Received: 11 July 2020 | Accepted: 14 November 2020

DOI: 10.1111/dme.14466

DIABETIC Medicine

RESEARCH: EPIDEMIOLOGY

# Differential risk factor profile of diabetes and atherosclerosis in rural, sub-urban and urban regions of South India: The KMCH-Non-communicable disease studies

**Ganesan Velmurugan**[1,2] | **Sundaresan Mohanraj**[1] | **Mani Dhivakar**[2] | **Ganesh Veerasekar**[1] | **Jennifer Brag-Gresham**[3] | **Kevin He**[3] | **Thomas Alexander**[1] | **Mathew Cherian**[1] | **Rajiv Saran**[3] | **Thalappil Pradeep**[2] | **Krishnan Swaminathan**[1,2]

[1]KMCH Research Foundation, Kovai Medical Centre and Hospital, Coimbatore, Tamilnadu, India

[2]DST Unit of Nanoscience and Thematic Unit of Excellence in Water Research, Department of Chemistry, Indian Institute of Technology, Chennai, Tamilnadu, India

[3]Department of Internal Medicine and Molecular and Integrative Physiology, Division of Nephrology, University of Michigan, Ann Arbor, MI, USA

**Correspondence**
Krishnan Swaminathan and Ganesan Velmurugan, KMCH Research Foundation, Kovai Medical Center & Hospital, Coimbatore 641014, Tamilnadu, India.
Email: snehasswaminathan@gmail.com (K. S.) and vel@kmchrf.org (G. V.)

**Funding information**
KMCH Research Foundation, Grant/Award Number: KMCH-NCD 2015

## Abstract

**Aims:** South Asia has emerged rapidly as an epicentre of non-communicable diseases (NCDs) specifically diabetes and cardiovascular diseases. The prevalence rate, risk factors and aetiology of NCDs in different socio-demographic settings are not clearly understood. This study was performed to assess the prevalence of diabetes and atherosclerosis and their risk factors in urban, sub-urban and rural communities of South India.

**Methods:** Three communities [Nallampatti (rural), Thadagam (sub-urban) and Kalapatti (urban)] in South India were selected for participation in the KMCH-NCD Studies. Study volunteers were administered a detailed questionnaire, underwent anthropometric measurements, clinical measurements including blood pressure, glycated haemoglobin ($HbA_{1c}$), non-fasting lipid profile and serum creatinine. Carotid intima-media thickness was measured using B-mode ultrasound. Multiple logistic regression analyses were performed to understand the association of risk factors with diabetes and atherosclerosis.

**Results:** A total of 2976 native participants, ≥20 years of age were screened. The prevalence of diabetes was 16%, 26% and 23% respectively in the rural, sub-urban and urban study populations. Association of obesity with diabetes was observed in only urban population while hypertension and dyslipidaemia showed association in both urban and semi-urban populations. Association of diabetes with atherosclerosis was observed in urban and semi-urban populations. Hypertension in semi-urban and obesity and dyslipidaemia in urban population showed association with atherosclerosis.

**Conclusions:** Diabetes and atherosclerosis burden reported in the three different communities were higher than previous reports, especially in rural and sub-urban regions. No traditional risk factor is identified to be associated with prevalence of diabetes and atherosclerosis in rural population. These findings suggest an urgent need for investigation into the role of non-traditional risk factors like environmental

Ganesan Velmurugan and Sundaresan Mohanraj contributed equally.

or occupational exposures may help to better understand the aetiology of diseases in non-urbanized communities.

**KEYWORDS**

atherosclerosis, diabetes, non-communicable diseases, public health, risk factors, rural health

## 1 | INTRODUCTION

Non-communicable diseases (NCDs) collectively have emerged as the leading cause of morbidity and mortality worldwide. Therefore NCDs have been increasing at the forefront of international policy discussions on health. South Asia, home to one-quarter of the world's population, is currently in the midst of an epidemiologic transition from infectious diseases and nutritional deficiencies to a dramatic rise in the burden of NCDs. In India the mortality due to NCDs increased from 39.7% in 1990 to 63.4% in 2017.[1] Among the NCDs, diabetes and cardiovascular diseases (CVDs) alone account for more than 50% of NCD-related mortality. An estimated 422 million (8.5%) adults were living with diabetes in 2014, compared to 108 million in 1980 worldwide.[2] In addition, 318 million (6.7%) adults suffer from glucose intolerance, which puts them at high of developing CVDs in future. Besides its impact on individuals, diabetes and its complications impose a huge obstacle on sustainable economic development of all countries due to health care costs and productivity loss.[3]

The rising prevalence of NCDs is taking place in the context of a rapidly urbanizing population in India.[4] Migration of rural people into urban areas in India is associated with increase in obesity and diabetes due to exposure to changes in lifestyle behaviours and diet.[5.] Intuitively, one expects a lower prevalence of NCDs in rural India, where traditionally more active lifestyles are prevalent compared to urban locales.[6] While data from rural India are sparse,[7] some reports suggest that NCDs are already the largest cause of death even in rural India.[8-10] In addition, there are extremely sparse NCD prevalence data from mushrooming sub-urban areas of India. Not surprisingly, significant gaps in knowledge continue to exist with respect to the epidemiology of NCDs in a country as diverse as India.

There have been laudatory attempts in the recent past with studies including the Prospective Urban Rural Epidemiology (PURE) study[11] and ICMR-INDIAB study[12] looking at the prevalence of NCDs in a representative sample from different Indian regions. These studies indicated the variations in carbohydrate and fat diet intake and lifestyle behaviours for the increased prevalence of diabetes in urban regions. The aetiology of diabetes and non-communicable diseases in the rural community, where prevalence of traditional risk factors is scarce is not largely addressed in these studies.

**Novelty statement**

- Half of the population in all the three regions (rural, semi-urban and urban) had either diabetes or pre-diabetes in South India.
- No association of traditional metabolic risk factors like obesity, hypertension, and dyslipidaemia was observed among diabetes and atherosclerosis in rural population.
- The non-association of traditional risk factors with metabolic diseases in rural population indicates the possible role of non-traditional risk factors like environmental chemicals.

Recent studies from rural India indicated the huge burden of diabetes and its complications with association of environmental factors like heavy metals and pesticide exposure. [13-18] However, it remains vital to understand disease patterns in different communities, as wide geographic variations in disease patterns are likely in a vast country like India. Such studies will have implications in redefining health policy specific to those regions and may also provide insights into novel pathophysiological mechanisms, as well as regional socio-cultural factors that may be at play. Such considerations served as the motivation to undertake this study designed to estimate the prevalence of diabetes and atherosclerosis in a rural, sub-urban and urban populations of Tamil Nadu and to evaluate their major risk factors. This study was aimed at assessing the prevalence of diabetes and atherosclerosis and its risk factors in rural, sub-urban and urban regions to explore novel pathophysiological mechanisms that may be at play by location, and to provide a platform for designing longer-term follow-up studies to assess the impact and potential solutions for the rising threat of NCDs in this part of southern India.

