Secular TRends in DiabEtes in India (STRiDE–I): Change in Prevalence in 10 Years Among Urban and Rural Populations in Tamil Nadu

Arun Nanditha, Chamukuttan Snehalatha, Krishnamoorthy Satheesh, Priscilla Susairaj, Mary Simon, Lakshminarayanan Vijaya, Arun Raghavan, Ramachandran Vinitha, and Ambady Ramachandran

Diabetes Care 2019;42:476–485 | https://doi.org/10.2337/dc18-1559

OBJECTIVE

The objective of the current study was to assess the secular trends in the prevalence of diabetes, prediabetes, and risk factors from two epidemiological surveys done 10 years apart in three adult populations of different geographic and socioeconomic backgrounds in Tamil Nadu, India.

RESEARCH DESIGN AND METHODS

This survey was conducted in 2016 using methodology similar to that used in 2006. Persons aged ≥20 years (*n* = 9,848) were screened for diabetes, prediabetes, and the risk variables. Fasting and 2-h plasma glucose, lipid profile, blood pressure, anthropometry, and socioeconomic and behavioral details were recorded. Comparative analyses of age-standardized prevalence were done. Prevalence ratios (PRs) between 2016 and 2006 of diabetes and also prediabetes were assessed using Poisson regression analyses.

RESULTS

Prevalence of diabetes increased from 18.6% (95% CI 16.6–20.5) to 21.9 (20.5–23.3) in the city, 16.4 (14.1–18.6) to 20.3 (18.9–21.6) in the town, and 9.2 (8.0–10.5) to 13.4 (11.9–14.8) in the periurban villages (PUVs) ($P < 0.0001$ in all). The PR showed a nonsignificant 8% rise in diabetes in the city, while significant increases had occurred in the town (39%) and PUVs (34%). Prevalence of prediabetes also increased. Age, family history of diabetes, and waist circumference were common risk determinants among the populations. Though general obesity and abdominal obesity increased, the latter was associated with the increased prevalence.

CONCLUSIONS

Prevalence of diabetes and prediabetes increased in all locations; the rise was significant only in the town and PUVs. Abdominal obesity is significantly associated with increased trend even among the villagers. Rural populations may be targeted for future public health measures to combat diabetes.

The latest estimate by the International Diabetes Federation in 2017 shows that the prevalence of diabetes among the adults (20–79 years of age) in India is 72.9 million (1). A phenomenal increase in diabetes in the last 10 years, from 40.9 million in 2007 to 72.9 million in 2017 (1.78-fold increase), occurred. The prevalence is likely to

India Diabetes Research Foundation and Dr. A. Ramachandran's Diabetes Hospitals, Chennai, India

Corresponding author: Ambady Ramachandran, ramachandran@vsnl.com

Received 20 July 2018 and accepted 19 December 2018

Clinical trial reg. no. NCT03490136, clinicaltrials.gov

increase further by 1.84-fold, i.e., to 134.3 million by 2045. Once again, India is likely to have the largest number of people with diabetes in the world (1). The prevalence of impaired glucose tolerance (IGT) is 2.9% (24 million) (1).

Asian countries, specifically, India and China, are undergoing rapid socioeconomic progress and are susceptible to many adverse consequences such as unhealthy lifestyle leading to high prevalence of diabetes and other noncommunicable diseases (2).

Epidemiological studies in India since 1980 have highlighted the changing trends in prevalence of diabetes, prediabetes, and associated risk factors (3–6). The prevalence of diabetes is higher in urban areas. The determinants of the rising prevalence vary among populations and with time. Unhealthy changes in lifestyle associated with urbanization, familial aggregation, and aging of the population are common risk associations. Large numbers of Indians have migrated to many Western and Asian countries, and the prevalence of diabetes among them is much higher than that of the host populations (2,7,8). In India (9–12) and other developing countries (13–15), lifestyle transition is a major determinant of the rising trends in diabetes, even in rural areas. The phenomenal increase in diabetes can be attributed to changes in dietary pattern, sedentary behavior, and obesity superimposed on the background of genetic and epigenetic susceptibility (16).

Regional disparities in dietary pattern, occupation, and demography are likely to influence the prevalence rates. The extent to which the risk factors are changing in different geographical areas in India and its influence on diabetes is not known. There are sparse data on the time-trend comparisons using standardized methods from low- and middle-income countries, which contribute to nearly 79% of the global prevalence of diabetes (1). Although there are studies showing the epidemiological transition in different Asian countries, only a limited number of studies (5,17) have compared the secular trends in diabetes within the same population at different time points using similar methodology. Such studies from the same region can help with understanding the temporal changes occurring in a specific population. Hence, the current study was done to assess the secular trends in the prevalence of diabetes and prediabetes and the changes in the associated risk factors in urban and rural areas, i.e., in a city, town, and periurban villages (PUVs) in the state of Tamil Nadu in South India, in a 10-year period (2006–2016). The census of 2011 for India indicated that 48.5% of Tamil Nadu is urbanized and has the highest rate of urbanization (18). We did cross-sectional epidemiological studies in the same city, town, and PUVs in 2006 (10) and in 2016 using similar methodology, and the changing trends are reported in this article.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The present epidemiological surveys were conducted from July 2016 to September 2017 in three geographical locations in Tamil Nadu, South India, where similar surveys had been done in 2006. Three locations, classified as city, town, and PUVs by the Indian census commission, were chosen in 2006. In India as per the census commission, a city has a population of >4 million and a town is smaller than a city, with a minimum population of 100,000 and at least 75% of the male working population engaged in nonagricultural pursuits. PUVs are defined as landscapes between a town and rural area. People in PUVs have low economic status and are mostly casual workers engaged in agricultural work. In 2016, the same locations were chosen: city, Chennai; town, Kanchipuram (80 km from Chennai); and PUVs, Panruti (186 km from Chennai). The methodologies used in selection of the study samples, screening, and biochemical procedures were similar in both surveys. For Chennai, the required sample size was 3,824, at 80% power with an α error of 5% and a design effect of 1.5 and an assumed increase in prevalence from 2006 to 2016 from 18.6 to 21.0%. In the town, the number was 3,547 assuming an increase from 16.4 to 19.0%, and the number for PUVs was 2,434 with an expected increase from 9.2 to 12.2%. Samples larger than the calculated numbers were studied. A total of 9,848 were tested (city, n = 3,850; town, n = 3,530; and PUVs, n = 2,468). Response rates were 86.5% in the city, 88.1% in the town, and 87.6% in the PUVs. A multistage random selection was done from streets with population characteristics similar to those in 2006, which gave a fair representation of all the socioeconomic strata. In the city, 5 corporation zones out of 10 marked in 2006 were randomly selected, in the town the selection was done from municipal wards, and in the PUVs panchayat census wards were used. We selected 18 villages in Panruti, which had a population ranging from 2,054 to 8,313 persons. All subjects aged $\geq$20 years were eligible to participate and were enumerated and invited by house visits. Families in which all eligible members gave written informed consent for participation were selected. There was no significant difference in the demographic characteristics of responders and nonresponders.

