क्षेत्रीय आयुर्विज्ञान संस्थान, इंफाल: मणिपुर
REGIONAL INSTITUTE OF MEDICAL SCIENCES, IMPHAL, MANIPUR
(स्वास्थ्य और परिवार कल्याण मंत्रालय,भारत सरकार के अंतर्गत एक स्वायत्त संस्थान)
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CIRCULAR

Imphal, the 18th August, 2025

No. 159/RIMS-MRU/2025: The **4th Research Masterclasses 2025**, of the Department of Health Research, Ministry of Health and Family Welfare, Government of India, will be conducted virtually, **on 29th August, 2025 (Friday).**

2. All the faculties (RIMS, Dental College, College of Nursing), members of EC, LRAC of MRU, Principal Investigators undertaking MRU funding projects (including under process projects) and residents are invited to take part in the session at Banting Hall, RIMS, Imphal.

Date: 29.08.2025 (Friday)
Time: 2:30 PM onwards
Venue: Banting Hall, RIMS, Imphal (ONLY SITE FOR PARTICIPATION FOR RIMS)

3. As per the directives issued by the DHR, **maximum participation** from our institute is strongly encouraged. MRU is submitting the attendance sheet to the DHR after the session concludes.

4. The research papers to be discussed during the research masterclass are available in the RIMS website: https://www.rims.edu.in/secure/ and also being shared with all concerned through their respective (personal/ departmental/ college) e-mail IDs.

18/08/2025

Prof. T. Jeetenkumar Singh,
Nodal Officer,
Multi-Disciplinary Research Unit,
RIMS, Imphal

Copy to:

1. The P.S. to Director, RIMS for kind information of Director
2. The P.A. to Medical Superintendent, RIMSH for kind information
3. The Dean (Academic), RIMS for kind information & permission to utilize the facilities at Banting Hall.
4. The Principal, Dental College, RIMS
5. The Principal, College of Nursing, RIMS } with a request for ensuring maximum participation.
6. The Head of Department, RIMS, Imphal .....
7. The Chairperson/Co-Chairperson/Member, LRAC, MRU, RIMS.....
8. The Member, EC, MRU, RIMS, Imphal.....
9. The Principal Investigator, RIMS .....
10. The IT section, RIMS – with a request for uploading the notice in the website & technical support on 29.8.25
11. Asst. Engineer (Elect./Civil), RIMS - with a request for ensuring uninterrupted power supply & optimum AC functioning.
12. The Care Taker, Banting Hall, RIMS, Imphal- for proper upkeep of the venue & the accompanying facilities.
13. Guard file.

No. R.11016/22/2024-HR
Government of India
Ministry of Health & Family Welfare
Deptt of Health Research

IRCS Building, 2nd Floor,
Red Cross Road
New Delhi – 110 001
14.08.2025

To
The Dean/ Principal/ Director of Medical Colleges/ Institutes

Subject: Request to attend Research Masterclasses, 2025 for MRU network– reg.

Sir/Madam

DHR-ICMR has initiated a dedicated platform to conduct Research Grand Rounds to strengthen the National research ecosystem through sustained collaboration and knowledge exchange. The objectives of the Research Grand Rounds are as follows:

I. To deliberate on research methodologies, analytical tools, and emerging scientific approaches
II. To strengthen the methodological understanding amongst researchers needed to implement different kinds of research.
III. To foster collaboration and connectivity across research institutions

2. These Research Grand Rounds will be organized as monthly webinars entitled 'Research Masterclass' on last Friday of each month. The speakers for these Research Masterclasses will be eminent research scientists in the country who will be discussing their original research work in details from methodological point of view.

3. The next Research Masterclass is scheduled for **29.08.2025 (Friday) at 2:30 PM**. The invited speaker is **Dr. Viswanathan Mohan**, Chairman, Madras Diabetes Research Foundation (ICMR - CCoE) & Dr. Mohan's Diabetes Specialties Centre (IDF Centre of Excellence in Diabetes Care), Chennnai, Tamil Nadu. The research paper to be discussed during the research masterclass is enclosed. The link for the research masterclass will be shared shortly.

4. Accordingly, it is requested to kindly disseminate the information in your institution and ensure maximum participation in Research Masterclass. Also, it is requested from your institute to share at least two questions related to research paper attached on the following email: **dhr-mru@gov.in** latest by 25.08.2025. These questions will be discussed with the speaker during masterclass.

Yours faithfully

(Dharkat R. Luikang)
Deputy Secretary

Copy to: The Nodal Officer of Multi-Disciplinary Research Units (MRUs)

Comparing Type 2 Diabetes, Prediabetes, and Their Associated Risk Factors in Asian Indians in India and in the U.S.: The CARRS and MASALA Studies

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OBJECTIVE

To assess the prevalence of diabetes and prediabetes and the associated risk factors in two Asian Indian populations living in different environments.

RESEARCH DESIGN AND METHODS

We performed cross-sectional analyses, using representative samples of 2,305 Asian Indians aged 40–84 years living in Chennai, India, from the Centre for cArdiometabolic Risk Reduction in South-Asia study (CARRS) (2010–2011), and 757 Asian Indians aged 40–84 years living in the greater San Francisco and Chicago areas from the U.S. Mediators of Atherosclerosis in South Asians Living in America (MASALA) study (2010–2013). Diabetes was defined as self-reported use of glucose-lowering medication, fasting glucose ≥126 mg/dL, or 2-h glucose ≥200 mg/dL. Prediabetes was defined as fasting glucose 100–125 mg/dL and/or 2-h glucose 140–199 mg/dL.