## 2 | MATERIAL AND METHODS

### 2.1 | Study areas

Three geographic areas were chosen based on contacts with administrative heads, logistics and ability to perform long-term follow-up. The geographic location of the study areas

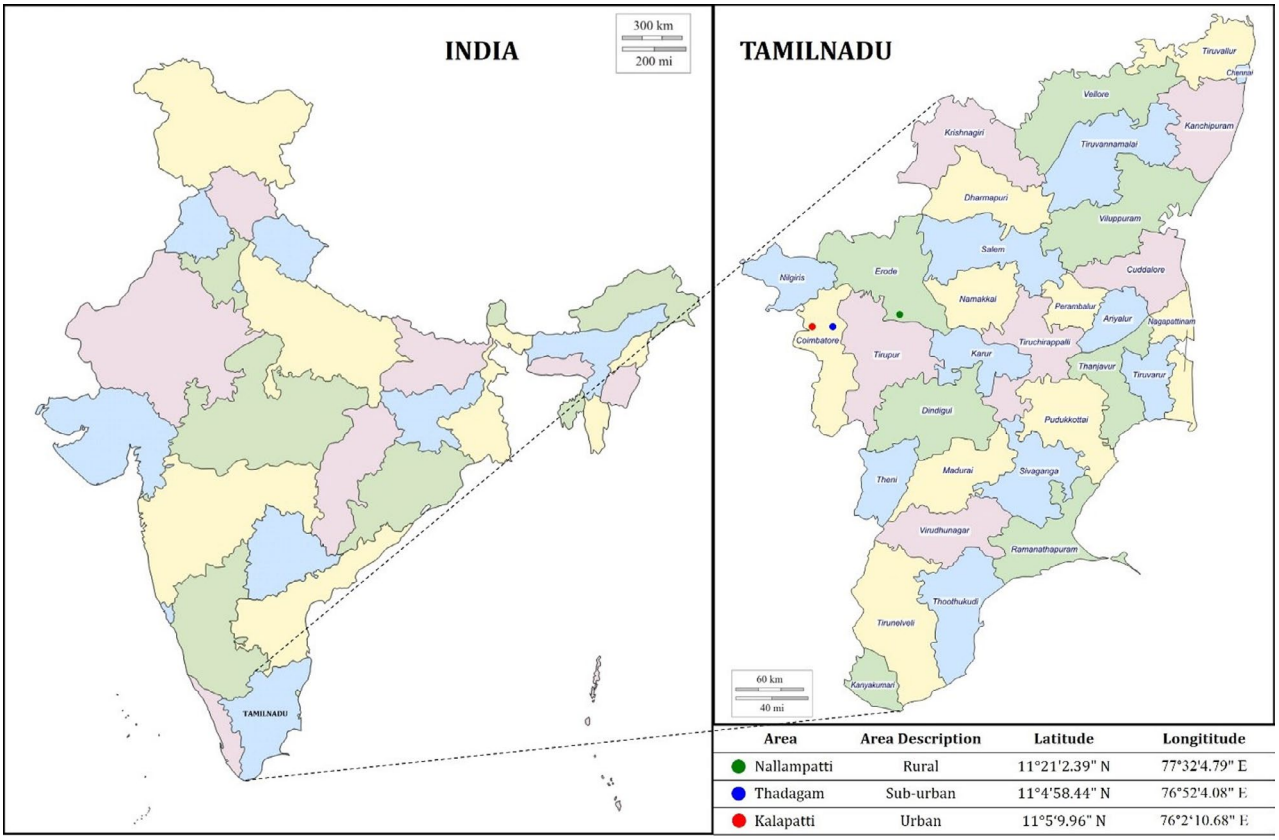
is provided in Figure 1. Nallampatti is a typical farming village located around 60 km from Coimbatore[15,16] chosen as a representative rural area. Thadagam, a brick kiln rich area located 15 km from Coimbatore and Kalapatti, located within Coimbatore city, were chosen as representative sub-urban and urban areas respectively. The individual studies were named Nallampatti-NCD study (NNCD), Thadagam-NCD study (TNCD) and Kalapatti-NCD study (KNCD). The studies were conducted on Sundays over a four-week period in each area from April 2015 – June, 2016. Each study population was informed of our visit through distribution of leaflets (door to door) and by "word of mouth" through the local government administrative workers and student volunteers. The exclusion criteria included age <20 years or >85 years, pregnancy and non-residents of the selected regions. All the three areas had a defined geographical boundary and the population data are collected from Government of India – Census 2011. Only the residents of these regions were invited for the study. The residence of the participants were cross-checked by verification with the government census data and the proof of residence documents like Aadhar card, voter ID card or driving license provided by the participants. The study design and protocol were approved by KMCH Ethics Committee (Ref. No. NNCD: EC/AP/365/02/2015; TNCD:EC/AP/405/09/2015; KNCD: EC/AP/464/07/2016) and informed written consent was obtained from all participants prior to participation and the principles of Declaration of Helsinki were followed.

## 2.2 | Retrieval of rural data

All demographic and clinical data of the 865 participants of KMCH - Nallampatti non-communicable disease – I (NNCD-I) study were retrieved from our database and used for the study. The variables included basic demographic details, lifestyle, disease history, medications, body weight, height, waist circumference, blood pressure, carotid intima-media thickness (CIMT) and blood investigations ($HbA_{1c}$, non-fasting lipid profile). The details of the study have been described previously.[15-17]

## 2.3 | Sample and data collection from sub-urban and urban regions

A detailed questionnaire as described previously [15-17] was administered to document the educational status, employment, alcohol intake, smoking status, pesticide exposure, family disease history and past medical history. About 5 ml of blood




| Area | Area Description | Latitude | Longitude |
|---|---|---|---|
| Nallampatti | Rural | 11°21'2.39" N | 77°32'4.79" E |
| Thadagam | Sub-urban | 11°4'58.44" N | 76°52'4.08" E |
| Kalapatti | Urban | 11°5'9.96" N | 76°2'10.68" E |

**FIGURE 1** Geographic location of the three study areas. Nallampatti, Thadagam and Kalapatti are represented by green, blue and red circles respectively. The study areas marked with circles are not to scale

sample was collected and clinical measurements were done and based on medical history or standard cut-off values, the disease end points were characterized.

## 2.4 | Anthropometric measurements

Demographics, anthropometric data and non-fasting blood were collected from all consented participants. Body weight was measured using an electronic weighing scale (SECA 813), height was measured using a stadiometer (SECA 208) and waist circumference was measured in centimetres using a non-stretchable measuring tape between the costal margins and the iliac crest at the end of expiration.

