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Cohort Profile

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Cohort Profile: The Center for cArdiometabolic Risk Reduction in South Asia (CARRS)

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Why was the cohort set up?

Emerging data, largely from the diaspora and largely cross-sectional, indicate that South Asians exhibit high rates of cardiovascular disease (CVD), diabetes, atypical dyslipidaemia profiles, and hepatic steatosis[1–7] at lower body weight and younger ages relative to populations with European and other ancestries.[8–10] It is hypothesized that these differences are rooted in some combination of distinctive pathophysiology, risk factor, phenotypic and socioeconomic characteristics.[11–13] In addition, South Asia exhibits differences in health service use, health care costs and quality of care compared with high-income countries (HICs).[14] Well-characterized prospective epidemiological cohorts help study the natural history of diseases and the evolution of care in the region. This can advance the knowledge and science of cardiometabolic diseases and provide the infrastructure for interdisciplinary and dynamic scientific explorations.[15]

The Center for cArdiometabolic Risk Reduction in South Asia (CARRS) is a population-based representative sociodemographically diverse cohort of 30 874 adults with prospective follow-up in three major cities in South Asia—Chennai and Delhi in India and Karachi in Pakistan.[16]

Who is in the cohort?

The cohort was representatively drawn from the adult populations aged 20 and older in Delhi (North India, population 20 million), Chennai (South India, population 8 million)[17] and Karachi (Pakistan, population 16 million),[18] three megacities with a cumulative population of 44 million individuals.

Study design and sampling

We used a population-based, multistage, cluster random sampling design based on local administrative boundaries to recruit adult men and women to be representative of each city. In 2010–12, CARRS-1 was recruited as

Key Features

- South Asians comprise nearly 2 billion people worldwide and are at high risk of cardiometabolic disease, even at young ages and low body weights.
- The CARRS cohort, a population-based representative sample of Chennai and Delhi in India and of Karachi in Pakistan, ages ≥20 years, was assembled in two waves [CARRS-1 (2010–12), $n = 16\,287$, 13 720 with biospecimens; and CARRS-2 (2014–16), $n = 14\,587$, 13 709 with biospecimens].
- CARRS-1 has completed five follow-up assessments after the baseline visit. CARRS-2 has completed one follow-up assessment after the baseline visit. The cohort had high participation rates at recruitment (∼90% in both waves).
- The CARRS Cohort has followed 30 874 individuals (27 429 with biospecimens) and accrued ∼115 000 person-years of follow-up, including a biorepository ($n = 360\,000$ aliquots) in India.
- CARRS provides scientific infrastructure and data for measuring incidence and secular trends of cardiometabolic diseases (CMD) and risk factors.
- Researchers interested in the collaborative project can contact Dr KM Venkat Narayan [knaraya@emory.edu] or Dr Dorairaj Prabhakaran [dprabhakaran@ccdcinida.org].

a probability sample of $n = 16\,287$ adults aged 20 years and older. In 2014–16, CARRS-2 was established as an independent probability sample of 14 587 newly recruited individuals, using methods identical to CARRS-1. Pregnant women and seriously ill individuals were excluded. Seriously ill individuals included bedridden individuals because of the difficulty in taking anthropometric measurements and future follow-up, as blood and other biological samples were collected in a camp.

Wards were the primary sampling units for Chennai and Delhi, and clusters were the primary sampling units for Karachi. In Chennai and Delhi, 20 wards were randomly selected from urban districts. Five Census enumeration blocks (CEBs) were randomly selected from each of the 20 randomly selected wards to get 100 CEBs from Chennai and Delhi. Finally, 20 households were selected per CEB in CARRS-1 (25 households in CARRS-2). In Karachi, 80 clusters were randomly selected and 25 households were randomly selected from each cluster. Two eligible participants, one man and one woman, aged 20 years or older, were selected from each household based on the 'Kish method', which has been used in the World Health Organization's STEPS surveys.[19] Census boundaries and population distribution were used to develop the sampling frame for wards and CEBs, and field staff enumerated households within CEBs to ensure up-to-date household maps and adequate coverage of the target population. Due to the random selection of CEBs there was no overlap in CEB or household selection between CARRS-1 and CARRS-2. We conducted household mapping for each of the newly selected CEBs to establish the sampling frame for random selection of households and participants.

How often have they been followed up?

Baseline assessments

Baseline assessments (demographics, risk factors, anthropometry and biospecimens) were conducted between September 2010 and December 2012 (Table 1).

Longitudinal follow-up assessments

Approximately 12 months after the baseline examination, participants were contacted for follow-up via in-person or telephone interviews. All participants were continually followed longitudinally for the development of cardiometabolic disease risk factors, manifest disease and mortality. Five follow-up visits have been completed in CARRS-1 following baseline. The first, third and fifth follow-up visits involved only the administration of survey questionnaires and ascertainment of CVD events and deaths. At the second and fourth follow-up visits, we included biospecimen data collection along with annual questionnaires, anthropometry and ascertainment of CVD events and deaths. The sixth follow-up is ongoing (November 2020 on) and was started during the COVID-19 pandemic using a hybrid of telephone and in-person surveys, due to precautions concerning face-to-face contact.