RESULTS

Age-adjusted diabetes prevalence was higher in India (38% [95% CI 36–40]) than in the U.S. (24% [95% CI 21–27]). Age-adjusted prediabetes prevalence was lower in India (24% [95% CI 22–26]) than in the U.S. (33% [95% CI 30–36]). After adjustment for age, sex, waist circumference, and systolic blood pressure, living in the U.S. was associated with an increased odds for prediabetes (odds ratio 1.2 [95% CI 0.9–1.5]) and a decreased odds for diabetes (odds ratio 0.5 [95% CI 0.4–0.6]).

CONCLUSIONS

These findings indicate possible changes in the relationship between migration and diabetes risk and highlight the growing burden of disease in urban India. Additionally, these results call for longitudinal studies to better identify the gene-environment-lifestyle exposures that underlie the elevated risk for type 2 diabetes development in Asian Indians.

Asian Indians appear to have a higher propensity toward developing type 2 diabetes than other race/ethnic groups. India is home to the second-largest population of individuals with type 2 diabetes worldwide (1). Furthermore, immigration to developed countries is traditionally associated with higher type 2 diabetes risk (2–4), and Asian Indian immigrants have a higher prevalence of type 2 diabetes than the general U.S. population (4–6). However, given that India has recently undergone

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rapid economic and nutrition transitions (7,8), it is unclear whether diabetes risk among Asian Indians immigrants in the U.S. differs from that of Asian Indians in urban India. Such a comparison of two genetically similar populations living in different environmental settings could shed light on the behavioral and environmental factors associated with increased diabetes risk in this ethnic group. We therefore compared the age-specific prevalence of type 2 diabetes and prediabetes in two current population-based studies of urban Asian Indians aged ≥40 years: n = 2,305 residents of Chennai, India, using data from the Centre for cArdiometabolic Risk Reduction in South-Asia study (CARRS) (2010–2011) (9), and n = 757 from the U.S.-based Mediators of Atherosclerosis in South Asians Living in America (MASALA) study (2010–2013) (10). We also analyzed the relative associations of demographic and anthropometric characteristics on prevalent glycemic status in urban Asian Indians in both India and the U.S.

RESEARCH DESIGN AND METHODS

The design, sampling strategy, recruitment, enrollment, and questionnaire and examination components of the MASALA and CARRS studies have previously been described in detail (9,10). In brief, CARRS is a multisite cohort study that recruited participant populations from three urban megacities in India and Pakistan (Delhi, Chennai, and Karachi). The baseline examination for this cohort included a representative cross-sectional survey conducted in each city between 2010 and 2011. For the purposes of this study, data were analyzed from the Chennai study site only, as this site was the only one to perform an oral glucose tolerance test (OGTT) in order to identify diabetes accurately. Households were selected for participation using multistage random sampling technique in order to be representative of the city of Chennai (9). A total of 6,920 individuals were screened for participation, of whom 6,906 (99%) provided questionnaire data. Fasting plasma glucose was obtained from 5,952 participants (86%) and 2-h post–glucose challenge on 4,051 participants. For this study, we limited our population to the 4,865 (70%) participants who were previously diagnosed with diabetes as determined by questionnaire data or who provided fasting and 2-h postchallenge glucose measurements.

Participants with existing cardiovascular disease as ascertained through self-report (n = 283) and those of age <40 years (n = 2,277) were excluded from the CARRS study for valid comparisons with MASALA.

MASALA is based on a community-based sample of South Asians living in the greater Chicago and San Francisco Bay areas. Data collection and assessment occurred between 2010 and 2013. The MASALA study was modeled to be similar to the Multi-Ethnic Study of Atherosclerosis (MESA) cohort study (11), and only individuals without a known history of cardiovascular disease were eligible. Recruitment was conducted using telephone-based recruitment methods, similar to the MESA study (11). Sampling frames were created by clinical site (either the University of California, San Francisco, or Northwestern University) and included all nine counties of the San Francisco Bay Area and the seven census tracts closest to the Northwestern University medical center, as well as suburban locations around Chicago where census data revealed high proportions of Asian Indian residents. Name, address, and telephone number were obtained for ~10,000 households in the targeted census tracts from commercial mailing list companies (InfoUSA, Omaha, NE, and Marketing Systems Group, Horsham, PA). Random samples of South Asian surnames from the desired geographic locations were created using a specific cultural coding algorithm to identify 162 ethnicities, 16 ethnic groups, 80 language preferences, 21 countries of origin, and 12 religions using a five-step matching process to classify a person's first and last name, thereby reducing selection bias among participants with uncommon South Asian surnames (10). All participants were screened by telephone and were invited to either the University of California, San Francisco, or the Northwestern University clinical field center for a 6-h baseline clinical examination. In total, 9,097 households were attempted to be reached. Within these households, 3,053 individuals were reached and 1,801 (59%) were eligible for participation (10). Of all those eligible, a total of 906 individuals participated in the study. However, for the purposes of our analysis, data were analyzed only for individuals who identified as being born in India (n = 757). Details regarding the eligibility criteria, questionnaire, and examination components in CARRS and MASALA are shown in Table 1.

