal glucose tolerance—ICMR-INDIAB study

Age group (years)	Male		Female		Urban		Rural		Overall	
	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD
20–29	1732	5.20 ± 0.73 (33 mmol/mol)	1673	5.11 ± 0.69** (32 mmol/mol)	1019	5.18 ± 0.65 (33 mmol/mol)	2386	5.15 ± 0.74 (33 mmol/mol)	3405	5.16 ± 0.71 (33 mmol/mol)
30–39	1902	5.26 ± 0.66 (34 mmol/mol)	2039	5.20 ± 0.70* (33 mmol/mol)	1110	5.31 ± 0.83 (35 mmol/mol)	2831	5.20 ± 0.62** (33 mmol/mol)	3941	5.23 ± 0.68 (34 mmol/mol)
40–49	1698	5.35 ± 0.64 (35 mmol/mol)	1505	5.35 ± 0.71 (35 mmol/mol)	927	5.42 ± 0.65 (36 mmol/mol)	2276	5.32 ± 0.68** (35 mmol/mol)	3203	5.35 ± 0.67 (35 mmol/mol)
50–59	991	5.41 ± 0.69 (36 mmol/mol)	838	5.47 ± 0.74 (36 mmol/mol)	452	5.50 ± 0.81 (37 mmol/mol)	1377	5.42 ± 0.68* (36 mmol/mol)	1829	5.44 ± 0.72 (36 mmol/mol)
60–69	726	5.48 ± 0.81 (36 mmol/mol)	516	5.47 ± 0.65 (36 mmol/mol)	289	5.59 ± 0.78 (38 mmol/mol)	953	5.45 ± 0.73* (36 mmol/mol)	1242	5.48 ± 0.75 (36 mmol/mol)
70 +	373	5.45 ± 0.66 (36 mmol/mol)	229	5.57 ± 0.74* (37 mmol/mol)	132	5.57 ± 0.57 (37 mmol/mol)	470	5.47 ± 0.72 (36 mmol/mol)	602	5.49 ± 0.69 (37 mmol/mol)
Total	7422	5.32 ± 0.70 (35 mmol/mol)	6800	5.28 ± 0.72* (34 mmol/mol)	3929	5.35 ± 0.74 (35 mmol/mol)	10,293	5.28 ± 0.69** (34 mmol/mol)	14,222	5.30 ± 0.71 (34 mmol/mol)

SD indicates one standard deviation; ICMR–INDIAB: Indian Council of Medical Research–INdia DIABetes study

*$p < 0.05$, **$p < 0.001$ compared to male and urban individuals

Table 2 Age-wise distribution of HbA1c by gender among individuals with normal glucose tolerance—CURES study

Age group (years)	Male		Female		Overall	
	n	mean ± SD	n	mean ± SD	n	mean ± SD
20–29	110	5.31 ± 0.40 (35 mmol/mol)	149	5.37 ± 0.44 (35 mmol/mol)	259	5.35 ± 0.43 (35 mmol/mol)
30–39	171	5.53 ± 0.45 (37 mmol/mol)	231	5.48 ± 0.43 (36 mmol/mol)	402	5.50 ± 0.44 (37 mmol/mol)
40–49	90	5.55 ± 0.47 (37 mmol/mol)	138	5.58 ± 0.53 (38 mmol/mol)	228	5.57 ± 0.51 (37 mmol/mol)
50–59	38	5.66 ± 0.45 (38 mmol/mol)	69	5.86 ± 0.50* (41 mmol/mol)	107	5.79 ± 0.49 (40 mmol/mol)
60–69	27	5.94 ± 0.64 (41 mmol/mol)	38	5.70 ± 0.42 (39 mmol/mol)	65	5.80 ± 0.53 (40 mmol/mol)
70 +	9	5.73 ± 0.33 (39 mmol/mol)	7	5.74 ± 0.70 (39 mmol/mol)	16	5.74 ± 0.50 (39 mmol/mol)
Total	445	5.52 ± 0.48 (37 mmol/mol)	632	5.53 ± 0.49 (37 mmol/mol)	1077	5.53 ± 0.48 (37 mmol/mol)

SD indicates one standard deviation; CURES: Chennai urban rural epidemiological study