Following a parallel process, the first follow-up visit of CARRS-2 participants was carried out during September 2018–July 2020.

What has been measured?

Data collection and procedures

Table 1 shows the measures, instruments and methods used in CARRS-1 and -2. Trained interviewers collected

Table 1 Available study measures

Domain	Variables	Measurement	CARRS-1						CARRS-2	
Year of measurement			Baseline 2010–12	1st FUP 2011–13	2nd FUP 2013–14	3rd FUP 2014	4th FUP 2016–17	5th FUP[a] 2017–18	Baseline 2014–16	1st FUP 2018–20
Questionnaires										
Sociodemographic	Contact information, age, sex, income, education, occupation, place of birth, marital status, household size[b], number of children[b]	Questionnaire	A				A		A	
Health behaviours	Physical activity	IPAQ[20]; GPAQ[21]	A				A		A	
	Sedentary behaviour/standing						A		A	
	Open place/garden						A			
	Tobacco use, alcohol use	Questionnaires	A	A	A	A	A	A	A	A
	Sleep duration and quality	Questionnaire	A						A	
Diet	Dietary habits; 24-h dietary recall (in subsample)	Modified Food frequency questionnaire (FFQ)and 24-h recall	A					A	A + S	
	Household food insecurity	Household food insecurity Access Scale[22]						A		
Family history	Family history of HTN; DM; dyslipidaemia; heart disease; stroke	Self-report	A						A	
Physician diagnosis of previous disease	Previously diagnosed HTN; DM; dyslipidaemia; heart disease; stroke; COPD	Self-report/medical records	A	A	A	A	A	A	A	A
Medication status	Cholesterol, glucose, lipid, and BP-lowering medication	Self-report	A	A	A	A	A	A	A	A
Quality of life (QoL)	Health-related QoL	EQ-5D questionnaires[23]	A				A		A	
Psychosocial	Stress, depression	PHQ-9 questionnaire[24]					A		A	A
		Lifetime/past depression-UK Biobank[25,26]								A
Cancer	Cancer, cancer stigma	Self-report					A	A	A	A
Complications	Foot ulcer, amputation, eyes: retinopathy and laser treatment	Self-report	A	A	A	A	A	A	A	A
Respiratory disease	COPD, Asthma and TB symptoms	Self-report	A							
		Self-report	A						A	

(Continued)

Table 1 Continued

Domain	Variables	Measurement	CARRS-1						CARRS-2	
Year of measurement			Baseline 2010–12	1st FUP 2011–13	2nd FUP 2013–14	3rd FUP 2014	4th FUP 2016–17	5th FUP[a] 2017–18	Baseline 2014–16	1st FUP 2018–20
Treatment history and expenditure	Heart disease; stroke; diabetes; diabetic complications; high BP; chronic kidney disease									
Drug information	Names of drug taken in previous week; duration of drug intake	Self-report	A		A		A		A	
Female reproductive history		Self-report	A				A	A	A	A
Fracture	Wrist/hip or spine	Self-report					A		A	
Environmental										
Ambient air pollution (available for Chennai and Delhi only)	Daily average $PM_{2.5}$ concentrations at 1 km x 1 km spatial resolution (Delhi complete, Chennai ongoing) from 2010–	B-attenuation monitors; gravimetric samplers[27]	A		A		A		A	
Built environment (available for Chennai and Delhi only)	Vegetation index, Road Networks, Gridwise built-up area %, intersections, light intensity at night, locations of polluting sources	Satellite observations and land use maps[28]	A		A		A		A	
	Time Activity	Questionnaire						A		A
CVD risk factors										
Anthropometry	Weight, height, waist and hip circumference	Tanita BC-418, Seca-213 Portable Stadiometer, Tape measure[16]	A		A		A		A	A
Blood pressure	Systolic and diastolic BP	Automated Omron HEM-7080[16]	A		A		A		A	A
Glucose	Fasting blood glucose; HbA1c	Hexokinase[16]; HPLC[16]	A		A		A		A	
	Fasting insulin, 30-min insulin, 2-h insulin	ECL immunoassay[29]	A[c]		A[c]		A[c]		A	
Lipid markers	Total cholesterol; HDL, LDL cholesterol; triglycerides	Direct; Friedewald Equation[16]; Martin/Hopkins Equation if triglyceride >400 mg/dl[30]; enzymatic methods	A		A		A		A	

(Continued)