In both studies, after at least a 9-h overnight fast, a 75-g OGTT was administered to participants without previously diagnosed diabetes who were willing and able to participate in the glucose challenge. Blood samples were obtained from a peripheral vein just before glucose ingestion (time 0) and at 30 and 120 min post–glucose challenge for plasma glucose measurements. Serum glucose was measured using the hexokinase method in both studies. Type 2 diabetes was defined similarly as self-reported use of glucose-lowering medication (either an oral agent or insulin), fasting glucose ≥126 mg/dL, or 2-h postchallenge glucose ≥200 mg/dL; prediabetes was defined as fasting glucose 100–125 mg/dL and/or a 2-h postchallenge glucose 140–199 mg/dL (12). BMI was classified by World Health Organization criteria (13). Normal weight was classified as BMI 18.5–24.99 kg/m^2, overweight was classified as BMI 25–29.99 kg/m^2, and obese was classified as BMI ≥30 kg/m^2. Asian-specific cut points for BMI classification were also used for sensitivity analyses (14).

Statistical Analysis

Prevalence values and 95% CIs were estimated by study site, sex, age-group, and BMI category. Participant characteristics were stratified by sex and were compared by study using χ^2 test or ANOVA as appropriate. The non–normally distributed variables of fasting and 2-h plasma glucose were log transformed. The effect of location of residence (India or the U.S.) on the odds of prediabetes and type 2 diabetes compared with normal glucose tolerance was assessed using standardized polytomous regression. Initially, an unadjusted regression model was created to compare the individual association between study location and prevalent glycemic status. Subsequent multivariable models were then created to adjust for covariates including age, sex, blood pressure, waist circumference, educational status, and years since migration to the U.S. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

Table 1—Eligibility, questionnaire, and exam components in CARRS and MASALA

Eligibility criteria	CARRS-Chennai	MASALA
Inclusion criteria	• Aged 20 years or older • Permanently residing in the selected household	• Self-identify as South Asian • Age range 40–84 years • Ability to speak and read English, Hindi, or Urdu.
Exclusion criteria	• Pregnant women were excluded from the study, as were bedridden individuals.	• Those with history of physician-diagnosed myocardial infarction (MI), stroke, or transient ischemic attack; with a history of heart failure, angina, or use of nitroglycerin; or with a history of cardiovascular procedures • Current atrial fibrillation, active cancer treatment, or life expectancy <5 years; impaired cognitive ability as judged by the reviewer; plans to move out of the study region in the next 5 years; currently living in or on the wait list for a nursing home • Individuals weighing >136 kg (300 lb) were also excluded owing to limitations with the computed tomography scanner
Questionnaires	• Questionnaires were used to gather demographic information including language use, family history of type 2 diabetes, medical history, and current medication use	• Questionnaires were used to gather demographic information including language use, medical history, family history of type 2 diabetes, and current medication use
Blood pressure	• Three seated blood pressure measurements were taken using an electronic sphygmomanometer • An average of the last two readings was used to assess systolic and diastolic blood pressure	• Three seated blood pressure measurements were taken using an automated blood pressure monitor • An average of the last two readings was used to assess systolic and diastolic blood pressure
Weight	• Participant weight was measured using a standing balance beam scale	• Participant weight was measured using a standing balance beam scale or digital weighing scale
Height	• Height was measured using a portable stadiometer	• Height was measured using a stadiometer
Waist circumference	• Waist circumference was measured using a nonstretch measuring tape at the site of maximum circumference halfway between the lower ribs and the anterior superior iliac spine	• Waist circumference was measured using a flexible tape measure at the site of maximum circumference halfway between the lower ribs and the anterior superior iliac spine

RESULTS

Table 2 displays participant characteristics by sex and study. Of the 2,305 participants from CARRS-Chennai, 54% were women. Of the 757 participants from MASALA, 46% were women. The mean duration of residence in the U.S. for MASALA study participants was 27.8 ± 10.8 years for men and 26.5 ± 10.8 years for women. Participants in the MASALA Study were on average older than those in CARRS-Chennai and had higher educational attainment. On average, for both sexes, participants in MASALA were taller and had greater weight and waist circumference measurements than those in CARRS-Chennai. Additionally, men in the MASALA study had a higher mean BMI than men in CARRS-Chennai; however, this was reversed among women. In both studies, fasting glucose was obtained from all participants who were willing to provide a sample; however, a 75-g OGTT was only administered to participants without a prior diagnosis of type 2 diabetes (MASALA $N = 617$, CARRS $N = 1,674$). Participants in the MASALA study had lower log fasting glucose values than participants in CARRS-Chennai but higher log fasting 2-h glucose values. Those in MASALA also had lower systolic and diastolic blood pressure levels and took more blood pressure–lowering medications than participants in CARRS-Chennai. Of those with a prior diagnosis of type 2 diabetes, participants in MASALA had on average a longer duration since diagnosis.

Age-adjusted type 2 diabetes prevalence was higher among Indians in CARRS-Chennai than those in the MASALA Study both overall (38% [95% CI 36–40] vs. 24% [95% CI 21–27]) and by sex (men 36% [95% CI 33–39] vs. 27% [95% CI 23–31]; women 42% [95% CI 39–45] vs. 23% [95% CI 19–28]). Of participants with type 2 diabetes, 65% of Asian Indians living in the U.S. and 71% of Asian Indians living in India had a previous diagnosis of diabetes. Age-adjusted prediabetes prevalence was lower in Asian Indians in Chennai than in the U.S. (overall 24% [95% CI 22–26] vs. 33% [95% CI 30–36], men 21% [95% CI 19–24) vs. 35% [95% CI 31–40], and women 25% [95% CI 23–28] vs. 29% [95% CI 24–34]). These patterns were consistent across age- and sex groups, but differences in type 2 diabetes prevalence by age were more significant in women (Fig. 1). In all categories of BMI, the prevalence of diabetes was higher in Asian Indians living in India than in Asian Indians living in the U.S. (Fig. 2). Differences in diabetes prevalence between the groups were significant in normal and overweight participants but were not significant in participants who were obese. In all categories of BMI, the prevalence of prediabetes was lower in native Asian Indians than those in the U.S. and was significantly different in participants with normal BMI. The pattern of higher diabetes prevalence and lower prediabetes prevalence in Asian Indians living in India than Asian Indians in the U.S. in all BMI categories was consistent using the Asian BMI cut points. However, when using the Asian specific cut points, the prevalence of diabetes and prediabetes was most significantly different in participants who were overweight.