## 2.5 | Measurement of blood pressure

Blood pressure was recorded using the electronic OMRON machine in the sitting position in the right arm (Model HEM-7130, Omron healthcare, Singapore) on two occasions 15 minutes apart. The average value was used to determine the hypertension status. We recorded blood pressures at least twice. The participants with high blood pressure (≥ 140/90 mm Hg) in the first visit were reinvited after a week and their hypertensive status was confirmed by remeasurement of blood pressure.

## 2.6 | Measurement of carotid intima-media thickness:

Carotid intima-media thickness (CIMT) was measured using two high resolution B-mode ultrasound machines (GE Healthcare, Venue 40, USA), in the supine position on scan bed with the head of the patient resting comfortably, neck slightly hyper-extended and the head tilted towards the opposite of the examined side. Both left and right common carotid arteries were depicted. The imaging was performed on field by two trained, final year radiology residents under the supervision of a senior radiologist.

## 2.7 | Measurement in blood samples

$HbA_{1c}$ was measured using an automated HPLC method (D-10-Biorad), and serum lipid levels were measured using an automated analyzer (Abbott Architect ci8200).

## 2.8 | Disease end points

Generalized obesity was defined as a BMI ≥25. Diabetes was defined as either having a history of diabetes on medications or HbA1c level of ≥48 mmol/ mol (6.5%) in those without a history of diabetes. Pre-diabetes was defined as HbA1c between 42 and 46 mmol/ mol (6.0–6.4%) (IEC) or 39 and 46 mmol/ mol (5.7%–6.4%) (American Diabetes Association) in those without a history of diabetes. Data were analyzed with both criteria to assess the differences in estimates of prevalence between these two groups. Hypertension was defined as either having a history of hypertension on medications or a systolic blood pressure of ≥140 mm Hg and/ or diastolic blood pressure ≥90 mm Hg on two occasions taken 15 minutes apart and re-verification after a week, in those without a history of hypertension.

Dyslipidaemia was defined as the presence of any one of the following abnormalities: Total Cholesterol ≥200 mg/ dl, LDL-C ≥ 130 mg/dl or HDL-C < 40 mg/dl in men and <50 mg/dl in women. Triglycerides were from non-fasting samples due to practical difficulties of obtaining fasting samples. Carotid atherosclerosis was defined as a CIMT ≥1 mm in either left or right or in both measurements. Participants with self-reported diseases were confirmed by review of their medical records and medications. Diabetes, hypertension, dyslipidaemia, smoking, alcohol intake and obesity were considered as traditional factors.

## 2.9 | Statistical analysis

Data were analyzed using SPSS version 15 and Graphpad Prism version 6.01. Descriptive results were expressed as means and standard deviations. The association between risk factors and disease outcomes was studied by multiple logistic regression analysis. Age, sex, smoking, alcohol and tobacco usage, body mass index, systolic and diastolic blood pressure, total lipid profile were employed as confounders for adjustment in diabetes population. In case of atherosclerosis, along with above mentioned confounders, diabetes, and familial ischaemic heart disease history were used for adjustment. Pearson correlation and linear regression were performed to explore the strength of relationship between traditional risk factors and $HbA_{1c}$. Multiple logistic regression analyses were performed to study the relation of the different factors with disease outputs after adjustment for confounding factors. No data points were excluded from analyses. Findings at $p < 0.05$ were considered significant in all analysis.

# 3 | RESULTS

A total of 2976 participants were screened in all three areas as follows; 865 participants in rural Nallampatti, 1030 participants in sub-urban Thadagam and 1081 in urban Kalapatti. We covered around 65%–75% of the total adult population in each region as per the government census data

(Supplementary Table S1). The baseline characteristics of all three study populations are outlined in Table 1. The age group most represented in all three demographics was between 41 and 60 years of age. Alcohol usage and smoking behaviour were exclusively prevalent only in the men population of all the three communities (Table 1). Smoking and occasional alcohol consumption was much higher in the rural population whereas daily alcohol consumption was higher in the urban population. Tobacco chewing habit was more prevalent in sub-urban than in other two populations. Obesity was highest in the urban population and similar in the rural and sub-urban population (48% vs 32 & 35%) respectively. On the other hand, prevalence of low BMI (underweight) was higher in the rural and sub-urban communities (13%, 14% respectively) while it was nearly 50% lower in the urban community (6.4%) (Table 1).

We observed highest prevalence of diabetes in sub-urban region (26%) followed by urban (23%) and rural region (16%). Among the diabetes population, 37% in rural, 33% in semi-urban and 54% in urban area were newly diagnosed as diabetes during this study. Among the self-reported people with diabetes under medical interventions, the rate of poor glycaemic control [HbA1c > 69 mmol/ mol (8.5%)] was 51% in rural, 59% in sub-urban and 22% in urban communities.

**TABLE 1** Characteristics of the participants in the three studies (NNCD, TNCD and KNCD)

| KMCH-NCD Studies | | Prevalence (%) | | |
|---|---|---|---|---|
| | | NNCD (n = 865) | TNCD (n = 1030) | KNCD (n = 1081) |
| Sex | Men | 48 | 46 | 41 |
| | Women | 52 | 54 | 60 |
| Age (years) | 20-40 | 33 | 27 | 32 |
| | 41-60 | 47 | 49 | 48 |
| | Above 60 | 20 | 24 | 21 |
| Alcohol intake (only Men) | Daily | 2.7 | 4.4 | 6.7 |
| | Occasionally/ Formerly | 50 | 12 | 33 |
| | Never | 47 | 83 | 30 |
| Smoking (only Men) | Daily | 31 | 14 | 19 |
| | Occasionally/ Formerly | 25 | 4 | 13 |
| | Never | 44 | 82 | 67 |
| Tobacco chewing | Daily | 14 | 22 | 10 |
| | Occasionally/ Formerly | 12 | 15 | 11 |
| | Never | 74 | 64 | 79 |
| BMI ($kg/m^2$) | Obese (≥ 25) | 32 | 35 | 48 |
| | Normal (24.9-18.6) | 55 | 51 | 46 |
| | Underweight (≤ 18.5) | 13 | 14 | 6.4 |
| $HbA_{1c}$ [mmol/mol (%)] | Diabetes [≥ 48 (≥ 6.5)] | 16 | 26 | 23 |
| | Pre-diabetes [IEC 42-46 (6.0-6.4)] | 18 | 16 | 11 |
| | Pre-diabetes [ADA 39-46 (5.7-6.4)] | 42 | 34 | 33 |
| Blood Pressure (mm Hg) | Raised blood pressure (≥140/90) | 38 | 48 | 40 |
| Total Cholesterol (mg/dl) | Hypercholesterolaemia (≥200) | 33 | 30 | 37 |
| LDL-Cholesterol (mg/dl) | Hyper LDL-cholesterolaemia (≥130) | 25 | 21 | 39 |
| CIMT (mm) | Atherosclerosis (≥1) | 10 | 9.1 | 7.9 |

The data are represented in percentages.