*$p < 0.05$ compared to males

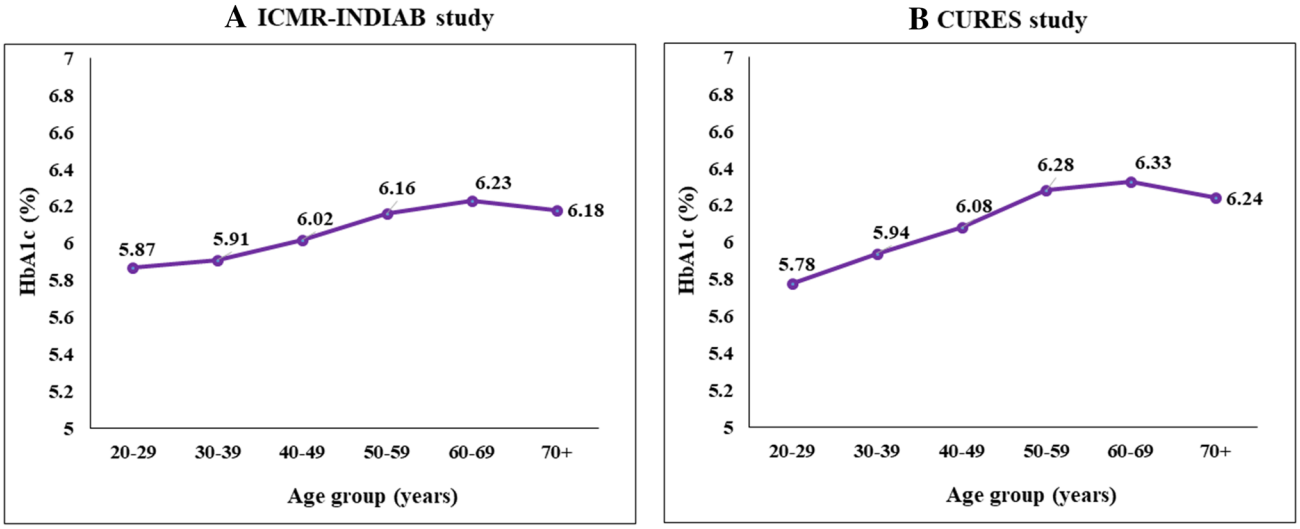

Fig. 1 Distribution plots for glycated haemoglobin (mean + upper limit of standard deviation) among normal glucose tolerance individuals

mol) or less. Values diagnostic of prediabetes ("at risk of diabetes") and diabetes have been defined as 5.7 to 6.4% (39 to 46 mmol/mol) and ≥ 6.5% (48 mmol/mol), respectively, and these have been validated in the Asian Indian population also [14]. Studies have evaluated and reported on the accuracy of HbA1c in different subsets of individuals. A study by Luzi et al. [15] suggested using a lower threshold for HbA1c for those with cardiovascular disease than the general population. In another study by Rizza et al. [16], increase in HbA1c levels was observed even among the young healthy nurses on night shifts compared to those with diurnal workers, irrespective of age, gender and BMI. These results indicate that sleep disruption can lead to subclinical metabolic alterations indicated by the rise in HbA1c levels that may be mistaken as diabetes. As no guideline, to the best of our knowledge, has suggested relaxation of these cutoffs with age, globally the same cut points are used for defining diabetes and states of impaired glucose homeostasis irrespective of age.

An earlier study by Ravikumar et al. [17] from Chandigarh also showed that HbA1c increases with age in subjects with NGT. Indeed, they showed that the 95th percentile of HbA1c exceeded 6.5% (48 mmol/mol) the ADA cut point for diagnosis of diabetes in the elderly (≥ 70 years of age). In individuals with normal glucose tolerance aged 40–74 years studied in the National Health