Of the 757 participants from MASALA, 189 (25%) had origins from one of four of the South Indian states of Tamil Nadu,

Table 2—Baseline participant characteristics by study center*

	Men		Women	
	CARRS-Chennai (*N* = 1,055)	MASALA (*N* = 408)	CARRS-Chennai (*N* = 1,250)	MASALA (*N* = 349)
Age (years)	51.2 (9.2)†	56.3 (10.0)†	49.7 (8.4)†	54.6 (8.7)†
Education: Bachelor's degree or higher	11.0†	93.1†	3.8†	87.4†
Weight (kg)	64.6 (12.6)†	74.2 (11.6)†	61.8 (11.9)†	64.0 (10.8)†
Height (cm)	163.1 (3.3)†	169.8 (4.1)†	150.1 (5.5)†	157.0 (5.9)†
BMI (kg/m^2)	24.2 (4.3)†	25.9 (4.4)†	27.4 (4.9)†	26.0 (4.0)†
Waist circumference (cm)	88.8 (11.4)†	95.7 (9.2)†	84.2 (11.0)†	88.9 (9.7)†
Log fasting glucose (mg/dL)§	4.7 (0.3)†	4.6 (0.2)†	4.7 (0.3)‡	4.5 (0.1)‡
Log 2-h glucose (mg/dL)‖	4.7 (0.4)†	4.8 (0.3)†	4.7 (0.3)†	4.8 (0.3)†
Systolic blood pressure (mmHg)	131.0 (21.0)‡	126.8 (14.7)‡	127.5 (20.7)‡	123.0 (17.0)‡
Diastolic blood pressure (mmHg)	85.4 (12.4)†	76.6 (8.7)†	83.3 (11.7)†	70.0 (9.8)†
Use of blood pressure–lowering medication	10.9†	36.8†	15.9†	26.3†
Self-reported diabetes diagnosis (%)	66.9	70.1	74.5†	56.8†
Years since diagnosis	6.4 (6.5)‡	11.2 (10.1)‡	6.0 (5.6)†	8.7 (6.3)†

Data are mean (SD) or % unless otherwise indicated. *Adjusted for age. †$P < 0.01$. ‡$P < 0.0001$. §Log fasting glucose: men, CARRS-Chennai (*N* = 1,027), MASALA (*N* = 402); women, CARRS-Chennai (*N* = 1,215), MASALA (*N* = 345). ‖Log 2-h glucose: men, CARRS-Chennai (*N* = 780), MASALA (*N* = 323); women, CARRS-Chennai (*N* = 894), MASALA (*N* = 294).

Karnataka, Andhra Pradesh, or Kerala. After restriction of participants from MASALA to only those with origins from South India, age-adjusted type 2 diabetes prevalence was again higher among Indians in CARRS-Chennai than those in the MASALA Study both overall (38% [95% CI 36–40] vs. 25% [95% CI 20–32]) and by sex (men 36% [95% CI 33–39] vs. 27% [95% CI: 19–35]; women 42% [95% CI 39–45] vs. 25% [95% CI 15–34]). Age-adjusted prediabetes prevalence was again lower in Asian Indians in Chennai than in those in the U.S. with origins from South India specifically (overall 24% [95% CI 22–26] vs. 33% [95% CI 26–39], men 21% [95% CI 19–24) vs. 36% [95% CI 27–45], and women 25% [95% CI 23–28] vs. 27% [95% CI 19–38]). These patterns were again consistent in all age- and sex groups, but differences in diabetes prevalence between Asian Indians in Chennai compared with Asian Indians in the U.S. with origins in South India were more significant than differences in prediabetes prevalence between these groups.

Table 3 shows the association of place of residence (either India [Chennai] or the U.S. [greater San Francisco and Chicago areas]) with glycemic status. After adjustment for age, sex, waist circumference, and systolic blood pressure, Asian Indians in the MASALA Study had a 50% (95% CI 0.4–0.6) decreased odds of type 2 diabetes but a 20% (95% CI 0.9–1.5) increased odds of prediabetes than those in CARRS-Chennai. The inclusion of education and years since migration in multivariable models somewhat attenuated the effect of place of residence on the odds of having diabetes compared with normal glucose tolerance. Income could not be assessed in the models, as it was found to be collinear with place of residence. The inclusion of height in multivariable models as a proxy for socioeconomic status prior to migration did not alter the effect of place of residence on the odds of having diabetes or prediabetes compared with normal glucose tolerance between the groups. However, the inclusion of height and education together in multivariable models significantly attenuated the effect of place of residence on the odds of having diabetes.