Table 1 Continued

Domain	Variables	Measurement	CARRS-1						CARRS-2	
Year of measurement			Baseline 2010–12	1st FUP 2011–13	2nd FUP 2013–14	3rd FUP 2014	4th FUP 2016–17	5th FUP[a] 2017–18	Baseline 2014–16	1st FUP 2018–20
Renal function	Serum creatinine; urinary creatinine; microalbuminuria, albumin: creatinine ratio	Jaffe kinetic[16] Spot urine[31]	A		A		A		A	
	24-ho urine		S							
	Cystatin C	Immunoturbidimetric[32]	S						S	
Advanced lipids	Apolipoprotein A1; apolipoprotein B	Immunoturbidimetry	S						S	
Advanced metabolic markers	30-min glucose, 2-h blood glucose; fasting insulin, 30-min insulin, 2-ho insulin	Hexokinase,[16] ECL immunoassay[16]	A[c]						A[c,d]	
Adipokines	Leptin, adiponectin	ELISA assay[33]	S							
Cotinine (saliva)			S							
Protein biomarkers (supported by Abbott Laboratories)										
Inflammation thrombogenisis/immune	High-sensitivity C-reactive protein	Particle-enhanced immunoturbidimetry	A							
Clinical vascular and myocardial disease and death										
Cardiovascular events	Heart failure, MI, stroke, revascularization, angina, PAD	Symptoms,[34,35] history, ECG, medical records	A	A	A	A	A	A	A	A
Mortality		Verbal autopsy	A	A	A	A	A	A	A	A
Electrocardiogram (ECG)										
ECG (only Delhi)					A		A		A	

FUP, follow-up; HTN, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; BP, blood pressure; TB, tuberculosis; PM2.5, particulate matter with a diameter of 2.5 micrometres or less; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; CVD, cardiovascular disease; PAD, peripheral artery disease; IPAQ, International Physical Activity Questionnaire; GPAQ, Global Physical Activity Questionnaire; EQ-5D, EuroQol five-dimension scale; PHQ-9, Patient Health Questionnaire; UK, United Kingdom; HPLC, high-performance liquid chromatography; ECL, electrochemiluminescence; A, available; S, sub-sample.

[a]CARRS-1, fifth follow-up conducted in Chennai and Delhi site only;

[b]Only available for CARRS-1 and -2 baseline.

[c]Data available for Chennai only.

[d]Available in a sub-sample for Delhi.

data from participants through detailed structured questionnaires on sociodemographic characteristics, lifestyle habits (e.g. physical activity, tobacco use, diet, alcohol use, health history, sleep and mental health), medical history (cardiometabolic diseases, cardiovascular events, cancer), quality of life, functioning and cost of disease and health care. Multilevel exposome assessments capture health exposures at the level of the individual [repeated measures of atherosclerotic cardiovascular disease (ASCVD) risk factors, health behaviours, sociodemographic factors), household (assets, air quality), and the environment (air pollution, neighbourhood food and the built environment]. Interviewers conducted physical assessments, including blood pressure, heart rate, height, weight, waist circumference, skin folds and body composition. Participant blood and urine samples were collected at neighbourhood camps during baseline visits following standardized procedures across sites. In follow-up visits, samples were collected from the home of participants. Samples were transported from the field to the laboratories for processing in cold conditions (4°C to 8°C) using cold icepacks. Further details are available in our earlier methods paper[16] and on the study website.[36]

Biorepository

India (Chennai and Delhi)

A biorepository of over 360 000 aliquots of sera, plasma, buffy coat and urine samples of participants recruited in Chennai and Delhi are stored in accredited, well-maintained institutional laboratories. The CARRS biorepository uses best practices for standardizing sample collection, maintaining a cold chain for sample transfer and handling, maintaining sample records, using consumables, power and cooling back-up systems, and de-identifying stored samples. In the laboratory, samples are processed and transferred to deep freezers (–80°C) within 3 hour. The biospecimens are labelled with unique ID, with no personal details. Multiple aliquots are prepared and stored for each participant to prevent repeated freezing and thawing of samples. All the storage details are recorded on Excel sheets for easy retrieval. Additional laboratory details are provided in the Manual of Procedure (MOPs) and may be downloaded at CARRS website.[36]

Methods for in-country analysis were standardized across laboratories prior to sample collection. As a measure of internal quality control, two levels of commercially available internal controls for every parameter were analysed before analysing the samples. Control rules from Westgard[37] for the rejection of runs were followed. In cases of rejection, the instrument was recalibrated, and internal controls were re-evaluated. Assay results were retrieved from the instrument in Excel format. The laboratories participated in an external quality assurance programme from RANDOX (UK)[38] for all serum chemistry (monthly), lipids (fortnightly), HbA1c (monthly) and urinary parameters (fortnightly). For insulin, we participate in the UK NEQAS programme.[39] The performance of the laboratories was well within specified limits.

Pakistan (Karachi)

The Karachi site has followed procedures similar to Chennai and Delhi. The samples were collected and transferred to the laboratory for storage according to the procedures set in the study protocol. In the laboratory, samples were processed and transferred to deep freezers (–80°C) in <3 . The facilities have a 24-h power supply to prevent the risk of thawing, and the freezer temperature is monitored twice per day and recorded for quality assurance.