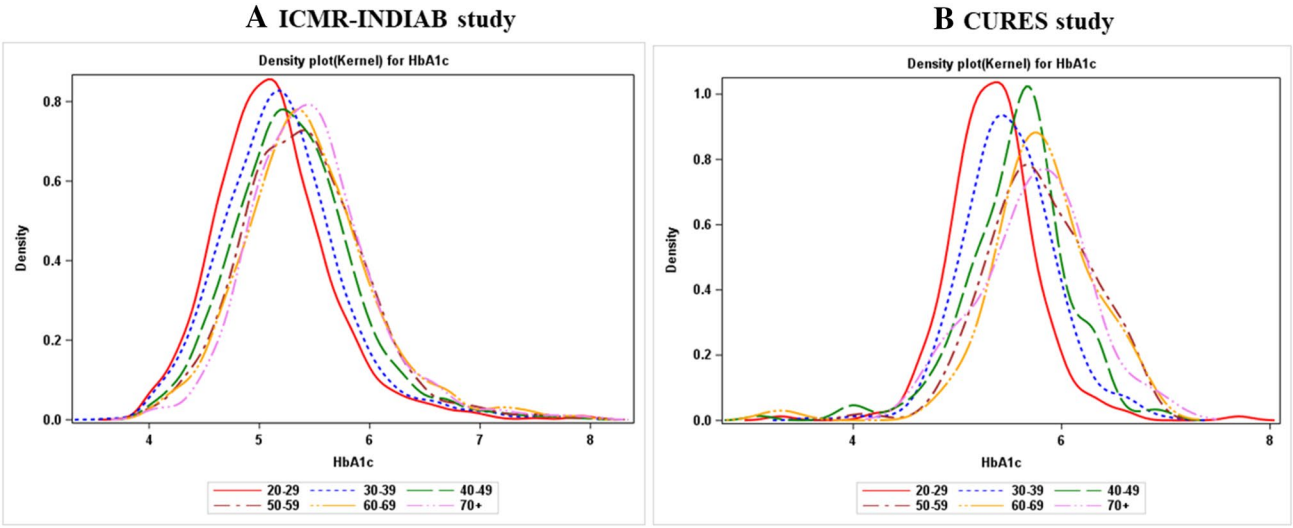

Fig. 2 Density plots for glycated haemoglobin among normal glucose tolerance individuals

and Nutrition Examination Survey (NHANES III), it was demonstrated that older individuals have higher HbA1c levels than younger individuals and that the HbA1c levels increased by 0.1% for each 10-year increase in age [18]. Similarly, in a cross-sectional analysis of HbA1c across five different age groups (< 40, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, and ≥ 70 years) in 2,473 nondiabetic participants of the Framingham Offspring Study (FOS), a 0.14% increase in HbA1c per decade was observed [19]. A cross-sectional survey of 7664 male Japanese workers aged 20–59 years observed an increase in HbA1c with age in all BMI groups and suggested that the age-dependent increase in HbA1c may be a consequence of the ageing process itself [20]. A cross-sectional survey of 4,580 healthy Chinese men and women, aged 20–85 years reported that age itself may cause an elevation in HbA1c independent of other factors, and also found a sex difference (with a lower mean HbA1c in women before menopause) [21]. A study by Nuttall [1] reported a modest age-related increase in HbA1c in an US adult population without known diabetes with a mean increase of 0.11% to 0.15% per decade depending on the analytic method used and concluded that the increase is only modest and has only a minor effect on a determined reference range in adults. However, Masuch et al. [2] have suggested upper reference limits for HbA1c of 6% (42 mmol/mol) for individuals aged 20–39 years, 6.1% (43 mmol/mol) for 40–59 years and 6.5% (48 mmol/mol) for those aged ≥ 60 years, based on their study in the Polish population. In the current study, we observed a 0.08% increase in HbA1c levels per decade with a higher increase in females (0.10%) compared to males (0.06%) and in the urban population (0.10%) compared to rural population (0.08%). These findings are important as there is paucity of data whether higher values of HbA1c even within the "normal" range are associated with future diabetes or dysglycaemia.

What could be the possible mechanisms for increase of HbA1c with age?

It was earlier believed that glycaemia worsens with age leading to increased HbA1c levels. However, studies by Ravikumar et al. [17] and Pani et al. [19] show that increase in HbA1c with age is independent of glycaemia. Possible non-glycaemia-related factors contributing to higher HbA1c at older ages include changes in haemoglobin glycation, in red cell mass or red cell survival, decline in glomerular filtration rates, increase in iron-deficiency anaemia with age or yet to be identified factors [17, 19].

What is the clinical significance of these findings?

We propose that in the younger age groups, the definitions used for diagnosing diabetes, i.e. HbA1c ≥ 6.5% (48 mmol/mol) and prediabetes, i.e. HbA1c between 5.7 and 6.4% (39–46 mmol/mol) can be followed. However, in older people, e.g. those above 60 years of age, one has to be careful not to over diagnose prediabetes or diabetes, as what is considered as "abnormal" HbA1c level at a younger age need not necessarily be "abnormal" at older ages and vice versa. We feel that this point is very rarely brought up in clinical discussions or when clinicians or laboratories give out the HbA1c values. This could potentially lead to inflation of the prediabetes and diabetes prevalence rates in older age groups. In the worst-case scenario, this could also lead to medicalization of a normal condition with unnecessary

prescription of medications, with the attendant risks of hypoglycaemia and other side effects, not to mention the psychological effects on the patient and the unwarranted expenses and strain on the already overburdened healthcare system. We therefore suggest that laboratories and diagnostic centres as well as clinicians should keep the normal variations of HbA1c with age in mind when diagnosing and treating diabetes or prediabetes.