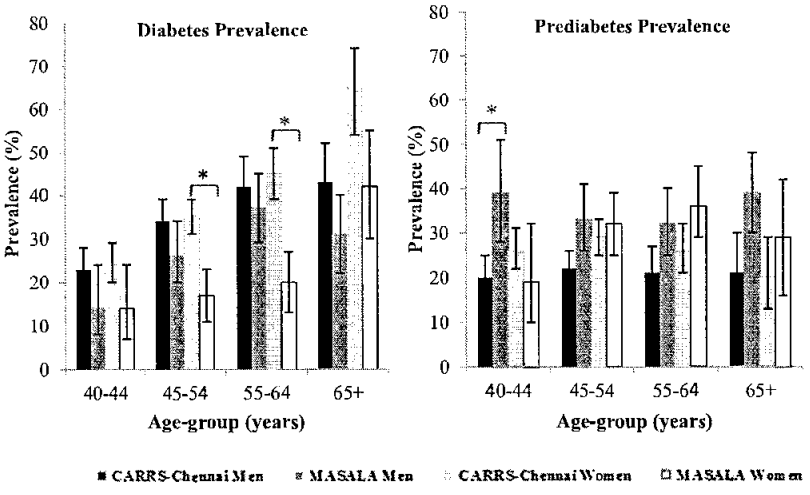

Figure 1—Age-specific prevalence of diabetes and prediabetes by study and sex. *$P < 0.05$.

CONCLUSIONS

Few studies have compared Asian Indians in India to those who have immigrated to the U.S. In this study comparing middle- to older-aged urban Asian Indians, we found that a community-based sample of Asian Indians in the U.S. had a lower prevalence of type 2 diabetes but a higher prevalence of prediabetes than Asian Indians living in urban south India. This was observed despite Asian

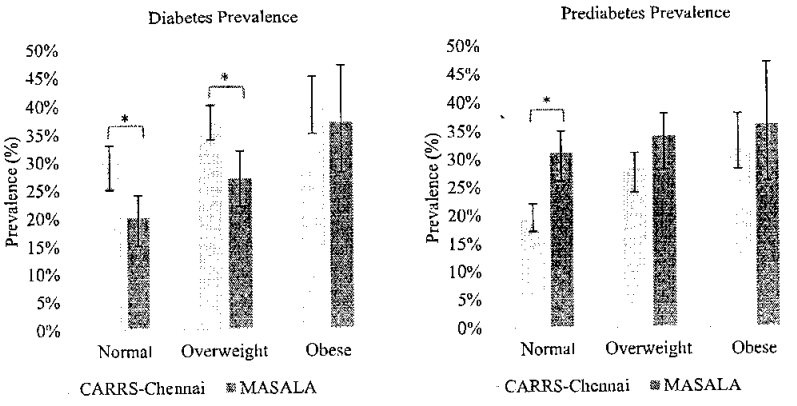

Figure 2—Prevalence of diabetes and prediabetes by study and BMI category. *$P < 0.05$.

Indians in the U.S. being older and heavier than those in India. Asian Indians in the U.S. also had better blood pressure levels than those in India, possibly explained by their higher usage of blood pressure–lowering medications. However, the adjustment for age, sex, waist circumference, and systolic blood pressure did not fully explain the increased odds of type 2 diabetes in Asian Indians in the CARRS-Chennai Study.

It is possible that India is in an early stage of the type 2 diabetes epidemic wherein those who are most susceptible to the disease develop it the earliest (15). It is also possible that Asian Indians who have immigrated to the U.S. have adopted more positive dietary and exercise habits, thereby lowering their risk for progression from prediabetes to overt type 2 diabetes (16). Contrary to previous findings that Asian Indians who migrate to the U.S. have poorer metabolic profiles than their counterparts in India (17,18), our results indicate that while Asian Indians in India had lower BMI and waist circumference measurements than those living in the U.S., they still had a higher prevalence of type 2 diabetes even at normal levels of BMI and in both sexes, thereby suggesting a shift in the association between migration and type 2 diabetes risk in this population. Paradoxically, both the overall and the age-specific prevalence of prediabetes were lower in Asian Indians living in India than in the U.S., which may be due to a more rapid conversion through the natural history of disease in Asian Indians living in India. Our results also add strength to the notion that factors besides age and central adiposity play a large role in type 2 diabetes development in Asian Indians (7) in both developed and developing country settings, since the adjustment for age, sex, waist circumference, and systolic blood pressure did not explain differences in the odds of prediabetes or type 2 diabetes between the two groups. Furthermore, while the prevalence of type 2 diabetes was lower in Asian Indians living in the U.S. than in India, it was still considerably higher than the general U.S. population (19–21), despite Asian Indians having an overall lower BMI.

Risk factors for type 2 diabetes development such as high-carbohydrate and/or -fat diets and sedentary lifestyles were once considered to influence those who had migrated to developed countries leading to an increased prevalence of diabetes in migrants than in those who remained in developing country settings (17,18). The results of our study are among the first to highlight a higher prevalence of diabetes in individuals living in India than their counterparts who have immigrated to the U.S. It is therefore possible that, given the rapid economic and nutritional transitions currently taking place in India (7,8), these factors now exacerbate risks in Asian Indians both in India and abroad. It is also possible that with more increased knowledge of beneficial diet and lifestyle choices, migrant Asian Indians may be shifting toward more health-promoting dietary patterns. A more thorough understanding of the dietary transitions taking place in India and in diaspora Indians could provide important insights into the development of type 2 diabetes in nonobese phenotypes. It is possible that Asian Indians in the U.S. may also have increased knowledge regarding diabetes prevention and greater access to health care (16,22) than Asian Indians in India. Such factors may serve to protect immigrant populations against type 2