The study protocol was approved by the Ethics Committee of India Diabetes Research Foundation (IDRF) and Dr. A. Ramachandran's Diabetes Hospitals. An independent data-monitoring committee reviewed the progress of the survey. Written permission from the Department of Public Health and Preventive Medicine, Government of Tamil Nadu, was obtained to conduct the survey in the selected locations. Periodic inspections were done by these authorities while the survey was being conducted. The study was registered on www.ClinicalTrials.gov (identifier: NCT03490136).

Demographic, Anthropometric, and Behavioral Assessment

Details of demography, anthropometry, education, monthly family income, occupation, physical activity, diet habits, smoking, and alcohol consumption were filled in a questionnaire by personal interview by trained team members. Height, weight, and waist circumference (WC) were measured by standard procedures (10). BMI was calculated as weight in kilograms divided by the square of height in meters. Generalized obesity was defined as BMI $\geq$23.0 kg/m^2. BMI between $\geq$23.0 and 24.9 kg/m^2 was considered overweight, and BMI $\geq$25.0 kg/m^2 was defined as obese. Abdominal obesity was indicated by WC of $\geq$90 cm for men and $\geq$80 cm for women (19).

Nutrient intake was recorded by trained dietitians using the 24-h dietary recall method. The total energy intake (kcal) and components of individual food constituents (carbohydrates, proteins, and fat [grams] were calculated with

an in-house dietary analysis program (visual basic programming tool) using the National Institute of Nutrition guidelines for India. Details of physical activity were recorded and quantified using a questionnaire originally used in U.K. Asian Indians (20) that was modified to suit the Indian environment (10,21,22). The quantification was based on the occupational activity and hours of moderate/vigorous activity and leisure-time activity. A score of 7–70 was used.

The economic status of the family was assessed by monthly family income in Indian rupees. The family income was divided in tertiles representing the lower-, middle-, and upper-income groups. The income data of the population in 2006 were also similarly categorized. Education level was categorized as no formal education, school education, and college education. Categorizes of occupation were laborers, homemakers/business, and executives/professional/clerical/students/retired.

Clinical Assessment

Each day 40–60 persons were tested. A clinician took down the medical history and measured the blood pressure in the sitting position using the electronic measuring device (Omron HEM 7132; Omron, Tokyo, Japan). An average of two readings taken at 5-min intervals was recorded. Self-reported history of diabetes and hypertension with details of diagnosis and medication were noted. Subjects with a history of hypertension and those with newly diagnosed diabetes with blood pressure readings ≥140/90 mmHg were categorized as hypertensive (23). Newly diagnosed patients with diabetes during the survey were referred to their physicians or the local public health center or hospital for management.

Biochemical Assessment

Blood samples were collected by door-to-door visits. Fasting samples were taken between 6:00 and 8:00 A.M. For known cases of diabetes, fasting and 2-h postprandial blood glucose was measured. All other subjects underwent an oral glucose tolerance test after 8–12 h of fasting. The fasting state was ensured by questioning the participants. Blood glucose was measured at fasting and at 2 h after consumption of 75 g oral glucose, using venous blood and Accu-Chek Performa (Roche Diagnostics, GmbH, Germany) by the hexokinase method and calibrated to read plasma glucose (24). In this survey, plasma glucose levels were measured using a glucometer to avoid errors that could occur while transporting the samples from distant places to the laboratory. In a subsample of 111 subjects, in addition to the glucose estimation by glucometer, venous blood collected in sodium fluoride was separated at the work site and plasma brought to the central laboratory. Glucose estimations were done within 6 h of collection. The correlation was as follows: reported plasma glucose = 17.1 + 0.887 × venous plasma glucose (glucometer), $P < 0.0001$. The glucometer values were corrected using the equation.

Diagnosis of diabetes and IGT was made using World Health Organization criteria (25). Diabetes was diagnosed if fasting plasma glucose (FPG) value was ≥7 mmol/L (≥126 mg/dL) or 2-h post glucose ≥11.1 mmol/L (≥200 mg/dL), impaired fasting glucose (IFG) if FPG was between 6.1 and <7 mmol/L (110–125 mg/dL), and IGT if the 2-h values were ≥7.8–11.0 mmol/L (≥140–199 mg/dL) with fasting values <6.1 mmol/L (<110 mg/dL).

All blood samples were centrifuged within an hour of collection, and aliquots were stored in freezers until they were sent to the IDRF laboratory. Fasting serum lipid profile was estimated by standard enzymatic procedures (Roche Diagnostics). HDL cholesterol was estimated by the direct assay method.

Statistical Analysis

Estimates of prevalence of diabetes and prediabetes were age standardized by a direct standardization method using the 2011 census data for the respective populations in Tamil Nadu. Means ± SD are reported for normally distributed variables. Student *t* test and one-way ANOVA were used for group comparisons. For skewed variables, median and interquartile ranges are given. Mann-Whitney *U* test or Kruskal-Wallis H test was used as relevant for comparisons. Trend χ^2 test or *z* test was used for comparing categorical variables.

Poisson regression analyses with robust variance were done for 2006 and 2016 to identify the risk variables associated with diabetes versus normoglycemia and prediabetes versus normoglycemia. Independent risk variables included in the models were age (units of 10), BMI (units of 5), WC (units of 10), sex (reference: female), family history of diabetes (reference: negative), monthly family income (three categories [reference: low income]), total calorie consumption (three categories [reference: low calorie]), physical activity (four categories [reference: heavy activity]), education (three categories [reference: no formal education]), occupation (three categories [reference: laborers]), smoking (reference: nil), and alcohol (reference: nil). The prevalence ratios (PRs) (2016 vs. 2006) of diabetes and prediabetes were calculated using Poisson regression analyses with corrections for the significant confounders identified in the above analyses.

RESULTS

Table 1 shows the characteristics of the current study cohorts in comparison with the corresponding data in 2006. Ratio of men and women was representative of the population in each location. Significant increases in age, BMI, and WC were seen in all of the three populations. Systolic blood pressure showed an increase in the urban areas, and diastolic blood pressure increased in all areas. Lipid levels increased in all locations ($P < 0.0001$). However, the total cholesterol–to–HDL cholesterol ratio improved in PUVs ($P < 0.0001$). In 2016, the majority of the populations (63–74%) had school education, and percentages with college education improved in all locations including the PUVs ($P < 0.0001$). The proportion of laborers increased and percentage of homemakers and numbers doing business decreased both in the urban and rural areas.