Although the American Diabetes Association [22] in its 'Standard of medical care in diabetes' report states that the FPG, 2-h PG during 75-g OGTT, and HbA1C are equally appropriate for diagnostic screening of diabetes/prediabetes, the concordance between the FPG, 2-h PG tests and any glucose-based tests and the HbA1C test is unsatisfactory. Some studies have reported that a greater number of people are diagnosed with prediabetes/diabetes by the 2-h PG cutpoints compared with FPG and HbA1C cut points [23]. In the Atherosclerosis Risk in Communities (ARIC) study, diagnosis of prediabetes by HbA1c was more specific, while prediabetes diagnosis by FPG was more sensitive for major clinical outcomes [24]. In a study among Asian Indians, we showed that diabetes rate diagnosed by HbA1c criteria was higher than that using the FPG and 2-h PG and it was also found that HbA1c identifies a different set of individuals with milder glucose intolerance [25]. All these indicate that there is no unanimous consensus on which diagnostic test is better for diagnosis of prediabetes/diabetes.

The strengths of the study include the following: a nationally representative sample; large sample size; the study population truly represents the general community as no specific selection criteria were implemented; the samples used both capillary blood glucose and venous plasma glucose and the HbA1c method was certified by the NGSP and standardized to the Diabetes Control and Complications Trial (DCCT) assay. Moreover, all participants underwent OGTT and finally all the HbA1c tests were done in the same, standardized, laboratory. The large ICMR-INDIAB study results were validated with another population-based (CURES) study which used venous plasma glucose to rule out diabetes. However, our study has a few limitations as well. The presence of variant haemoglobins or haemoglobinopathies could potentially have introduced error into HbA1c measurements in parts of the country where such variants are prevalent. However, this is unlikely to have affected the overall results of our study, given that even in the few states where haemoglobinopathies are frequent, sampling adults of all ages was done and this would have avoided any obvious bias. Moreover, the Variant II machine we used for estimating the HbA1c level is capable of picking up the presence of most haemoglobin variants and those found to have variants were excluded from analysis. Iron-deficiency anaemia is another factor that could conceivably have affected our results because studies have shown that severe iron-deficiency anaemia could falsely increase HbA1c levels. However, considering the large sample size, it is unlikely that this could have significantly affected the results of this study. An unexpected result is a subtle decrease in HbA1c among ≥ 70 years group despite the frequent concomitant therapy that is often taken by elderly which may include corticosteroids and statins, for chronic disease such as inflammatory, cancer, cardiovascular and allergic diseases. This most likely reflects survivor bias, as the healthiest people would be expected to survive > 70 years. In our population-based studies, we have earlier reported a decrease in prevalence rates of diabetes among the elderly, for the same reason [5, 12].

In conclusion, the study demonstrates that the HbA1c levels increase normally with age. We suggest that age-specific cut-offs be used while utilizing HbA1c to diagnose diabetes and prediabetes, so as to minimize the risk of overdiagnosis and unnecessary initiation of treatment in elderly people who could have physiological, age-related, increase in HbA1c levels.

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Author contribution RMA and VM conceived the study, designed it, and were involved in implementation of the study, training the team, designing quality assurance measures and interpretation of the data. MD, RP and RU were involved in the design and coordination of the study and interpretation of the data. AKD, PVR, BS, AK, AB, AG, SB and NT were responsible for the supervision of the study in their respective states. SKM, SJ, TK and RSD provided scientific input for the study, were involved in the quality control and helped to revise the report. NE helped in the field coordination of the study. UV and RS were responsible for data management and statistical analyses. MD, RMA and VM drafted the manuscript and all authors contributed to the critical revision of the manuscript for important intellectual content. RMA and VM take full responsibility for the overall content of this work

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Institutional Ethics Committee of the Madras Diabetes Research Foundation, Chennai, Tamil Nadu, India.

Informed consent Written informed consent was obtained from all the study participants.

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