Table 3—Risk factors associated with prediabetes and type 2 diabetes

		Prediabetes		Type 2 diabetes		
Model	Covariates	OR	95% CI	OR	95% CI	*P*
1	Migrant AI*	1.39	(1.14, 1.69)	0.73	(0.59, 0.90)	<0.01
2	Migrant AI*	1.18	(0.93, 1.50)	0.46	(0.36, 0.59)	<0.01
	Age-group (years)	1.21	(1.08, 1.38)	1.55	(1.38, 1.74)	<0.01
	Sex**	1.48	(1.18, 1.85)	1.47	(1.19, 1.84)	<0.01
	Waist circumference (cm)	1.03	(1.02, 1.04)	1.05	(1.04, 1.06)	<0.01
	SBP (mmHg)	1.01	(1.00, 1.02)	1.02	(1.01, 1.03)	<0.01
3	Migrant AI*	1.52	(0.85, 2.73)	0.73	(0.39, 1.35)	0.07
	Age-group (years)	1.23	(1.08, 1.40)	1.55	(1.37, 1.75)	<0.01
	Sex**	1.46	(1.16, 1.84)	1.43	(1.14, 1.78)	<0.01
	Waist circumference (cm)	1.03	(1.02, 1.04)	1.05	(1.04, 1.06)	<0.01
	SBP (mmHg)	1.01	(1.01, 1.02)	1.02	(1.01, 1.03)	<0.01
	Education	0.88	(0.60, 1.31)	0.64	(0.43, 0.94)	0.06
	Years since migration	0.99	(0.98, 1.01)	1.00	(0.99, 1.02)	0.81
4	Migrant AI*	1.50	(0.97, 2.32)	0.88	(0.57, 1.35)	0.05
	Age-group (years)	1.20	(1.06, 1.37)	1.51	(1.33, 1.71)	<0.01
	Sex**	1.24	(0.90, 1.72)	1.04	(0.75, 1.43)	0.41
	Height	0.99	(0.98, 1.01)	0.98	(0.96, 1.0)	0.09
	Waist circumference (cm)	1.03	(1.02, 1.04)	1.05	(1.03, 1.06)	<0.01
	SBP (mmHg)	1.01	(1.01, 1.02)	1.02	(1.01, 1.03)	<0.01
	Education	0.83	(0.55, 1.26)	0.56	(0.37, 0.85)	0.02

AI, Asian Indian; SBP, systolic blood pressure. *Asian Indians living in India (CARRS-Chennai study) were used as the referent group. **Males were used as the referent group.

diabetes risk; however, further research is needed in this area.

Our study directly compared the age-specific prevalence of prediabetes, type 2 diabetes, and the associated risk factors between Asian Indians living in the U.S. and India. While there were differences in the sampling frames and sociodemographic characteristics between the two studies, both are large population-based samples with similar anthropometric and laboratory measures that are representative of Asian Indians in large urban centers either in India or in the U.S. Additionally, while participants from CARRS are primarily of South Indian origin and participants from MASALA migrated from all parts of India, it is possible that the differences in type 2 diabetes prevalence between the groups could be attributed to differences in regional origins. However, when we restricted our analyses to participants from MASALA with origins in South India only, the finding of a high prevalence of diabetes and a relatively lower prevalence of prediabetes in Asian Indians from CARRS compared with Asian Indians from MASALA remained virtually unchanged. These results suggest that the differences in type 2 diabetes prevalence between the groups are likely not attributable to region of origin.

Furthermore, while there were large differences in education status as well as height between Asian Indians living in India and the U.S., adjustment for education and height in multivariable models as proxy measures for socioeconomic status prior to migration attenuated the effect of migration on the odds of diabetes between the two groups. These results suggest a possible healthy migrant effect, whereby individuals with greater access to education as well as early maternal and childhood nutrition were more likely to have the means for migration. However, while participants from the MASALA study had high levels of educational attainment, diabetes prevalence in this group was still considerably higher than that in the general U.S. population (20,21), thereby suggesting that factors besides education attainment play a large role in diabetes risk in Asian Indians.

Being that our study directly compares two distinct Asian Indian populations from differing geographic regions (Chennai, India, and the greater San Francisco and Chicago areas of the U.S.) the results cannot be generalized to Asian Indians living in other parts of India or the U.S. However, several studies have noted an increasingly high prevalence of diabetes in urban India (23–25) with recent evidence indicating a rise of diabetes in rural areas of India as well (26). Therefore, the high prevalence of diabetes in one urban Indian city as reported in this study may be indicative of an even larger burden of disease in India yet to come. Furthermore, the diabetes prevalence in MASALA study participants was similar to what was found in a recently published study of Asian Indians in Michigan (27). However, additional national level data are needed to assess the prevalence of diabetes among Asian Indians living in the U.S.

Our findings point to a high prevalence of type 2 diabetes in urban India with a paradoxically low prevalence of prediabetes compared with urban Asian Indians in the U.S. Furthermore, the increased type 2 diabetes prevalence in Asian Indians in India is evident in both sexes, in all age-groups, and at all levels of BMI and therefore cannot be explained by differences in anthropometry or age alone. These findings suggest the need for collaborative longitudinal research efforts between India and the U.S. Such collaborations could help identify the gene-environment-lifestyle exposures that underlie the elevated risk for type 2 diabetes development in Asian Indians.