Event and death ascertainment

The CARRS study event ascertainment protocols were standardized across sites and used multiple confirmatory approaches to classify new CVD events and deaths. In annual interviews with participants, for those reporting myocardial infarction (MI), stroke or a hospital visit since the latest follow-up, medical records [e.g. including biochemical and imaging tests such as creatine kinase-MB (CK-MB), troponins, electrocardiography (ECG), brain computed tomography or magnetic resonance imaging] were obtained. Medical records were then scanned by fieldworkers at participants' homes. Next-of-kin interviews (verbal autopsies) were conducted among participants who had died, to identify causes of death.[40,41] Based on the data collected by a questionnaire and any other available information, the cause of death or the sequence of causes that led to death are evaluated and classified by two physicians. If two different causes were reported, a third physician reviews the verbal autopsy and provides a tie-breaking ascertainment of the cause of death. Verbal autopsy data are available for 89% of deaths recorded among CARRS participants.

Quality assurance and quality control strategies

The CARRS Study quality assurance plan uses a framework that comprehensively considers each phase of the study, with detailed quality control and quality assurance strategies (Table 2). Standardized protocols are used for data collection and transfers, and technical laboratory staff were trained before any fieldwork and are re-trained intermittently. All laboratory methods, such as test kits and

Table 2 Quality assurance and control

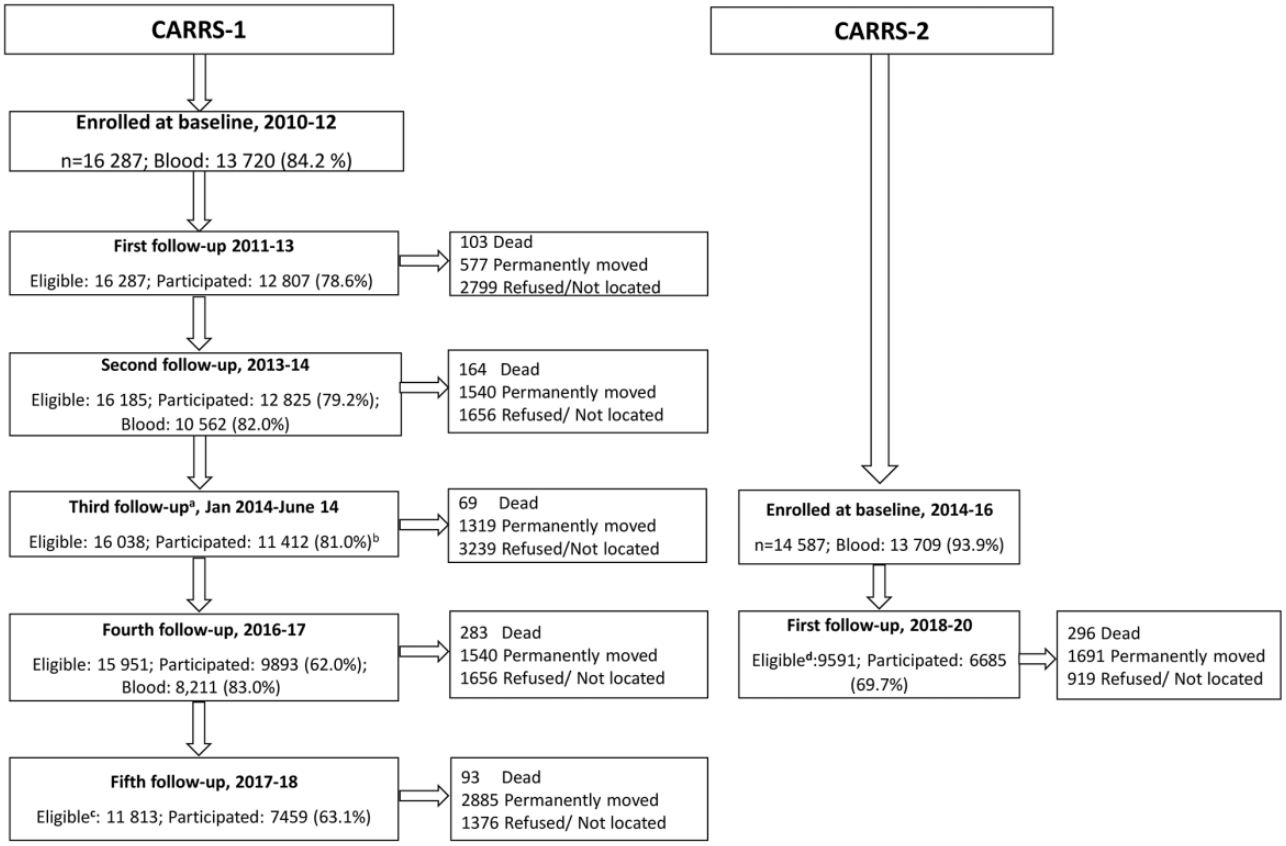
Level	Phases		
	Design and planning	Data collection	Data analysis
Institutions	• IRB review • Manuals of procedures	• Oversight of broad study processes • Co-ordination of timelines, activities	• Audits to evaluate validity of findings
Investigators	• CITI Certification	• Oversight of study activities	• Internal and external peer reviews
Data collecting personnel	• Extensive training • Easy-to-carry SOPs	• Random checks of data collection and documentation; re-train	• Data cleaning and accounting/ imputing missing data/data errors
Survey instruments and equipment	• Peer review • Translation into local language(s) • Central procurement of materials	• Established validity • Regular checks of completeness • Regular calibration of tools	• Identify errors that can be corrected • Identify and consider discarding or imputing seriously compromised data
Specimen handling	• Training (labelling, handling, storage)	• Monitoring adherence to protocols • External temperature gauge labels	• Plot distributions of parameters • Ongoing analysis to detect outliers
Laboratory	• NABL and CAP certification	• Specific assay protocols/ calibration	• Intra- and inter-assay checks
Documentation	• Develop checklists, logbooks	• Training in legible documentation	• Audit logbooks
Data storage	• Establish data transfer/back-up	• Locked password-protected; back-up	• De-identified datasets
Data handling	• Data cleaning; verification	• Use of electronic tablets (collection)	• Validity checks; reporting on outliers