In 2006 and 2016, the mean age of people with diabetes was similar in the city and in PUVs (49.4 ± 11.5 vs. 49.8 ± 10.8 years, $P = 0.560$, and 47.5 ± 10.8 vs. 47.7 ± 11.9 years, $P = 0.531$, respectively). In the town, it was higher in 2016 (51.9 ± 10.7 vs. 47.7 ± 9.7 years, $P < 0.0001$). The mean age of those with newly diagnosed diabetes in Chennai (45.2 ± 11.3 vs. 46.6 ± 10.9 years, $P = 0.190$) and PUV (43.9 ± 11.4 vs. 45.6 ± 11.9 years, $P = 0.262$) were similar in the 2006 and 2016 surveys, respectively. In the town, there was an increase in the mean age (44.6 ± 9.9 vs. 48.1 ± 10.9 years, $P = 0.003$).

Table 1—General characteristics of the three study populations in 2006 and 2016

	City			Town			PUVs			One-way ANOVA/trend
	2006	2016	Intragroup *P*	2006	2016	Intragroup *P*	2006	2016	Intragroup *P*	χ^2 for 2016
n	2,192	3,850		2,290	3,530		2,584	2,468		
Male:female	1,053:1,139	1,784:2,066		988:1,302	1,603:1,927		1,280:1,304	1,140:1,328		
Age (years)	38.2 ± 12.8	41.7 ± 12.5	<0.0001	36.8 ± 11.6	44.5 ± 12.8	<0.0001	38.0 ± 11.9	40.4 ± 12.9	<0.0001	<0.0001
BMI (kg/m^2)	24.2 ± 4.7	25.4 ± 4.7	<0.0001	23.7 ± 4.7	25.5 ± 4.8	<0.0001	21.5 ± 4.2	22.9 ± 4.4	<0.0001	<0.0001
WC (cm)	83.7 ± 11.2	87.9 ± 10.8	<0.0001	81.9 ± 11.1	86.6 ± 11.1	<0.0001	77.9 ± 10.2	81.4 ± 11.4	<0.0001	<0.0001
Blood pressure (mmHg)										
Systolic	121.6 ± 13.2	122.5 ± 18.5	0.045	119.6 ± 12.9	122.7 ± 18.8	<0.0001	118.1 ± 11.9	115.9 ± 16.2	<0.0001	<0.0001
Diastolic	76.9 ± 9.4	82.3 ± 11.3	<0.0001	77.0 ± 8.3	81.5 ± 10.9	<0.0001	75.3 ± 8.4	76.6 ± 11.1	<0.0001	<0.0001
Lipid profile (mmol)										
Total cholesterol	4.4 ± 1.3	4.7 ± 1.0	<0.0001	4.1 ± 1.1	4.5 ± 0.9	<0.0001	3.8 ± 1.2	4.4 ± 0.9	<0.0001	<0.0001
Triglycerides*	1.3 (0.9–1.8)	1.4 (1.0–2.0)	<0.0001	1.2 (0.9–1.8)	1.3 (0.9–1.9)	<0.0001	1.1 (0.9–1.6)	1.1 (0.8–1.7)	<0.0001	<0.0001
HDL cholesterol	1.2 ± 0.3	1.1 ± 0.3	<0.0001	1.1 ± 0.2	1.1 ± 0.3	—	1.1 ± 0.2	1.1 ± 0.2	—	0.460
Total–to–HDL cholesterol ratio	4.1 ± 1.1	4.5 ± 1.4	<0.0001	3.9 ± 1.1	4.2 ± 1.3	<0.0001	3.8 ± 1.0	4.1 ± 1.3	<0.0001	<0.0001
Diet										
Total calories (kcal)	2,022 ± 354	2,210 ± 210	<0.0001	1,960 ± 332	2,128 ± 138	<0.0001	1,897 ± 304	2,019 ± 173	<0.0001	<0.0001
Carbohydrates (%)	65.4 ± 5.0	63.1 ± 3.8	<0.0001	66.8 ± 4.2	67.5 ± 2.7	<0.0001	69.9 ± 3.2	70.9 ± 3.7	<0.0001	<0.0001
Protein (%)	11.1 ± 1.2	11.5 ± 1.4	<0.0001	10.4 ± 1.1	11.9 ± 1.6	<0.0001	9.8 ± 0.9	10.4 ± 1.6	<0.0001	<0.0001
Fat (%)	22.8 ± 5.0	25.4 ± 3.6	<0.0001	21.3 ± 4.6	20.6 ± 2.7	<0.0001	18.6 ± 2.9	18.7 ± 3.2	<0.0001	<0.0001
Education										
No formal education	180 (8.2)	375 (9.7)	0.053	250 (10.9)	422 (12.0)	0.243	590 (22.8)	664 (26.9)	<0.0001	<0.0001
School	1,490 (68.0)	2,548 (66.2)	0.163	1,763 (77)	2,590 (73.7)	0.002	1,854 (71.7)	1,552 (62.9)	<0.0001	<0.0001
College	390 (17.8)	927 (24.1)	<0.0001	277 (12.1)	518 (14.7)	0.006	140 (5.4)	252 (10.2)	<0.0001	<0.0001
Occupation										
Laborers	540 (24.6)	1,205 (31.3)	<0.0001	768 (33.5)	1,413 (40.0)	<0.0001	1,112 (43.0)	1,318 (53.4)	<0.0001	<0.0001
Homemaker/business	1,052 (48.0)	1,545 (40.1)	<0.0001	1,179 (51.4)	1,778 (50.4)	0.472	1,238 (48.0)	925 (37.5)	<0.0001	<0.0001
Executive/professional	603 (27.5)	1,100 (28.5)	0.423	430 (15.0)	339 (9.6)	<0.0001	234 (9.1)	225 (9.1)	0.961	<0.0001
Physical activity										
Sedentary	656 (29.9)	1,217 (31.6)	0.179	409 (17.9)	711 (20.1)	0.041	267 (10.3)	267 (10.8)	0.594	<0.0001
Light	835 (38.1)	1,607 (41.7)	0.007	1,061 (46.3)	1,733 (49.1)	0.039	1,047 (40.5)	874 (35.4)	<0.0001	<0.0001
Moderate	307 (14.0)	572 (14.9)	0.360	283 (12.4)	543 (15.4)	0.002	492 (19.0)	531 (21.5)	0.030	<0.0001
Heavy	394 (18.0)	454 (11.8)	<0.0001	537 (23.4)	543 (15.4)	<0.0001	778 (30.1)	796 (32.3)	0.098	<0.0001

Data are mean ± SD or *n* (%) unless otherwise noted. Comparison data for years 2006 vs. 2016 in the three study populations for mean ± SD were done using Student *t* test; for *n* (%), *z* test was used. One-way ANOVA was used for comparing the mean ± SD of interpopulation data, Kruskal-Wallis test was used for the median values, and trend χ^2 was used for comparing the percentages in 2016.
*Median value (interquartile range) is shown for skewed variable, and *P* values were computed by Mann-Whitney *U* test.