Abbreviations: BMI, Body mass index; CIMT, Carotid intima-media thickness; $Hb_{A1c}$, glycated haemoglobin; LDL, Cholesterol – Low density lipoprotein-cholesterol.

**TABLE 2** Multiple logistic regression with diabetes as the dependent variable in the three different populations

| | NNCD (Rural) | | TNCD (Sub-urban) | | KNCD (Urban) | |
|---|---|---|---|---|---|---|
| | Odds ratio (95% CI) | | | | | |
| | Unadjusted | Adjusted[#] | Unadjusted | Adjusted[#] | Unadjusted | Adjusted[#] |
| Age Group | | | | | | |
| 20-40 years | 1 | 1 | 1 | 1 | 1 | 1 |
| 41-59 years | 2.27[****] (1.15–3.41) | 1.85[**] (1.01–2.24) | 2.59[**] (1.25–3.12) | 1.45[**] (1.17–2.84) | 2.01[**] (1.85–3.11) | 1.33[*] (1.15–2.38) |
| Above 60 years | **3.87**[****] (2.43–6.15) | **2.88**[***] (1.31–5.4) | **5.01**[****] (1.84–7.30) | **3.78**[***] (2.30–5.20) | **2.27**[****] (1.63–3.42) | **2.10**[****] (1.88 – 3.90) |
| Sex | | | | | | |
| Women | 1 | 1 | 1 | 1 | 1 | 1 |
| Men | **1.58**[*] (1.05–2.34) | 0.91 (0.46 −1.80) | 1.12 (0.88 −1.63) | 0.68 (0.43–1.07) | 1.12 (0.84–1.50) | 0.98 (0.72–1.35) |
| Alcohol intake (only men) | | | | | | |
| Never | 1 | 1 | 1 | 1 | 1 | 1 |
| Formerly/ Occasionally | 1.93 (1.09–3.42) | 1.04 (0.12–8.70) | 1.23 (0.72–2.11) | 1.34 (0.53–2.44) | 0.98 (0.62–1.58) | 0.80 (0.46–1.38) |
| Daily | 2.89 (0.57–14.6) | 1.57 (0.72–3.34) | 1.03 (0.49–2.14) | 0.97 (0.38–2.53) | 1.01 (0.43–2.38) | 0.82 (0.32–2.10) |
| Smoking (only mens) | | | | | | |
| Never | 1 | 1 | 1 | 1 | 1 | 1 |
| Formerly/ Occasionally | 0.55 (0.12–2.53) | 0.78 (0.14–4.41) | 1.86 (0.64 – 5.37) | 1.57 (0.49–4.98) | 0.86 (0.32–2.28) | 0.70 (0.22–2.24) |
| Daily | 2.52 (1.40–4.52) | 1.92 (0.87–4.24) | 1.61 (0.82–2.56) | 2.79 (1.50–5.18) | 1.33 (0.79–2.23) | 1.58 (0.85–2.93) |
| Obesity | | | | | | |
| Non-obese | 1 | 1 | 1 | 1 | 1 | 1 |
| Obese | 1.34 (0.87–2.06) | 1.72 (0.98–2.83) | **2.55**[*] (1.08–3.60) | 1.70 (0.84–2.43) | **1.68**[***] (1.24–2.27) | **1.51**[**] (1.10–2.08) |
| Blood pressure | | | | | | |
| Normotensive | 1 | 1 | 1 | 1 | 1 | 1 |
| Hypertensive | **2.90**[****] (1.93–4.37) | 1.40 (0.88–2.23) | **1.65**[****] (1.23–2.21) | **2.03**[****] (1.37–2.99) | **2.67**[****] (1.95–3.67) | **1.54**[*] (1.08–2.20) |
| Dys- lipidaemia | | | | | | |
| Normal | 1 | 1 | 1 | 1 | 1 | 1 |
| High | **2.22**[**] (1.36–3.62) | 1.19 (0.59–2.40) | **1.88**[**] (1.25–2.84) | **1.84**[*] (1.02–3.32) | **2.51**[****] (1.64–3.83) | **1.88**[*] (1.15–3.10) |

$p < 0.05$ was considered statistically significant in all analyses.

*$p < 0.05$,

**$p < 0.01$,

***$p < 0.001$,

****$p < 0.0001$.

Pre-diabetes as defined by both WHO/ International Expect Committee (IEC) and American Diabetes Association (ADA) criteria was higher in rural areas than semi-urban and urban demographics. Hypertension was present in approximately 50% of sub-urban study population compared to 37–39% in rural and urban population respectively. Hypercholesterolaemia was prevalent in nearly one-third of all the three populations. LDL cholesterol was detected