IRB, institutional review board; CITI, Collaborative Institutional Training Initiative; SOP, standard operating procedures; NABL, National Accreditation Board for Testing and Calibration Laboratories; CAP, College of American Pathologists.

procedures for biospecimen collection, processing and storage, as well as methods of analysis across the three sites, are standardized. The details of quality control have been described in detail elsewhere.[16]

Strategies for cohort retention

The CARRS study has so far achieved impressive participant retention rates. Our well-trained, enthusiastic field staff employ multiple retention strategies: (i) openly communicating with participants and responding quickly to questions or problems that may arise; ii) providing participants with their data, i.e. blood pressure, anthropometry and biospecimen (blood and urine) findings, at a promised time and explaining the results of the reports; (iii) providing a lifestyle modification pamphlet to participants with abnormal biochemical parameters and providing diet charts to participants who request this information; (iv) facilitating getting appointments with local physicians or at AIIMS if the reports suggest the need for medical attention; (v) providing means to contact study staff (e.g. issuing pre-stamped postcards) in the event of changes in residential, contact or health status; (vi) offering non-monetary incentives (e.g. a wall clock with the CARRS logo) to individuals who assisted in facilitating the camps (collecting blood samples and anthropometric data), as a token of appreciation; and (vii) conducting interviews and other measurements in the privacy of the participants' homes as per their



[a] Telephonic follow-up ; [b] n=1948 participants were not followed in third follow-up and response rate calculated excluding participants not followed in third follow-up; [c] follow-up in Chennai & Delhi site only; Blood % calculated as those who provide blood during that follow-up divided by those who participated
CARRS-2- [d] Data reported only for Chennai and Delhi;
Note: CARRS-1: first, second, third and fourth follow-up conducted for Chennai, Delhi and Karachi; fifth follow-up conducted for Chennai and Delhi only;

Figure 1 Flow chart of participants

convenient time. Furthermore, three attempts are made to trace relocated participants through neighbours, relatives and employers.

Database development and data management

From 2011 to 2018, data were collected on paper-based questionnaires and transferred into an electronic database. Since 2018, data collection was transitioned entirely to tablet-based surveys. Tablet-based questionnaires facilitate the easier acquisition of data (eliminates the transfer of data from paper forms to electronic databases), execution of skip patterns and application of instant data-checking rules. The co-ordinating team at Delhi is responsible for centralized data management across all sites. Standard operating procedures for data management, data dictionary and annotated forms for baseline and respective follow-up questionnaires have been developed at the co-ordinating centre

What has it found?

The overall number of participants recruited at baseline and at each follow-up is shown in Figure 1. In CARRS-1, 17 274 individuals from 10 002 households were approached in three study sites (7596 participants in Chennai, 5420 in Delhi and 4258 in Karachi). The overall response rate was 94.3% at the participant level. Overall, 13 720 of the participants (84.2%) recruited into the study contributed biospecimens (Supplementary Table S1, available as Supplementary data at *IJE* online).