Table 2—Trends in prevalence of diabetes, prediabetes, obesity, and hypertension

	City			Town			PUVs		
	2006	2016	*P*	2006	2016	*P*	2006	2016	*P*
n	2,192	3,850		2,290	3,530		2,584	2,468	
Male:female	1,053:1,139	1,784:2,066		988:1,302	1,603:1,927		1,280:1,304	1,140:1,328	
Age-adjusted prevalence, % (95% CI)									
Diabetes									
Total	18.6 (16.6–20.5)	21.9 (20.5–23.3)	0.003	16.4 (14.1–18.6)	20.3 (18.9–21.6)	<0.0001	9.2 (8.0–10.5)	13.4 (11.9–14.8)	<0.0001
Male	20.9 (17.9–23.9)	22.9 (20.9–25.1)	0.233	17.1 (13.9–20.2)	20.2 (18.2–22.2)	0.057	10.4 (8.6–12.3)	17.0 (14.7–19.4)	<0.0001
Female	16.7 (14.2–19.3)	21.0 (19.1–22.9)	0.004	15.9 (12.6–19.3)	20.4 (18.6–22.3)	0.001	8.0 (6.2–9.7)	10.1 (8.4–11.9)	<0.0001
Self-reported	11.7 (9.1–14.3)	13.5 (12.4–14.6)	0.049	11.1 (8.2–14.0)	12.1 (11.1–13.1)	0.264	5.8 (4.3–7.3)	6.7 (5.7–7.7)	<0.0001
New	6.9 (6.2–7.6)	8.4 (7.5–9.3)	<0.0001	5.3 (4.7–5.9)	8.2 (7.4–9.0)	<0.0001	3.4 (2.9–3.9)	6.7 (5.7–7.7)	<0.0001
Prediabetes									
Total	12.4 (10.9–13.9)	19.0 (17.6–20.4)	<0.0001	6.1 (5.0–7.2)	21.0 (19.5–22.5)	<0.0001	7.8 (6.7–8.9)	14.6 (13.1–16.1)	<0.0001
Male	12.1 (10.0–14.2)	16.6 (14.7–18.7)	0.001	5.1 (3.6–6.6)	19.4 (17.1–21.7)	<0.0001	7.1 (5.6–8.5)	11.4 (9.5–13.3)	<0.0001
Female	11.4 (9.3–13.4)	20.9 (18.9–22.9)	<0.0001	5.3 (3.6–7.0)	22.6 (20.2–24.9)	<0.0001	8.0 (6.3–9.6)	17.8 (15.5–20.1)	<0.0001
iIGT	7.4 (6.2–8.5)	11.5 (10.4–12.6)	<0.0001	4.3 (3.3–5.3)	11.7 (10.5–12.9)	<0.0001	5.5 (4.6–6.5)	8.2 (7.1–9.3)	<0.0001
Male	9.4 (7.6–11.3)	11.2 (9.6–12.8)	<0.0001	4.5 (3.1–6.0)	11.7 (9.8–13.5)	<0.0001	5.4 (4.1–6.6)	6.4 (4.9–7.9)	<0.0001
Female	7.0 (5.4–8.6)	11.7 (10.2–13.3)	<0.0001	4.4 (2.4–6.3)	12.0 (10.2–13.8)	<0.0001	5.8 (4.4–7.2)	10.1 (8.4–11.9)	<0.0001
iIFG	3.5 (2.7–4.3)	4.3 (3.6–4.9)	<0.0001	0.8 (0.4–1.3)	4.3 (3.6–5.0)	<0.0001	1.9 (1.4–2.5)	3.1 (2.4–3.8)	<0.0001
Male	2.6 (1.7–3.6)	3.8 (2.8–4.7)	<0.0001	0.6 (0.1–1.0)	3.9 (2.9–5.0)	<0.0001	1.7 (1.0–2.4)	1.8 (1.0–2.5)	0.553
Female	4.6 (3.3–5.9)	4.6 (3.7–5.6)	0.970	1.0 (0.4–1.7)	4.5 (3.5–5.6)	<0.0001	2.2 (1.4–3.0)	4.2 (3.1–5.3)	<0.0001
IFG + IGT	1.5 (1.0–2.0)	3.2 (2.7–3.8)	<0.0001	1.0 (0.5–1.4)	5.0 (4.3–5.7)	<0.0001	0.4 (0.2–0.7)	3.3 (2.6–4.0)	<0.0001
Male	1.3 (0.6–2.1)	1.7 (1.1–2.3)	0.005	1.2 (0.4–1.9)	3.7 (2.8–4.6)	<0.0001	0.4 (0.1–0.8)	3.2 (2.2–4.2)	<0.0001
Female	1.9 (1.1–2.7)	4.6 (3.7–5.5)	<0.0001	0.7 (0.3–1.2)	6.0 (4.9–7.1)	<0.0001	0.4 (0.01–0.9)	3.5 (2.5–4.5)	<0.0001
Prevalence of GO, AO, and HTN, *n* (%)									
GO: total	1,289 (58.8)	2,632 (68.4)	<0.0001	1,232 (53.8)	2,401 (68.0)	<0.0001	810 (31.3)	1,123 (45.5)	<0.0001
BMI ≥25 kg/m^2	895 (40.8)	1,854 (48.2)	<0.0001	818 (35.7)	1,772 (50.2)	<0.0001	504 (19.5)	722 (29.3)	<0.0001
BMI ≥23–25 kg/m^2	394 (18.0)	778 (20.2)	0.041	414 (18.1)	629 (17.8)	NS	306 (11.8)	401 (16.2)	<0.0001
AO	1,030 (47.0)	2,426 (63.0)	<0.0001	982 (42.9)	2,049 (58.0)	<0.0001	678 (26.2)	1,018 (41.2)	<0.0001
HTN	445 (20.3)	1,136 (29.5)	<0.0001	391 (17.1)	1,012 (28.7)	<0.0001	384 (14.9)	363 (14.7)	0.873

z test was done for comparing the intragroup differences. Prediabetes total = iIGT, iIFG, and IGT + IFG. AO, abdominal obesity (male ≥90 cm, female ≥80 cm); GO, generalized obesity; HTN, hypertension (≥140/90 mmHg).

Total calorie consumption increased significantly ($P < 0.0001$) in urban areas. In the city, fat consumption increased. No changes were seen in the dietary pattern in the PUVs. Moderate and heavy levels of physical activity were higher among persons in the PUVs ($P < 0.0001$).

Table 2 shows the comparison of glucose intolerance and prevalence of generalized obesity, abdominal obesity, and hypertension in the study periods.