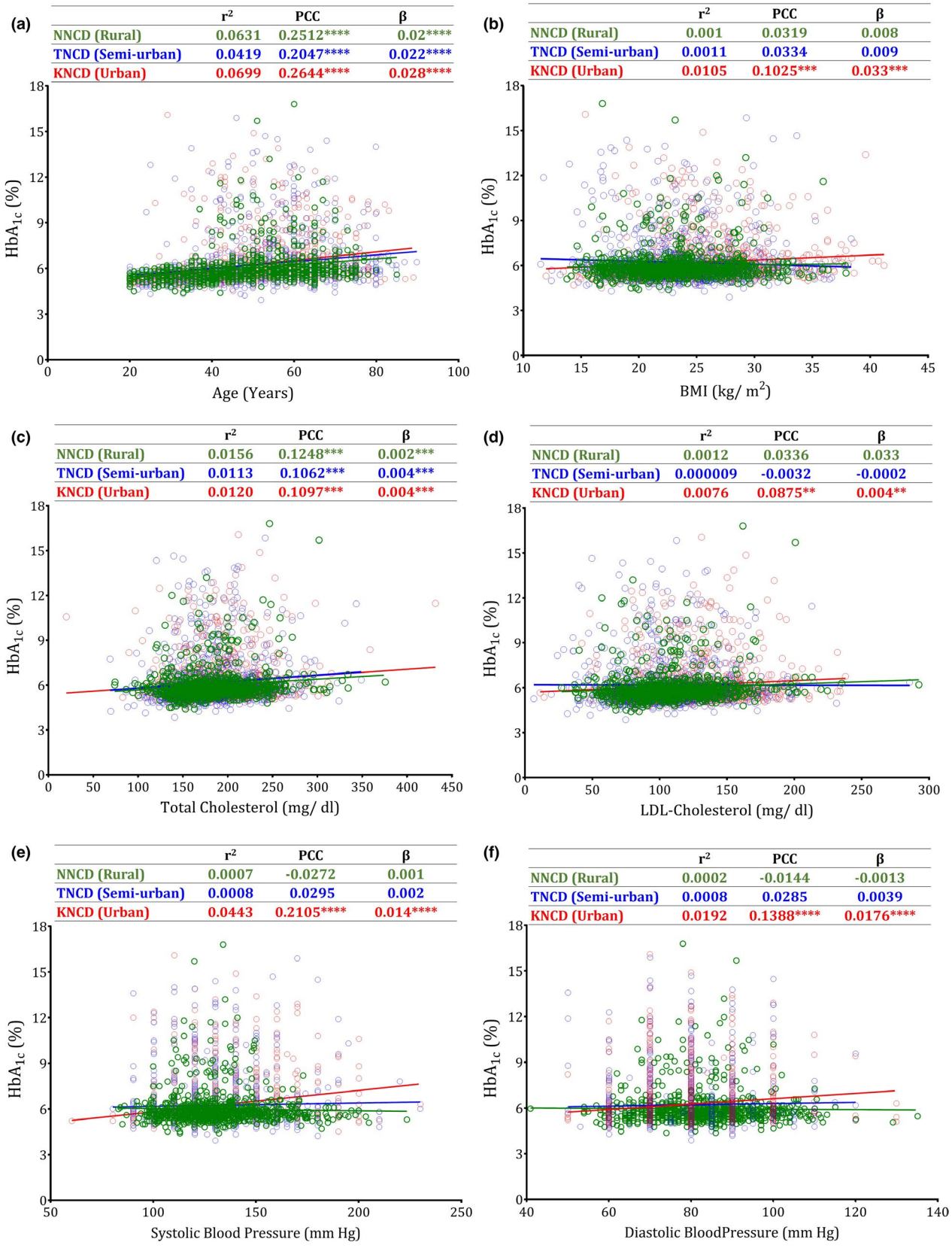



**FIGURE 2** Regression plot of traditional risk factor for diabetes versus $HbA_{1c}$ in the three populations. A. Age vs $HbA_{1c}$ B. BMI vs $HbA_{1c}$ C. Total cholesterol vs $HbA_{1c}$. D. LDL-cholesterol vs $HbA_{1c}$. E. Systolic blood pressure vs $HbA_{1c}$. F. Diastolic blood pressure vs $HbA_{1c}$. The hollow circles represent individual values and straight line represents the trend line. The green, blue and red circles/ lines represent the rural, semi-urban and urban populations respectively. *$p < 0.05$; **$p < 0.01$, ***$p < 0.001$, ****$p < 00001$. PCC, Pearson correlation coefficient, β, regression coefficient

**TABLE 3** Multiple logistic regression with atherosclerosis as the dependent variable in the three different populations

| | NNCD (Rural) | | TNCD (Sub-urban) | | KNCD (Urban) | |
|---|---|---|---|---|---|---|
| | Odds ratio (95% CI) | | | | | |
| | Unadjusted | Adjusted[#] | Unadjusted | Adjusted[#] | Unadjusted | Adjusted[#] |
| Age Group | | | | | | |
| 20-40 years | 1 | 1 | 1 | 1 | 1 | 1 |
| 41-60 years | **4.51**$^{****}$ (1.82–6.07) | **2.47**$^{***}$ (1.29–4.19) | **3.85**$^{**}$ (2.25–5.44) | **1.84**$^{**}$ (1.12–3.38) | **4.89**$^{**}$ (2.10–5.77) | **3.18**$^{*}$ (1.66–4.28) |
| Above 60 years | **3.20**$^{****}$ (1.62–3.95) | **3.84**$^{***}$ (2.52–4.62) | **4.12**$^{***}$ (1.85–5.67) | **2.98**$^{**}$ (1.85–4.12) | **5.23**$^{****}$ (3.28–7.25) | **2.42**$^{**}$ (1.85–3.25) |
| Sex | | | | | | |
| Women | 1 | 1 | 1 | 1 | 1 | 1 |
| Men | **2.45**$^{****}$ (1.54–3.91) | 1.71 (0.79–3.69) | **3.63**$^{****}$ (2.26–5.85) | **3.17**$^{***}$ (1.68–5.99) | **2.40**$^{****}$ (1.52–3.80) | **2.02**$^{*}$ (1.24–3.29) |
| Alcohol intake | | | | | | |
| Never | 1 | 1 | 1 | 1 | 1 | 1 |
| Formerly/Occasionally | 2.02 (0.95–3.98) | 1.51 (0.64–3.59) | 1.43 (0.71–2.89) | 1.17 (0.47–2.91) | 0.78 (0.18–3.33) | 0.73 (0.30–1.80) |
| Daily | 1.19 (0.15–9.52) | 0.902 (0.85–9.53) | 1.99 (0.81–4.92) | 1.08 (0.36–3.25) | 0.88 (0.41 −1.88) | 0.76 (0.15–3.78) |
| Smoking | | | | | | |
| Never | 1 | 1 | 1 | 1 | 1 | 1 |
| Formerly/Occasionally | 1.53 (0.34–6.86) | 1.10 (0.12–10.5) | 2.48 (0.54 −11.5) | 3.59 (1.11–11.6) | 1.76 (0.51–6.07) | 3.74 (0.77–18.2) |
| Daily | **2.55**$^{**}$ (1.45–4.50) | 1.24 (0.56–2.72) | **2.39**$^{**}$ (1.39–4.09) | 0.79 (0.36–1.71) | 0.86 (0.36–2.03) | 0.98 (0.36–2.64) |
| Obesity | | | | | | |
| Non-obese | 1 | 1 | 1 | 1 | 1 | 1 |
| Obese | 1.18 (0.72–1.94) | 1.25 (0.72–2.19) | 1.22 (0.70–2.15) | 2.03 (0.99–4.13) | **1.84**$^{**}$ (1.53–2.33) | **1.26**$^{*}$ (1.05–1.88) |
| Diabetes(ADA) | | | | | | |
| Non-diabetes | 1 | 1 | 1 | 1 | 1 | 1 |
| Pre-diabetes | **2.51**$^{**}$ (1.40–4.50) | 1.59 (0.84–2.98) | **3.34**$^{****}$ (1.81–6.19) | **2.19**$^{*}$ (1.06 −4.50) | **2.75**$^{**}$ (1.43–5.27) | 1.55 (0.77–3.13) |

(Continues)