In CARRS-2, 17 139 individuals in 13 842 households were approached: 5626 participants in Chennai, 6416 in Delhi and 5097 in Karachi. The overall response rate was 85.1% at the participant level. Table 3 shows the baseline

Table 3 Baseline characteristics for CARRS-1 and -2

	CARRS-1 (N = 16 287)		CARRS-2 (N = 14 587)	
Variable(s)	N		N	
	16 287		14 587	
Age (years), mean (SD)		42.4 (13.3)		43.9 (13.4)
Male, *n* (%)		7758 (47.7)		6755 (46.3)
Education, *n* (%)				
Up to primary schooling		3604 (22.1)		3628 (24.8)
High school to secondary		9924 (60.9)		8386 (57.5)
Graduation and above		2759 (16.9)		2573 (17.7)
Income (INR), *n* (%)				
<10 000		11 537 (71.3)		8212 (57.2)
10 000–20 000		2667 (16.5)		3694 (25.7)
≥20 000		1975 (12.2)		2450 (17.1)
Employed, *n* (%)		7636 (46.9)		6976 (46.5)
Current tobacco use, *n* (%)		3757 (23.1)		3463 (23.7)
Current alcohol use, *n* (%)		2376 (14.6)		1940 (13.3)
Anthropometric and biochemical measures				
Body mass index (kg/m^2), mean (SD)	12 472	25.5 (5.2)	14 397	25.9 (5.4)
Height (cm), mean (SD)	13 795	158.3 (9.4)	14 478	159 (9.3)
Weight (kg), mean (SD)	12 531	63.7(13.8)	14 407	65.4 (14.5)
Systolic blood pressure, mean (SD)	15 486	122.8(19.9)	14 505	125.4 (20.1)
Diastolic blood pressure, mean (SD)	15 486	81.4(11.9)	14 505	81.1 (11.7)
Laboratory parameters				
Total cholesterol (mg/dL), mean (SD)	13 717	179.8 (39.4)	13 708	174.8 (39.2)
Triglycerides (mg/dL), median (P25, P75)	13 716	121 (87, 172)	13 708	119 (85.4, 170.4)
High-density lipoprotein cholesterol (mg/dL), mean (SD)	13 713	43.3(11.4)	13 706	42.3(10.9)
Low-density lipoprotein cholesterol (mg/dL), mean (SD)	13 432	109.7(32.1)	13 415	104.5 (32.4)
HbA1c %, mean (SD)	13 633	6.2(1.5)	13 693	6.1(1.5)
Fasting plasma glucose (mg/dL), mean (SD)	13 720	109.2(43.7)	13 709	109(46.8)
Plasma glucose at 30 min (mg/dL), mean (SD)	4005[c]	158.5(49)	5982[a]	161.5(48.6)
Plasma glucose at 120 min (mg/dL), mean (SD)	4059[c]	116.3(60.3)	5903[a]	121.3(61.7)
Insulin fasting (μU/ml), median (P25, P75)	7858[a]	8.6 (5.8, 12.7)	4455[b]	10 (6.4, 15.3)
Insulin at 30 min (μU/ml), median (P25, P75)	3613[c]	46.2 (32, 71.2)	2714[b]	74.2 (46.9, 115.4)
Insulin at 120 min (μU/ml), median (P25, P75)	3613[c]	35.7 (24.1, 59.7)	2648[b]	46 (25.9, 84.7)
Serum urea (mg/dL), mean (SD)	13 708	22.5(9.1)	13 705	23(8.5)
Serum creatinine (mg/dL), mean (SD)	13 703	0.8(0.4)	13 701	0.7(0.3)
Urine microalbumin (mg/dL) median (P25, P75)	13 327	2.6 (1.1, 6.6)	13 219	3 (0.7,6.9)
Urine creatinine (mg/dL), mean (SD)	9843[a]	74.6 (45.5, 122)	13 220	83.0 (49.2, 137)
Apolipoprotein A (mg/dL), median (P25, P75)	4244[b]	123.9 (110.9, 138.7)		na
Apolipoprotein B (mg/dL), median (P25, P75)	4244[b]	94.9 (78.8, 112.4)		na
HsCRP (mg/L), median (P25, P75)	9085[a]	2.75 (1.21, 5.66)		na

Low-density lipoprotein cholesterol calculated using Friedwald formula.

HbA1c, glycated haemoglobin; HsCRP, high-sensitivity C-reactive protein; P25, 25th percentile; P75, 75th percentile; INR, Indian rupee; na, not available.

[a]Data available only for Chennai and Delhi.

[b]Data available for Delhi only.

[c]Data available for Chennai only.

characteristics of CARRS-1 and -2 participants. Thus far, the CARRS study has followed 30 874 individuals aged ≥20 years (27 429 with biospecimens) and accrued ∼115 000 person-years of follow-up (Table 4). In CARRS-1, 95% of the participants had at least one follow-up. Participants with at least one follow-up and those with no follow-up data were largely similar, with the exception of employment status (see Supplementary Table S2, available as Supplementary data at *IJE* online). In CARRS-2, the response rate for the first follow-up was 69.7% (Figure 1).

Table 4 CARRS-1 & -2 duration of follow-up and deaths reported

	CARRS-1	CARRS-2
Number surveyed at baseline	16 287	14 587
Number with blood taken at baseline	13 720	13 709
Duration of follow-up, years, median (P25, P75)	5.7 (5.1, 6.1)	3.9 (3.6, 4.2)[a]
Accumulated person-years since baseline	89 488	24 117[a]
All cause deaths, *n*	712	296[a]

CARRS-1: first, second, third and fourth follow-up conducted for Chennai, Delhi and Karachi; fifth follow-up conducted for Chennai and Delhi only.
P25, 25th percentile; P75, 75th percentile.
[a]CARRS-2 data reported only for Chennai and Delhi.