Diabetes

The prevalence of diabetes was 21.9% (95% CI 20.5–23.3), 20.3 (18.9–21.6), and 13.4 (11.9–14.8) in the city, town, and PUVs, respectively. The prevalence had increased significantly compared with the previous survey ($P < 0.003$ in the city and $P < 0.0001$ in other locations). The increase was statistically significant among men only in the PUVs ($P < 0.0001$), but significant increase occurred in women in all locations ($P < 0.0001$). Self-reported diabetes increased in all locations. Percentage of new diabetes increased in both the urban and rural areas ($P < 0.0001$).

Prediabetes

Increasing trends in total prediabetes (isolated IFG [iIFG], isolated IGT [iIGT], and IFG + IGT) and its individual categories were noted in all locations ($P < 0.0001$). Prevalence of iIGT was more common than other forms of prediabetes. Maximum increase in prediabetes occurred in the town.

Compared with the data of 2006, significant increases in generalized obesity and abdominal obesity occurred in all three populations; the highest percentage of increase was observed in the PUVs (Table 2). In the urban areas, prevalence of hypertension increased significantly. Generalized obesity increased by 16.3, 26.4, and 45.4% in the city, town, and PUVs, respectively. Higher percentages of increase in abdominal obesity was seen in all populations (34, 35.2, and 57.2%). The highest increase in both variables occurred in the PUVs ($P < 0.0001$).

Table 3 shows the PRs of diabetes (2016 vs. 2006) and the risk associations for diabetes versus normoglycemia,

Table 3—PR between 2016 versus 2006 of diabetes and also prediabetes: results of Poisson regression analyses

	City			Town			PUVs		
	β (95% CI)	Exp(B) (95% CI)	*P*	β (95% CI)	Exp(B) (95% CI)	*P*	β (95% CI)	Exp(B) (95% CI)	*P*
Diabetes									
2006 vs. 2016 PR	0.08 (−0.01 to 0.17)	1.08 (0.99–1.19)	0.08	0.33 (0.22–0.44)	1.39 (1.25–1.55)	<0.0001	0.29 (0.14–0.43)	1.34 (1.15–1.54)	<0.0001
Variables									
Positive FH	0.45 (0.37–0.53)	1.57 (1.45–1.70)	<0.0001	0.38 (0.28–0.47)	1.46 (1.33–1.60)	<0.0001	0.71 (0.49–0.93)	2.03 (1.63–2.53)	<0.0001
Age (years)	0.53 (0.50–0.56)	1.70 (1.64–1.75)	<0.0001	0.54 (0.51–0.58)	1.72 (1.66–1.79)	<0.0001	0.47 (0.41–0.53)	1.60 (1.51–1.69)	<0.0001
WC (cm)	0.18 (0.13–0.24)	1.20 (1.14–1.27)	<0.0001	0.26 (0.23–0.30)	1.30 (1.26–1.35)	<0.0001	0.40 (0.34–0.46)	1.50 (1.41–1.59)	<0.0001
Sex (male)	0.10 (0.01–0.20)	1.11 (1.01–1.22)	0.033				0.18 (0.02–0.33)	1.19 (1.02–1.39)	0.024
BMI (kg/m^2)	0.09 (0.03–0.15)	1.09 (1.03–1.16)	0.004						
College education	−0.19 (−0.31 to −0.06)	0.83 (0.73–0.94)	0.004						
Executive	0.14 (0.05–0.23)	1.15 (1.06–1.26)	0.002						
Sedentary PA							0.31 (0.12–0.50)	1.36 (1.12–1.65)	0.002
Prediabetes									
2006 vs. 2016 PR	0.43 (0.31–0.56)	1.54 (1.36–1.75)	<0.0001	1.39 (1.20–1.58)	4.01 (3.31–4.86)	<0.0001	0.63 (0.46–0.79)	1.87 (1.59–2.20)	<0.0001
Variables									
Age (years)	0.26 (0.22–0.31)	1.30 (1.25–1.36)	<0.0001	0.29 (0.25–0.34)	1.34 (1.28–1.40)	<0.0001	0.25 (0.19–0.30)	1.28 (1.21–1.35)	<0.0001
BMI (kg/m^2)	0.21 (0.16–0.26)	1.24 (1.18–1.30)	<0.0001	0.19 (0.14–0.24)	1.21 (1.15–1.28)	<0.0001			
WC (cm)							0.26 (0.19–0.32)	1.29 (1.21–1.38)	<0.0001
Positive FH	0.19 (0.07–0.30)	1.20 (1.08–1.35)	0.001						
Sex (male)							−0.26 (−0.42 to −0.10)	0.77 (0.66–0.90)	0.001

Dependent variables: diabetes vs. normoglycemia and prediabetes vs. normoglycemia. Risk variables identified by independent Poisson regression for 2006 and 2016 were combined and included in the analysis. Independent risk variables included in the models were age (units of 10), BMI (units of 5), WC (units of 10), sex (reference: female), family history of diabetes (reference: negative), physical activity (four categories) (reference: heavy activity), education (three categories) (reference: no formal education), and occupation (three categories) (reference: laborers). Study years 2006 vs. 2016 were included to calculate the PR. FH, family history of diabetes; PA, physical activity.