**TABLE 3** (Continued)

| | NNCD (Rural) | | TNCD (Sub-urban) | | KNCD (Urban) | |
|---|---|---|---|---|---|---|
| | Odds ratio (95% CI) | | | | | |
| | Unadjusted | Adjusted[#] | Unadjusted | Adjusted[#] | Unadjusted | Adjusted[#] |
| Diabetes | **4.97**[***] (2.63–9.38) | 1.74 (0.85–3.54) | **4.73**[****] (2.56–8.76) | **2.36**[*] (1.16–4.79) | **3.28**[*] (1.74–6.14) | **1.52**[*] (1.07–3.00) |
| Blood pressure | | | | | | |
| Normotensive | 1 | 1 | 1 | 1 | 1 | 1 |
| Hypertensive | **2.67**[****] **(1.72–4.17)** | 1.48 (0.90–2.45) | **5.50**[****] (3.20–9.45) | **2.92**[***] (1.53–5.58) | **2.45**[****] (1.55–3.85) | 1.09 (0.66–1.80) |
| Dys-lipidaemia | | | | | | |
| Normal | 1 | 1 | 1 | 1 | 1 | 1 |
| High | **3.73**[***] (1.78–7.85) | 1.15 (1.22–8.13) | 0.94 (0.52–1.71) | 1.84 (0.83–4.09) | **1.95**[**] (1.50–2.80) | **1.32**[*] (0.88–2.16) |

$p < 0.05$ was considered statistically significant in all analyses.

*$p < 0.05$,

**$p < 0.01$,

***$p < 0.001$,

****$p < 0.0001$.

to be above normal level largely in urban population (39%) compared to sub-urban (21%) and rural (25%) populations. Atherosclerosis was higher in rural population (10%) followed by sub-urban and urban population (9.1% and 7.8% respectively).

Within the people with diabetes in all three demographics (Supplementary Table S2), the findings of interest were as follows. The proportion of men with diabetes was higher in rural population whereas sex distribution was similar in semi-urban and urban areas. The prevalence of diabetes was highest in the 41–60 yeara age group in all three areas. On multiple regression analysis, middle and older age groups were associated with higher odds for diabetes compared with all three populations. Hypertension and dyslipidaemia were correlated with diabetes only in the sub-urban and urban populations, whereas obesity was correlated with diabetes only in the urban population. (Table 2). Family history of diabetes was higher in urban population (36%) compared to both sub-urban and rural populations (18%, 18% respectively). A positive linear correlation was observed between age and $HbA_{1c}$ in all the three populations (PCC =0.251, $\beta = 0.02$, $p < 0.0001$ for NNCD; PCC = 0.205, $\beta = 0.02$, $p < 0.0001$ for TNCD; PCC = 0.264, $\beta = 0.028$, $p < 0.0001$ for KNCD) (Figure 2A). On multiple logistic regression analysis, obesity was found to be associated with diabetes only in urban population (Odds ratio – 1.51; $p > 0.001$) after adjustment for confounding factors (Table 1). Obesity is one of the well-recognized risk factors for diabetes but on analysis, positive correlation was observed with $HbA_{1c}$ only for urban population (PCC = 0.103, $\beta = 0.033$, $p < 0.001$ for KNCD) and not for sub-urban (PCC = 0.033, $\beta = 0.009$, $p = 0.07$ for TNCD) and rural populations (PCC = 0.032, $\beta = 0.008$, $p = 0.08$ for NNCD) (Figure 2B).

A positive association was observed between total cholesterol and $HbA_{1c}$ in all the three populations (Figure 2C) but on analysis with LDL cholesterol, a positive trend was detected only in urban population (PCC = 0.10, $\beta = 0.004$, $p < 0.01$ for KNCD) but no association was found for the other two populations (PCC = −0.003, $\beta = -0.0002$, $p = 0.9168$ for TNCD; PCC = 0.034, $\beta = 0.033$, $p = 0.146$ for NNCD) (Figure 2D). More than 60% of the diabetes population was hypertensive in all the three demographics (Supplementary Table S2). While an association was detected between the blood pressure and $HbA_{1c}$ levels in urban population (PCC =0.21, $\beta = 0.014$, $p < 0.0001$ for systolic BP; PCC = 0.14, $\beta = 0.018$, $p < 0.0001$ for diastolic BP in KNCD) (Figure 2E,F), no significant association of $HbA_{1c}$ was detected with both systolic (PCC = −0.027, $\beta = 0.001$, $p = 0.362$ for TNCD; PCC = 0.029, $\beta = 0.002$, $p = 0.674$ for NNCD) (Figure 2E) and diastolic blood pressure (PCC =0.026, $\beta = 0.004$, $p = 0.346$ for TNCD; PCC = −0.014, $\beta = -0.001$, $p = 0.427$ for NNCD) (Figure 2F) in both the sub-urban and rural populations.

Within the atherosclerosis population in all three demographics (Supplementary Table S3), the following were the findings of interest. Paradoxically, rural participants had higher prevalence of atherosclerosis followed by sub-urban and urban areas. Atherosclerosis was approximately twice as high in men compared to women in all three demographics. No significant family history of cardiovascular disease was noted in any of the three populations. History of alcohol intake and smoking was much higher among the population with carotid atherosclerosis of rural area while a similar trend was seen in tobacco chewers in sub-urban population (Supplementary Table S3). The prevalence of hypertension among people with carotid atherosclerosis was highest in sub-urban population compared to the other two demographics (Supplementary Table S3). On multiple regression analysis, older age, men sex showed higher odds ratio while no association with alcohol intake and smoking was observed in all three populations. Among the metabolic factors, diabetes was found to be associated with atherosclerosis in semi-urban and urban population but not in rural participants. Hypertension showed association with atherosclerosis only in sub-urban population, whereas obesity and dyslipidaemia showed association in urban population (Table 3).

## 4 | DISCUSSION

Our study highlights the heavy burden of major NCDs in all three different geographic units in a zone within South India, much higher than prior reports. The most concerning aspect of the study results is the huge burden of NCDs, not only in urban, but also in rural and sub-urban populations where the dual burden of lack of awareness and healthcare facilities likely leads to delayed diagnosis and treatment.