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Author Contributions. U.P.G. analyzed data, wrote the manuscript, drafted tables and figures, and revised the manuscript and approved the final manuscript for submission. K.M.V.N. contributed to concept, design, analysis, and interpretation of the data; reviewed and revised the manuscript; and approved the final manuscript for submission. R.G.P. and M.D. oversaw the CARRS research operations and contributed to the design and data collection of the CARRS study. M.K.A. obtained the funding for the CARRS study, contributed to the design of the CARRS study, contributed to the discussion and interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript for submission. R.M.A. contributed to the discussion and interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript for submission. N.R.K. contributed to the discussion and interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript for submission. V.M. contributed to the discussion and interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript for submission. A.M.K. obtained the funding for the MASALA study; collected the data; contributed to concept, design, analysis, discussion, and interpretation of the data; reviewed and revised the manuscript; and approved the final manuscript for submission. U.P.G. 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.

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Metabolic non-communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17)

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Summary

Background Non-communicable disease (NCD) rates are rapidly increasing in India with wide regional variations. We aimed to quantify the prevalence of metabolic NCDs in India and analyse interstate and inter-regional variations.

Methods The Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) study, a cross-sectional population-based survey, assessed a representative sample of individuals aged 20 years and older drawn from urban and rural areas of 31 states, union territories, and the National Capital Territory of India. We conducted the survey in multiple phases with a stratified multistage sampling design, using three-level stratification based on geography, population size, and socioeconomic status of each state. Diabetes and prediabetes were diagnosed using the WHO criteria, hypertension using the Eighth Joint National Committee guidelines, obesity (generalised and abdominal) using the WHO Asia Pacific guidelines, and dyslipidaemia using the National Cholesterol Education Program—Adult Treatment Panel III guidelines.

Findings A total of 113 043 individuals (79 506 from rural areas and 33 537 from urban areas) participated in the ICMR-INDIAB study between Oct 18, 2008 and Dec 17, 2020. The overall weighted prevalence of diabetes was 11·4% (95% CI 10·2–12·5; 10 151 of 107 119 individuals), prediabetes 15·3% (13·9–16·6; 15 496 of 107 119 individuals), hypertension 35·5% (33·8–37·3; 35 172 of 111 439 individuals), generalised obesity 28·6% (26·9–30·3; 29 861 of 110 368 individuals), abdominal obesity 39·5% (37·7–41·4; 40 121 of 108 665 individuals), and dyslipidaemia 81·2% (77·9–84·5; 14 895 of 18 492 of 25 647). All metabolic NCDs except prediabetes were more frequent in urban than rural areas. In many states with a lower human development index, the ratio of diabetes to prediabetes was less than 1.

Interpretation The prevalence of diabetes and other metabolic NCDs in India is considerably higher than previously estimated. While the diabetes epidemic is stabilising in the more developed states of the country, it is still increasing in most other states. Thus, there are serious implications for the nation, warranting urgent state-specific policies and interventions to arrest the rapidly rising epidemic of metabolic NCDs in India.

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Introduction

South Asia, home to nearly a quarter of the world's population, is currently undergoing an epidemiological transition with an explosion in the prevalence of non-communicable diseases (NCDs).[1,2] India, the largest country in the region, is also the largest contributor to the NCD burden. Several studies conducted over the last two decades have revealed the high total burden of diabetes, hypertension, and dyslipidaemia in India.[3–6] However, most of these studies have relied on self-report of these conditions, do not use robust methodology for diagnosis, represent secondary analyses of data from surveys not specifically focused on NCDs, or are not truly representative of the population of the country. Also, none of these studies provide information on the prevalence of prediabetes, which limits their utility in assessing the current status of the diabetes epidemic in India and predicting its future trajectory. Furthermore, as regions and states in India differ widely from each other in ethnic composition, dietary habits, and socioeconomic development, overall NCD estimates for the country are likely to mask wide inter-regional and intraregional differences. Provision of health care is the responsibility of states in India; therefore, obtaining granular state-level data is of utmost importance to enable state governments to plan and implement programmes aimed at preventing and managing NCDs in their respective jurisdictions. This assumes particular

Research in context

Evidence before this study

We searched PubMed, Google Scholar, IndMED, and the Cochrane Database of Systematic Reviews, and scanned relevant reference lists and review articles, for studies published before April 10, 2023, reporting on the prevalence of non-communicable diseases (NCDs) among Asian Indians, using the key words "diabetes", "prediabetes", "metabolic NCDs", "hypertension", "obesity", "dyslipidemia", "urban", "rural", "India", "Asian Indians", and "South Asians". We used a combination of MeSH terms and free text for the search, which was limited to publications in English. The key inclusion criteria were original studies (published or reports), participants aged 20 years or older, and studies conducted in Asian Indians. Available evidence suggests a high and increasing prevalence of diabetes, hypertension, dyslipidaemia, and obesity in India. However, many of the studies retrieved relied on self-report of these conditions, lacked robust methodology for diagnosis, or represented secondary analyses of data from surveys not specifically focused on NCDs. Many of them were also not conducted on a truly representative population of India, which limits their utility in assessing intraregional and inter-regional differences in disease prevalence and the generalisability of their results to the whole of a vast and diverse country such as India.