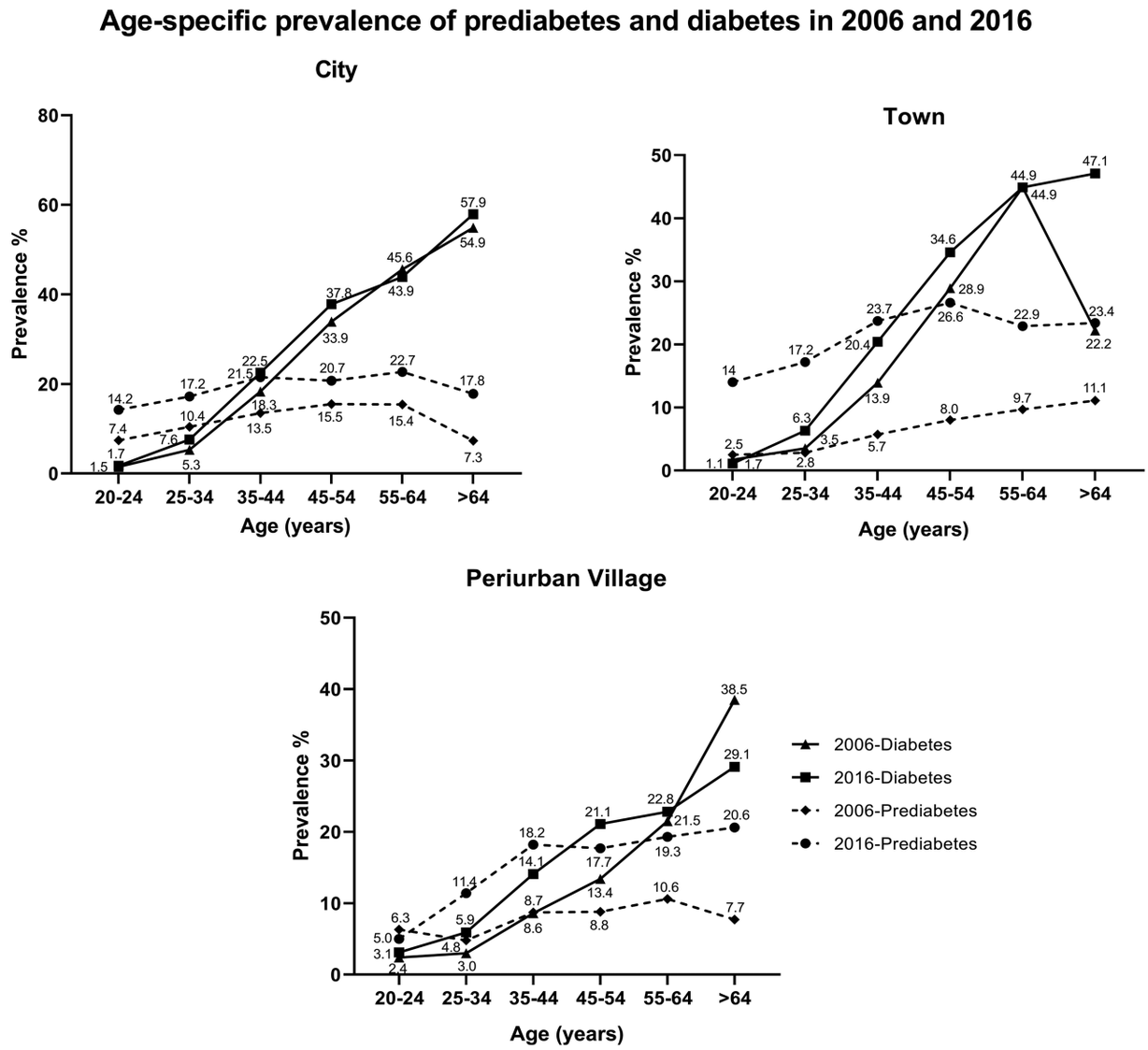

Figure 1—Age-specific prevalence of prediabetes and diabetes in 2006 and 2016.

analyzed by Poisson regression in the three locations. The PR for diabetes for the city (2016 vs. 2006) was not significant (PR 1.08 [95% CI −0.01 to 0.17]; P = 0.08), whereas the ratios were significant for the town (PR 1.39 [95% CI 1.25–1.55], $P < 0.0001$) and PUV (PR 1.34 [95% CI 1.15–1.54], $P < 0.0001$).

In all locations, age, positive family history of diabetes, and WC were associated with the increasing trend in diabetes. Male sex showed an association with the increase in the city and PUVs. BMI showed an association only in the city. In the city, people with higher education level had lower prevalence and persons having high-income occupations had higher prevalence. In PUVs, sedentary activity was associated with diabetes. Total dietary calorie consumption was not independently associated with diabetes. Smoking and alcohol consumption were not associated with diabetes.

Table 3 also shows the PR for prediabetes in 2016 versus 2006. The ratio increased significantly ($P < 0.0001$) in all populations; the highest increase occurred in the town (PR 4.01 [95% CI 3.31–4.86], $P < 0.0001$) followed by the PUVs (PR 1.87 [95% CI 1.59–2.20], $P < 0.0001$). Age was the only common risk association, and BMI was associated with the rising trend in the town. Family history and BMI were associated with the trend in the city. In the PUVs, age and WC showed a positive association and male sex had a higher prevalence.

Figure 1 shows that compared with prevalence in 2006, prevalence of diabetes increased in all age-groups in all three populations. The takeoff point for diabetes was between 25 and 34 years. In the city, the age-specific increase was not significant. In the town, an increasing trend was observed at all ages. At ≥64 years of age, the increase was highly significant ($P < 0.0001$), and the maximum increase was at ≥64 years ($P < 0.022$). A significant fall in the prevalence after the age of 64 years was present in the town in 2006. In the PUVs, the increase in 2016 was significant until the age of 64 years.

Age-specific prevalence of prediabetes increased in 2016 in all populations (Fig. 1). The maximum change was in the town, followed by the PUV. The prevalence started increasing at 25–34 years in all populations. In the city, the increasing trend was present until 64 years; in the town, the maximum increase was at 45–54 years; and in the PUV, the rising trend continued until ≥64 years.

The percentage of smokers was 22.5, 15.0, and 36.8% and alcohol consumption was reported by 30.7, 25.3, and 39% in the city, town, and PUVs, respectively.

CONCLUSIONS

In this study from Tamil Nadu in India, we observed that in the last 10 years the prevalence of diabetes and prediabetes increased in all populations studied. However, varied secular changes were noted among the populations. Significant variations in the PR were observed. In the city, the prevalence (21.9%) had increased only by 8% in 10 years (PR 1.08 [95% CI 0.99–1.19], $P = 0.08$), indicating the probability of the prevalence reaching a plateau. The greatest increase, by 39%, was seen in the town (PR 1.39 [95% CI 1.25–1.55], $P < 0.0001$), and the prevalence (20.3%) was almost similar to that in the city. In the PUVs, a 34% increase in the prevalence in 10 years, from 9.2 to 13.4%, was seen in 2016 (PR 1.34 [95% CI 1.15–1.54], $P < 0.0001$). The prevalence was lower in the PUVs compared with the urban areas. It is important to note that a significant increase occurred among the populations in 2016, with much lower BMI and WC compared with the urban populations.

Prevalence of diabetes in urban India seems to be higher among the states that are economically stronger (1). At present, the total prevalence of diabetes is chiefly contributed by the urban population. Our study shows that the prevalence of diabetes in 2016 is 21.9% in the city of Chennai. The estimate was similar to that reported by the Center for cArdio-metabolic Risk Reduction in South Asia (CARRS) Study (26) in 2015, which was 22.8%. In that study, diagnosis of diabetes was made using the FPG and/or HbA_{1c} values. The survey also reported that the prevalence in Delhi was 16.8%.

A series of studies in Tamil Nadu, in South India, had shown the changing scenario in lifestyle with associated increase in the prevalence of diabetes and prediabetes in the rural areas (6,10,27). Reports from other South Indian states, Pondicherry (28), Andhra Pradesh (29), Karnataka (30), and Kerala (31), had also highlighted the rising trend in diabetes in rural parts. Studies from other parts of India also showed a similar scenario (11). The recent INdia DIABetes (INDIAB) study (9) reported an increase in rural prevalence in many parts of India.