In one of the most up-to-date systematic review of studies in South Asia, the estimated prevalence of type 2 diabetes was 7.5% for 2005 and 7.6% for 2010.[19] The study also concluded that the prevalence of diabetes was strongly associated with increased age, men gender and urban residency. The landmark ICMR-INDIAB study published in 2011 showed an urban diabetes prevalence of 13% and rural prevalence of 7.8% in Tamilnadu.[6] However, our results showed a roughly two-fold higher prevalence of diabetes and pre-diabetes (IEC) in both demographic areas compared to the above studies (Table 1). Additionally, the prevalence of diabetes was highest in sub-urban area where not many studies have been performed in the past. Pre-diabetes was staggeringly high if ADA criteria for diabetes were applied. Significant methodological reasons may explain the differences as we used $HbA_{1c}$ to define diabetes and pre-diabetes while the other studies used capillary glucose. While capillary glucose estimation is feasible to implement in large-scale epidemiological studies, it has its own limitations including factors

like temperatures, strip factors, hand contamination especially if not washed properly and interfering medications.[20] Arguments in favour of $HbA_{1c}$ as a diagnostic test for diabetes include less biological variability, superior attributes and prediction of complications, to the extent that various Expert Committees have presented compelling grounds for the use of $HbA_{1c}$ as a diagnostic test.[21,22] In addition, there is good evidence that a $HbA_{1c}$ cut-off of ≥42 mmol/mol (6%) is optimal for diagnosing diabetes with a high level of accuracy in the Indian population.[23] We therefore feel that our definition of diabetes based on a validated $HbA_{1c}$ (from a nationally accredited lab) of ≥46 mmol/mol (6.5%) or those with a history of diabetes is truly representative of diabetes in the study population. Apart from the methodological reasons, further explanations for the doubling of diabetes in our study may be related to a true increase in disease prevalence over the last five years in all demographics, aggravated by novel non-traditional risk factors that we do not comprehend fully at this point of time. In addition, the prevalence of poor glycaemic control was more than 50% in rural and sub-urban communities indicating either improper adherence to medications or due to the probable interruption of endocrine-disrupting chemicals on the action of these drugs. Poor glycaemic control represents a huge challenge to sustainable economic development in all countries because of healthcare costs and productivity loss.[3]

There are unique aspects of our study results, which are worth discussion. While we were not surprised by the prevalence of diabetes, hypertension and atherosclerosis in an urban setting, the burden of these three entities was much higher than anticipated in sub-urban and rural areas. Particularly concerning was the extremely high prevalence of diabetes and hypertension in the sub-urban population of Thadagam, much more than the urban population of Kalapatti. Around 50% and 25% of the sub-urban population had hypertension and diabetes respectively, the highest among the three demographics. While it is possible that this could be an overestimate, we recorded blood pressures at least twice a week apart if the blood pressure values were ≥140/90 mm Hg in the first visit. The answer to this very high prevalence in diabetes and hypertension may lie within the brick kilns of Thadagam. Once an agricultural area, Thadagam has moved to the highly remunerative brick kiln business due to the booming construction industry in and around Coimbatore. There are around 100 brick kilns with more than 300 chambers supplying unbaked bricks to these kilns. Such brick kilns are highly polluting industries resulting in emissions of gaseous pollutants like ambient particulate matter (PM), sulfur dioxide, carbon monoxide and dioxide as well as oxides of nitrogen.[24] There has been emerging interest in role of air pollution in impaired glucose regulation, hypertension and cardiovascular disease. There are a number of mechanistic pathways postulated to explain the above links including endothelial dysfunction, inflammation of the visceral adipocytes, hepatic insulin resistance, increased blood pressure and increased autonomic tone.[25] Studies show that for every 10 $\mu g/m^3$ increase in certain types of particulate matter, the risk of future diabetes increases by 10% and the risk of diabetes-related mortality increases by 1%.[25,26] It is therefore plausible that non-traditional risk factors like air pollution related to the brick kiln industry may have a role in the worrying prevalence of diabetes and hypertension in this sub-urban area of Thadagam. Further studies on the magnitude, duration and frequency of air pollution in this area and its effects on NCDs are currently being planned by our study group. This will hopefully provide further insights into the burden of NCDs in this area.

The high prevalence of atherosclerosis (10%), diabetes (16%) and hypertension (38%) in a rural farming population is worriable. None of the Indian studies so far has documented a diabetes prevalence or atherosclerosis burden in a rural population at >10%. While physical (in) activity, genetics, energy dense diet and other classical risk factors may explain the explosion of diabetes and CVDs in urban India, they may not explain all the burden of diabetes and CVDs in rural India. A couple of non-traditional risk factors have excited our interest, especially in rural farming communities, to explain the increasing prevalence of NCDs in rural India. Unregulated pesticide and heavy metal use (from fertilizers) are two largely less explored areas that may have a huge relevance to cardiovascular disease in rural communities. We have published literature possibly linking heavy metals and pesticides with human diabetes in Nallampatti[16,17] and other villages.[13,14,28] There are mechanistic pathways linking exposure to organophosphate pesticides and hyperglycaemia by way of disruption of glucose metabolism and modulation of gut microbiota.[27,28] Heavy metals like arsenic, either from groundwater sources or from fertilizers, rice and vegetables have the potential to aggravate diabetes by multiple mechanisms.[28,29] In addition, there is some evidence to suggest an additive effect of smoking in those who are exposed to heavy metals in terms of a higher risk of diabetes.[30] It has to be pointed that the number of smokers in the village was much higher than the sub-urban and urban areas. Whether this additive effect has a relevance in the high prevalence of diabetes and atherosclerosis in spite of lower presence of other traditional risk factors in Nallampatti participants is not clear. However, it will be pure speculation at this point to boldly hypothesize a causal association.

There are significant limitations to our study. It is possible that there is a selection bias as the sampling was convenient rather than representative of the population. But on analysis with the government census data, we have 65–73% of the adult population in the respective study areas. This convenient sampling could have exaggerated the prevalence of disease. We did a random glucose but not fasting

and 2-hour glucose due to logistical issues. In spite of the practicality of of using HbA1c as a screening test to diagnose diabetes, there are evidences to suggest that HbA1c is much inferior to oral glucose tolerance test (OGTT) in terms of under-estimating diabetes prevalence in Asian populations. Carotid intima thickness images were not independently verified due to manpower issues. We plan to address all these limitations in future long-term follow-up studies.

To summarize, we report high prevalence of diabetes and atherosclerosis in three different demographics, a completely rural farming village, a sub-urban brick kiln area and an urban area within city limits. Our prevalence estimates are much higher than those currently available. More concerning is the prevalence of NCDs in sub-urban and rural areas, where the long-term consequences can potentially be devastating. We also believe that there are non-traditional risk factors at play that may be at least partly responsible for increasing the NCD burden in rural and sub-urban areas. Larger studies are needed to explore the huge burden of NCDs in different Indian demographics, particularly to define the role of both traditional and non-traditional risk factors, which may be amenable to interventions at individual, health systems, societal and policy levels.

## ACKNOWLEDGEMENTS

The authors acknowledge Dr. Nalla G. Palaniswami and other trustees of KMCH Research Foundation for their support. GV acknowledges Indian Institute of Technology Madras for providing Institute post-doctoral fellowship. We acknowledge KMCH College of Nursing, Microbiological Laboratory, all the village and town administrative heads and volunteers who had devoted their time for this study.

## CONFLICT OF INTEREST

None.