The median (interquartile range) duration of follow-up (years) for CARRS-1 and -2 were 5.7 (5.1, 6.1) and 3.9 (3.6, 4.2) years, respectively (Table 4).

The CARRS study has enriched the literature on cardiometabolic diseases in urban South Asia. Cross-sectional findings indicate a scientifically informative distribution of exposures at individual and environmental levels, weight status and patterns of phenotypical presentation. The cohort has revealed that urban South Asians, on average, have a high lifetime risk of type 2 diabetes, even in normal weight individuals,[8] and a high prevalence of type 2 diabetes (28%),[42] dyslipidaemia,[43,44] hypertension (29%)[45] and hepatic steatosis at younger ages and relatively low body mass index (BMI) [underweight/normal weight prevalence (43%)].[46] We have also documented a high prevalence of multimorbidity, with steep mortality risks as the number of morbidities grows and the link between chronic disease and quality of life.[47] Significant findings from the CARRS study also indicate the relationship between socioeconomic disparities in health-related quality of life score, demonstrating the significantly lower health-related quality of life in key demographic groups and those with chronic conditions[48] as well as the association between sleep and hypertension, drawing attention to lifestyle-related risk factors.[49] Comparison of temporal changes in diabetes prevalence and achievement of diabetes care goals were conducted by comparing baseline data for CARRS-1 and -2; we found that between 2010 and 2016, the prevalence of self-reported diabetes increased as did glycaemic and lipid control among those with diabetes.[50]

Furthermore, the CARRS study has facilitated comparisons of resident South Asians with other populations through data pooling with global studies and cohorts. These include cross-national and multi-ethnic studies examining the role of vegetarian diet in cardiometabolic disease,[51,52] risk factors for diabetes and prediabetes,[53] the incidence of diabetes[9,10] and the prevalence of chronic kidney disease.[31,54,55] These studies have demonstrated the continued disproportionately high risk of cardiometabolic conditions and kidney disease in urban South Asians relative to other ethnic groups and relative to residents of other regions.

What are the main strengths and weaknesses?

Limitations

First, CARRS relies on self-reported measures of some behaviours (e.g. diet, physical activity, sleep). There is an opportunity in the future to add wearable technologies and more precise measurements, at least in subsamples, to validate the self-reported measures. Second, the cohort is representative of urban South Asia, limiting generalizablity to rural areas in the overall populations of these settings. Concurrently, we have adapted the CARRS protocol to measure non-communicable disease (NCD) burdens in rural populations in separate studies, such as the Solan Surveillance Study in Himachal Pradesh, India,[56] and UDAY study in Sonipat and Vishakhapatnam.[57] Furthermore, rapid socioeconomic development in South Asia is bringing expanded urbanization in previously rural areas and also rural-to-urban migration. Therefore, the lessons learned from the CARRS cohort will be valuable as the rest of the region also urbanizes. Over 60% of South Asia is projected to be urban by 2030. Third, whereas we have created a biorepository, we have not yet done genomic, epigenomic and metabolomic analyses, but plans are under way to make this possible. It has taken persistence and major effort to maintain and retain the cohort. One ongoing challenge is the need for infrastructural funding to sustain the cohort and to energize investigators to focus on grants related to scientific questions to answer, rather than always be on the lookout for programme funding.

Strengths

Over the past 10 years, CARRS has built a strong and extensive network of collaborators and interdisciplinary investigators, a robust field- and data-co-ordinating unit and robust and flexible international partnerships of high

scientific quality.[31,43,51,54,55,58,59] The study has been an invaluable resource in the region, fostering collaborations among 20 unique institutions across five continents and 70 investigators across multiple disciplines. These collaborations have already led to three large funded chronic disease intervention studies,[60–63] four training grants[64] and many smaller grants.

The cohort infrastructure has many scientific strengths. Those enrolled are representative of two major cities in India and one megacity in Pakistan, and its findings can be of value to major population growth centres in South Asia and beyond. Furthermore, CARRS was established using representative sampling methods to recruit adult samples at two time points, (CARRS-1 and -2), which allows for secular comparison and longitudinal follow-up with the accumulation of person-years which enables the study of incidence. The study also has recruited adults as young as 20 years old, much younger than the enrolment for most studies of CVD in adults. This is critical in a population where NCD and its risk factors emerge at younger ages than the global average. In addition, CARRS has high response rates at recruitment and high retention rates at follow-up. The study also has a biorepository of over 360 000 aliquots of sera, plasma, buffy coat and urine samples of the Indian participants stored in a well-maintained laboratory in India, which can be used in the future. The high-quality data collected from this study have enabled the application of conventional and customized statistical, machine learning and bioinformatics methods, as well as the pursuit of methodological innovations. Last, a very important part of this cohort is the collection of multiple sources of data on causes of death; the verbal autopsy data collected in CARRS overcome the issue of poor records on causes of deaths in India and Pakistan, where the majority of deaths occur at home.