A systematic review and meta-analysis of the global rural diabetes prevalence covering 1990–2012 showed that in low- and middle-income countries, the rural prevalence had increased from 1.8 to 7.5% (32). High prevalence of diabetes in rural areas is reported from other South Asian countries, such as Bangladesh (11), Pakistan (33), and Sri Lanka (13).

In the earlier studies, diabetes prevalence in Chennai was higher in high socioeconomic stratum (4,10). Presently this association is not observed in the urban areas. In 2016, income did not show an association with diabetes prevalence in any of the three locations, whereas in the 2006 survey in the city, high income was associated with a higher prevalence of diabetes (10). The current study suggests a rising trend of diabetes in the low- and middle-income groups. The INDIAB study (9) also observed a transition occurring in India, with diabetes prevalence increasing in rural India as well as among the people of lower socioeconomic status living in the urban areas.

The strong associations of generalized obesity and abdominal obesity with diabetes are well-known. Interestingly, this study showed that abdominal obesity had a higher increase than generalized obesity in all the populations and its association with diabetes was more significant. BMI was found to be a determinant only in the city. The significance of the Asian phenotype of obesity, namely, high abdominal obesity with normal BMI, was seen in all the populations studied, particularly in the PUVs. The rise in WC was more predominant than that of BMI in the rural population (57.2%) than in the city (34%) and in the town (35.2%). Since nearly 60% of India's population lives in rural areas, the major contribution to the future increase in the prevalence of diabetes will be by the rural population.

The present increase in prevalence of diabetes among Indian populations, especially in the rural areas, could have been partially influenced by the complex interaction between genes and environmental factors. Epigenetic changes occur during life and commonly in response to environmental stimuli, providing gene-environmental interaction (34), and are known to induce persistent changes in gene expression patterns and alter physiology (35). Intrauterine exposure to diabetes itself increases the risk of diabetes and obesity in the offspring (36). Several animal and human studies suggest that DNA methylation, a class of epigenetic modification, is sensitive to early environmental factors including maternal diet (37). It has been shown that Indian newborn babies, especially among the rural population, have low birth weight and lean body mass but higher subcutaneous adiposity (38), which is related to an intrauterine imbalance between two related micronutrients (vitamin B_{12} and folate) (39). Further, B_{12} supplementation has been shown to influence methylation of genes associated with diabetes and its intermediate traits. Overall, there is strong evidence that in addition to the "thrifty phenotype" genes, a combination of antenatal, epigenetic, and postnatal influences renders a high risk of diabetes in the South Asian populations (40).

The mean age of newly diagnosed diabetes was similar in the city and the PUVs, but it showed an increase in the town in 2016. No reduction in the age of people with new diabetes was seen. Self-reported diabetes had increased in all populations, indicating better awareness and improved health seeking behavior, even among the rural population.

In 2006 a significant reduction in IGT was noted in Chennai and the PUVs compared with corresponding prevalence in previous years (10). During the same period, Mohan et al. (5) observed a rapid conversion of IGT to diabetes in Chennai with a reduction in the prevalence of IGT. In the current study, the prevalence of prediabetes increased in urban and rural populations.

Presently, the rise in prevalence of diabetes in India (2) and other South Asian countries (14,15) is contributed chiefly by the urban population. Rural to urban migration was shown to be associated with increase in obesity and

diabetes (12). The recent studies in India (9,10,14,15) and other South Asian countries (7) indicate that adoption of urban lifestyle within the rural habitats produces similar detrimental changes resulting in health hazards. The trend is likely to change, since many of the Asian countries show rising trends in the prevalence of diabetes in the rural populations as well. Our present study has demonstrated definite evidence of this phenomenon. The population living in rural areas is higher in India. In the future the major contribution to population with diabetes is likely to be due to the rising rural prevalence of diabetes. Although we have demonstrated this phenomenon in the southern state of Tamil Nadu, it is possible that a similar phenomenon will be occurring in rest of the country.

The current study has the merit that the survey was done in the same three populations of varied urbanization, by virtue of which the transitions occurring in a decade in the pattern of diabetes and its risk associations could be assessed. Moreover, the good response rates of participants in all the study locations give strength to our findings.

The limitations of our study included subjective assessments of dietary habits and physical activity. We have used similar quantification of dietary habits and statistical methodology in both the surveys so that the comparative assessments are more valid. Objective measurements of physical activity are time-consuming and may not be acceptable to the large number of people surveyed. Plasma glucose levels were measured using a glucometer to avoid the errors that could occur if the blood samples had to be transported from distant places to the laboratory. These readings correlated well with those obtained in the laboratory. A correlation factor has also been applied.

In summary, the findings of the 2016 survey highlight a transition in the secular trends of diabetes and prediabetes in different populations studied in Tamil Nadu. In a decade of time, the prevalence of diabetes in the city showed only a nonsignificant increase, whereas a higher percentage increase occurred in the town and PUVs. The prevalence in the town is closer to that in the city.

Recent regional and national studies (9,10,27–31) show that the prevalence of diabetes is increasing in all regions of India including the rural areas. There have been attempts by governmental and nongovernmental agencies to promote preventive endeavors at the national level. However, more urgent focus on prevention is needed for India and also other developing nations to curb the diabetes epidemic. National policies have to be enforced in all countries.

Acknowledgments. The authors acknowledge the help rendered by the epidemiology and laboratory team of the IDRF (C.K. Sathish Kumar, M. Karthikeyan, A. Catherin Seeli, R. Sekar, and G. Sridhar). The authors thank D.T. Arasu and his team, of I5 Clinical Research Private Limited, Chennai, India, for helping with the epidemiological screening and data entry. The authors thank Stephen Sharp, MRC Epidemiology Unit, Cambridge, U.K., for advice on statistical analyses. The authors thank the participants of the epidemiology survey.