## AUTHOR CONTRIBUTIONS

GV[1], SM, GV[2], TA, MC, TA, TP and KS conceived and designed the experiments. GV[1], SM, GV[2] and KS were involved in sample and data collection. GV and KS analysed the data. TA, MC, TP and KS contributed reagent/ materials/ analysis tools. GV, SM and KS wrote the manuscript. JB, KH, RS, TP and KS revised the manuscript. All authors read and approved the final manuscript.

## FUNDING INFORMATION

This study was funded by KMCH Research Foundation, India under KMCH-NCD studies – Phase I.

## DATA AVAILABILITY STATEMENT

Complete data, clinical details and samples are available for researchers on reasonable request to the corresponding author, but providing data or samples will depend on the approval of Institute ethics committee.

## ORCID

*Ganesan Velmurugan* https://orcid.org/0000-0001-7536-4472
*Krishnan Swaminathan* https://orcid.org/0000-0002-7020-4186

## REFERENCES:

1. Institute for Health Metrics and Evaluation (IHME). *Findings from the Global Burden of Disease Study 2017*. Seattle, WA: IHME; 2018.
2. World Health Organization. Global report on Diabetes; 2016.
3. International Diabetes Federation. *IDF Diabetes Atlas, 9th edn*. Brussels, Belgium: International Diabetes Federation, 2019. https://www.diabetesatlas.org
4. Fall CH. Non-industrialised countries and affluence. *Br Med Bull*. 2001;60:33-50.
5. Ebrahim S, Kinra S, Bowen L, et al. The effect of rural-to-urban migration on obesity and diabetes in India: a cross-sectional study. *PLoS Med*. 2010;8(5):10.
6. Anjana RM, Pradeepa R, Das AK, et al; ICMR– INDIAB Collaborative Study Group. Physical activity and inactivity patterns in India - results from the ICMR-INDIAB study (Phase-1) [ICMR-INDIAB-5]. *Int J Behav Nutr Phys Act*. 2014;11(1):26.
7. Kinra S, Bowen LJ, Lyngdoh T, et al. Sociodemographic patterning of non-communicable disease risk factors in rural India: a cross sectional study. *BMJ*. 2010;341.
8. Joshi R, Cardona M, Iyengar S, et al. Chronic diseases now a leading cause of death in rural India— mortality data from the Andhra Pradesh Rural Health Initiative. *Int J Epidemiol*. 2006;35:1522-1529.
9. Gajalakshmi V, Peto R. Verbal autopsy of 80,000 adult deaths in Tamilnadu, South India. *BMC Public Health*. 2004;4:47.
10. 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.
11. Dehghan M, Mente A, Zhang X, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. *Lancet*. 2017;10107:2050-2062.
12. Anjana RM, Pradeepa R, Deepa M, et al;ICMR–INDIAB Collaborative Study Group. Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: phase I results of the Indian Council of Medical Research-INdia DIABetes (ICMR-INDIAB) study.
13. Swaminathan K, Thangavel G. Pesticides and human diabetes: a pilot project to explore a possible link. *Practical Diabetes*. 2015;32(3):111-113.
14. Velmurugan G, Ramprasath T, Swaminathan K, et al. Gut microbial degradation of organophosphate insecticides-induces glucose intolerance via gluconeogenesis. *Genome Biol*. 2017;18:8.
15. Swaminathan K, Veerasekar G, Kuppusamy S, et al. Noncommunicable disease in rural India: are we seriously underestimating the risk? The Nallampatti noncommunicable disease study. *Ind J Endocrinol Metab*. 2017;21:90-95.

16. Velmurugan G, Swaminathan K, Veerasekar G, et al. Metals in urine in relation to prevalence of pre-diabetes, diabetes and atherosclerosis in rural India. *Occup Environ Med*. 2018;75:661-667.
17. Velmurugan G, Swaminathan K, Mohanraj S, et al. Association of co-accumulation of arsenic and organophosphate insecticides with diabetes and atherosclerosis in a rural agricultural community: KMCH-NNCD-I study. *Acta Diabetol*. 2020; https://doi.org/10.1007/s00592-020-01516
18. Swaminathan K, Sundaram M, Prakash P, Subbiah S. Diabetic ketoacidosis: an uncommon manifestation of pesticide poisoning. *Diabetes Care*. 2013;36(1):e4.
19. Cheema A, Adeloye D, Sidhu S, Sridhar D, Chan KY. Urbanization and prevalence of type 2 diabetes in Southern Asia: a systematic analysis. *J Glob Health*. 2014;4(1):010404.
20. Ginsberg BH. Factors affecting blood glucose monitoring: sources of errors in measurement. *J Diabetes Sci Technol*. 2009;3(4):903-913.
21. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014;37(Suppl 1):S81-S90.
22. International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes. *Diabetes Care*. 2009;32(7):1327-1334.
23. Mohan V, Vijayachandrika V, Gokulakrishnan K, et al. $A_{1c}$ cut points to define various glucose intolerance groups in Asian Indians. *Diabetes Care*. 2010;33(3):515-519.
24. Skinder BM, Pandit AK, Sheikh AQ, Ganai BA. Brick kilns: Cause of Atmospheric Pollution. *J Pollut Eff Cont*. 2014;2(112): https://doi.org/10.4172/2375-4397.1000112
25. Eze IC, Hemkens LG, Bucher HC, et al. Association between ambient air pollution and diabetes mellitus in Europe and North America: systematic review and meta-analysis. *Environ Health Perspect*. 2015;123(5):381-389.
26. Li C, Fang D, Xu D, et al. Main air pollutants and diabetes-associated mortality: a systematic review and meta-analysis. *Eur J Endocrinol*. 2014;171(5):R183-R190.
27. Rahimi R, Abdollahi M. A review on the mechanisms involved in hyperglycemia induced by organophosphorus pesticides. *Pestic Biochem Physiol*. 2007;88(2):115-121.
28. Velmurugan G, Ramprasath T, Mithieux G, Swaminathan K, Ramasamy S. Gut microbiota, endocrine disrupting chemicals and diabetes epidemic. *Trends Endocrinol Metab*. 2017;28:614-628.
29. Tseng CH. The potential biological mechanisms of arsenic-induced diabetes mellitus. *Toxicol Appl Pharmacol*. 2004;197:67-83.
30. Yang A, Cheng N, Pu H, et al. Occupational metal exposures, smoking and risk of diabetes and prediabetes. *Occup Med*. 2016;67:217-223.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Velmurugan G, Mohanraj S, Dhivakar M, et al. Differential risk factor profile of diabetes and atherosclerosis in rural, sub-urban and urban regions of South India: The KMCH-Non-communicable disease studies. *Diabet Med*. 2021;38:e14466. https://doi.org/10.1111/dme.14466