Future directions

Together with conventional risk factors, stored biorepository data can be used to better understand the granular natural history and pathophysiological pathways (by incorporating molecular, protein-based and cellular biomarkers) of diverse CVD and diabetes phenotypes. In the near term, the cohort will be leveraged to investigate pathophysiological, environmental, genomic and sociobehavioural exposures on subclinical and clinical cardiometabolic disease phenotypes, with implications for the prevention and treatment of conditions such as heart failure and diabetes. The future establishment of an offspring cohort through recruiting the children of participants may facilitate investigations into the development of NCDs over the life course and familial origins of the disease.

Can I get hold of the data? Where can I find out more?

Data from CARRS-1 baseline and first three follow-up visits are available through the NHLBI BioLINCC.[65] For additional information and collaboration, please contact the investigators: Dr KM Venkat Narayan, e-mail: [knaraya@emory.edu] and Dr Dorairaj Prabhakaran, email: [dprabhakaran@ccdcinida.org].

CARRS Investigators Group

Steering Committee: Dorairaj Prabhakaran, KM Venkat Narayan, Nikhil Tandon, V Mohan, Muhammed M Kadir, Mohammed K Ali. Names that follow of institutions, investigators and team members are listed in alphabetical order: Aga Khan University (AKU), Karachi: Zafar Fatami, Muhammed M Kadir; All India Institute of Medical Science (AIIMS), New Delhi: Deksha Kapoor, Lakshmy Ramakrishnan, Nikhil Tandon; Centre for Chronic Disease Control (CCDC)/Public Health Foundation of India (PHFI), New Delhi: Vamadevan S Ajay, Ruby Gupta, Naveen Kaushik, Dimple Kondal, Sailesh Mohan, Dorairaj Prabhakaran, Garima Rautela, Roopa Shivashankar; Emory University, Atlanta, USA: Mohammed K Ali, Mark Hutcheson, Unjali P Gujral, Ram Jaganathan, Shivani A Patel, Lisa Staimez, KM Venkat Narayan. Madras Diabetes Research Foundation (MDRF), Chennai: RM Anjana, M Deepa, V Mohan, R Pradeepa; data collection team: Chennai: M Kumar, JV Anthony, A Arul Dass, L Dhanasekar, L Gomathi, D Kalaivani, M Lenin, M Nandhakumar, K Parthiban, G Sampath, P Saravana Kumar, R Saravanan, G Shobana, T Suresh, S Tamilselvi, D Velmurugan, A Vivek, A Xavier Suresh, A Chiranjeevi A; laboratory staff: Akila N, Bharathy B, Irin Jayakumari A, Revathy M, SatishRaj S, Vijay Baskar S; data entry operator and scanner: Nirmala N. Delhi: field supervisor: Tripurari Prasad Singh; field interviewers: Anita Yadav, Anshu Arya, Kafal Kashyap, Makhan Kumar, Arun Dhillon, Arshit Kondal, Manju Sharma, Minakshi lal, Rukhsar Kazmi, Virendra Kumar, Sonia Mehta, Ravi Kumar, Lalit Kumar and Baldev Dhiman; laboratory staff: Savita Dhatwalia; Priyanka Nautiyal, Darshan Bisht; Geeta Singh, Narendra Dutt, Tarun Kumar, Ram Narayan Singh; data entry operators: Naresh Kumar, Sanjeev Sakral, Pankaj Sharma, Rajesh Singh; information technology and database development: Ramanathan K, Naveen Kaushik. Karachi: field supervisor: Mehboob John Samuel; field interviewers and

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Ethics approval

Ethical approval for this study was provided by the Institutional Review Boards (IRBs) of PHFI (IRB00006658), AIIMS (IEC/NP-17/07.09.09), MDRF (MDRF/EC/EPI/2009/10) Chennai, India, AKU (1468-CHS-ERC-2010) and Emory University (IRB00044159). In addition, the study has received regulatory approval from the Health Ministry Screening Committee (HMSC) of India.

Supplementary data

Supplementary data are available at *IJE* online.

Author Contributions

D.P., K.M.V.N., M.K.A., N.T., V.M. designed the study. D.P., K.M.V.N., M.K.A., M.M.K., N.T., V.M., M.D., R.S., V.S.A., S.M. directed the study's implementation. G.R., De.K., R.G. helped in study's implementation. D.K., S.A.P., K.M.V.N. drafted the manuscript. D.K., S.A.P., K.M.V.N., M.K.A., D.P., N.T. designed the analytical strategy and helped to interpret the findings. D.P., N.T., M.K.A., V.M., U.P.G. and all listed authors provided critical comments for manuscript.

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Conflict of interest

None declared.

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