Funding. The study was funded by the IDRF.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. A.N., C.S., and A. Ram. developed the study plan, designed and supervised the conduct of the study, and prepared the manuscript. A.N., C.S., and A. Ram. analyzed data and interpreted the results. K.S., P.S., and M.S. participated in fieldwork, study coordination, and data collection. L.V. helped with data management and statistical analyses. A. Rag. and R.V. contributed to discussion and reviewed the manuscript. All authors read and approved the final manuscript. A. Ram. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 8th edition [Internet], 2017. Available from www.diabetesatlas.org/IDF_Diabetes_Atlas_8e_interactive_EN/. Accessed 14 May 2018
2. Ramachandran A, Ma RC, Snehalatha C. Diabetes in Asia. Lancet 2010;375:408–418
3. Ramachandran A, Snehalatha C. Current scenario of diabetes in India. J Diabetes 2009;1:18–28
4. Ramachandran A, Snehalatha C, Kapur A, et al.; Diabetes Epidemiology Study Group in India (DESI). High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. Diabetologia 2001;44:1094–1101
5. Mohan V, Deepa M, Deepa R, et al. Secular trends in the prevalence of diabetes and impaired glucose tolerance in urban South India–the Chennai Urban Rural Epidemiology Study (CURES-17). Diabetologia 2006;49:1175–1178
6. Shrivastava U, Misra A, Mohan V, Unnikrishnan R, Bachani D. Obesity, diabetes and cardiovascular diseases in India: public health challenges. Curr Diabetes Rev 2017;13:65–80
7. Misra A, Ramchandran A, Jayawardena R, Shrivastava U, Snehalatha C. Diabetes in South Asians. Diabet Med 2014;31:1153–1162
8. Sattar N, Gill JM. Type 2 diabetes in migrant south Asians: mechanisms, mitigation, and management. Lancet Diabetes Endocrinol 2015;3:1004–1016
9. Anjana RM, Deepa M, Pradeepa R, et al. Prevalence of diabetes and prediabetes in 15 states of India: results from the ICMR-INDIAB population-based cross-sectional study. Lancet Diabetes Endocrinol 2017;5:585–596
10. Ramachandran A, Mary S, Yamuna A, Murugesan N, Snehalatha C. High prevalence of diabetes and cardiovascular risk factors associated with urbanization in India. Diabetes Care 2008;31:893–898
11. Akhtar SN, Dhillon P. Prevalence of diagnosed diabetes and associated risk factors: evidence from the large-scale surveys in India. J Soc Health Diabetes 2017;5:28–36
12. Ebrahim S, Kinra S, Bowen L et al.; Indian Migration Study group. The effect of rural-to-urban migration on obesity and diabetes in India: a cross-sectional study. PLoS Med 2010;7:e1000268.
13. Jayawardena R, Ranasinghe P, Byrne NM, Soares MJ, Katulanda P, Hills AP. Prevalence and trends of the diabetes epidemic in South Asia: a systematic review and meta-analysis. BMC Public Health 2012;12:380
14. Ramachandran A, Snehalatha C, Shetty AS, Nanditha A. Trends in prevalence of diabetes in Asian countries. World J Diabetes 2012;3:110–117
15. Nanditha A, Ma RC, Ramachandran A, et al. Diabetes in Asia and the Pacific: implications for the global epidemic. Diabetes Care 2016;39:472–485
16. Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. Diabetes Care 2011;34:1249–1257
17. Han C, Zhang M, Luo X, et al. Secular trends in the prevalence of type 2 diabetes in adults in China from 1995 to 2014: a meta-analysis. J Diabetes 2017;9:450–461
18. Office of the Registrar General & Census Commissioner, India. Census of India 2011 [Internet]. Available from http://www.censusindia.gov.in/2011census/C-series/C-13.html Accessed 5 March 2018
19. WHO Western Pacific Region International Association for the Study of Obesity, International Obesity Task Force. *The Asia Pacific Perspective: Redefining Obesity and its Treatment*. St. Leonards, Australia, Health Communications Australia Pty Limited, 2000, p. 22–29
20. McKeigue PM, Pierpoint T, Ferrie JE, Marmot MG. Relationship of glucose intolerance and hyperinsulinaemia to body fat pattern in south Asians and Europeans. Diabetologia 1992;35:785–791
21. Ramachandran A, Snehalatha C, Latha E, Vijay V, Viswanathan M. Rising prevalence of NIDDM in an urban population in India. Diabetologia 1997;40:232–237
22. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V; Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired

glucose tolerance (IDPP-1). Diabetologia 2006; 49:289–297
23. Chobanian AV, Bakris GL, Black HR, et al.; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560–2572
24. Freckmann G, Schmid C, Baumstark A, Pleus S, Link M, Haug C. System accuracy evaluation of 43 blood glucose monitoring systems for self-monitoring of blood glucose according to DIN EN ISO 15197. J Diabetes Sci Technol 2012; 6:1060–1075
25. World Health Organization. *Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia: Report of a WHO/IDF Consultation*. Geneva, World Health Organization, 2006, p. 1–50
26. Deepa M, Grace M, Binukumar B, et al.; CARRS Surveillance Research Group. High burden of prediabetes and diabetes in three large cities in South Asia: the Center for cArdio-metabolic Risk Reduction in South Asia (CARRS) Study. Diabetes Res Clin Pract 2015;110:172–182
27. Ramachandran A, Snehalatha C, Baskar AD, et al. Temporal changes in prevalence of diabetes and impaired glucose tolerance associated with lifestyle transition occurring in the rural population in India. Diabetologia 2004;47:860–865
28. Shrivastava SR, Ghorpade AG. High prevalence of type 2 diabetes melitus and its risk factors among the rural population of Pondicherry, South India. J Res Health Sci 2014;14:258–263
29. Nirmala PV, Gudivada M, Lashmi C. Comparative study of the prevalence of type-2 diabetes mellitus in various demographic regions of Andhra Pradesh, India: a population based study. Int J MCH AIDS 2016;5:103–111
30. Padmanabha UR, Nalam U, Badiger S, Nagarajaiah P. Prevalence and risk factors of type 2 diabetes mellitus in the rural population of Mangalore, South India. Natl J Community Med 2017;8:456–461
31. Harikrishnan S, Sarma S, Sanjay G, et al. Prevalence of metabolic syndrome and its risk factors in Kerala, South India: analysis of a community based cross-sectional study. PLoS One 2018;13:e0192372
32. Zabetian A, Sanchez IM, Narayan KM, Hwang CK, Ali MK. Global rural diabetes prevalence: a systematic review and meta-analysis covering 1990-2012. Diabetes Res Clin Pract 2014;104: 206–213
33. Basit A, Fawwad A, Qureshi H, Shera AS; NDSP Members. Prevalence of diabetes, pre-diabetes and associated risk factors: second National Diabetes Survey of Pakistan (NDSP), 2016-2017. BMJ Open 2018;8:e020961
34. Davegårdh C, García-Calzón S, Bacos K, Ling C. DNA methylation in the pathogenesis of type 2 diabetes in humans. Mol Metab 2018; 4:12–25
35. Waterland RA, Michels KB. Epigenetic epidemiology of the developmental origins hypothesis. Annu Rev Nutr 2007;27:363–388
36. Dabelea D, Hanson RL, Lindsay RS, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes 2000;49:2208–2211
37. Martin EM, Fry RC. Environmental influences on the epigenome: exposure- associated DNA methylation in human populations. Annu Rev Public Health 2018;39:309–333
38. Yajnik CS. Early life origins of insulin resistance and type 2 diabetes in India and other Asian countries. J Nutr 2004;134:205–210
39. Yajnik CS, Deshpande SS, Jackson AA, et al. Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune Maternal Nutrition Study. Diabetologia 2008;51:29–38
40. Wells JCK, Pomeroy E, Walimbe SR, Popkin BM, Yajnik CS. The elevated susceptibility to diabetes in India: an evolutionary perspective. Front Public Health 2016;4:145