Added value of this study

The present report from the Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) study, the largest nationally representative population-based study on diabetes and metabolic NCDs undertaken in India covering all 28 states of the country, two union territories, and the National Capital Territory of Delhi, shows that India now has a much higher prevalence of metabolic NCDs than shown by previous estimates. The study reports on the prevalence of diabetes and prediabetes in different states of India using robust sampling and diagnostic methods and therefore helps in assessing the present status of the diabetes epidemic and its likely future trajectory. The diabetes epidemic is in transition in India, with some of the states having already peaked while others are still in the early take-off stage. The study also shows that while the prevalence rates of diabetes, hypertension, obesity, and dyslipidaemia are higher in urban areas, the rural prevalence rates are much higher than previously reported.

Implications of all the available evidence

There is a sizeable population in India at risk of cardiovascular disease and other long-term organ complications due to metabolic NCDs, which are likely to pose a major public health challenge in the near future. There is also evidence that the NCD epidemic is spreading to rural areas, which lack the health infrastructure needed to effectively diagnose and manage these conditions. This calls for urgent government-level initiatives for prevention and management of NCDs through strengthening of the public health-care system and reorientation of priorities in provision of health care. The granular state-level data on these NCDs will be of particular interest to state governments in India, which are primarily responsible for providing health care in their respective jurisdictions and will enable them to design evidence-based interventions to effectively arrest the progress of NCDs and manage their complications.

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importance in view of recent evidence that mortality and morbidity due to NCDs is much higher in low-income and middle-income countries such as India, compared with wealthier nations.[7]

The Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) study is the largest survey on diabetes and other metabolic NCDs undertaken in India, and covers all 28 states, two of the union territories, and the National Capital Territory of Delhi (hereafter referred to as states and union territories).[8] The present paper analyses the results of the ICMR-INDIAB study to quantify the prevalence of metabolic NCDs, namely diabetes, hypertension, obesity, and dyslipidaemia in a representative sample of adults in both urban and rural India, and attempts to identify region-wise and state-wise differences in the status of these NCDs in the country.

Methods

Sampling and study population

The ICMR-INDIAB study is a cross-sectional, population-based survey of adults aged 20 years and older.[8–15] The methodological details of the study have been published elsewhere.[8] Briefly, the study sampled urban and rural residents in 31 states and union territories of India using a stratified multistage sampling design.[8] In order to obtain a truly representative sample of the population, we used three-level stratification based on geography, population size, and socioeconomic status of each state. The primary sampling units were villages in rural areas and census enumeration blocks in urban areas. Using a systematic sampling method, 24 and 56 households were selected from urban and rural areas, respectively. Door-to-door assessment was done and from each household, one individual was selected based on the WHO Kish method,[16] to avoid selection bias with respect to sex and age. The study was conducted in a phased manner between November, 2008, and December, 2020. In phase 1, four regions representing the south (Tamil Nadu), north (Chandigarh), east (Jharkhand), and west (Maharashtra) of the country were studied from Oct 18, 2008, to April 16, 2010. The remaining states were surveyed as follows: phase 2 consisted of undivided Andhra Pradesh (subsequently divided into Andhra Pradesh and Telangana), Bihar, Gujarat,

Karnataka, and Punjab (survey period, Sept 24, 2012, to July 26, 2013), the north east phase included Assam, Arunachal Pradesh, Manipur, Meghalaya, Mizoram, Nagaland, Sikkim, and Tripura (survey period, Dec 5, 2011, to Nov 14, 2017), phase 3 included Delhi, Madhya Pradesh, Rajasthan, and Uttar Pradesh (survey period, Aug 24, 2017, to March 8, 2018), phase 4 included Kerala, Goa, Puducherry, Haryana, and Chhattisgarh (survey period, Dec 10, 2018, to July 10, 2019), and phase 5 included Himachal Pradesh, Uttarakhand, Odisha, and West Bengal (survey period, Sept 1, 2019 to Dec 31, 2020). Details of the sampling strategy and phases have been published previously.[8–15]

Individuals who were temporarily away from home during the survey period and those who were terminally ill were excluded.

The study was approved by the Institutional Ethics Committee of the Madras Diabetes Research Foundation and individual states, and written informed consent was obtained from all study participants.

Procedures

In all individuals, a standardised, structured questionnaire was used to collect information on demographic and socioeconomic characteristics. Weight, height, waist circumference, and blood pressure were measured and BMI calculated using standardised techniques (details in appendix p 14).[17] In all individuals, capillary blood glucose (CBG) measurement was performed using a glucose meter (One Touch Ultra, LifeScan Johnson & Johnson, Milpitas, CA, USA) after ensuring an overnight fast of at least 8 h. In individuals without a previous diagnosis of diabetes, an oral glucose tolerance test (OGTT) was done using an 82·5 g oral glucose load (equivalent to 75 g of anhydrous glucose) and the 2 h post-load CBG was estimated, whereas in those with self-reported diabetes, only fasting blood glucose was measured. In all individuals with diabetes and on every fifth individual, a venous sample was drawn for assessment of HbA_{1c} and lipids. Samples were centrifuged within 1 h at the survey site, and serum was transferred to separate labelled vials and temporarily stored in −20°C freezers until they were transferred to the central laboratory in Chennai. All biochemical assays were carried out by the same team of laboratory technicians using standardised methods throughout the study period.

See Online for appendix

HbA_{1c} was estimated by high-pressure liquid chromatography using the Variant II Turbo machine (Bio-Rad, Hercules, CA, USA), which is certified by the National Glycohemoglobin Standardization Program as having documented traceability to the Diabetes Control and Complications Trial reference method.[18] Serum cholesterol (cholesterol esterase oxidase–peroxidase–amidopyrine method), serum triglycerides (glycerol phosphate oxidase–peroxidase–amidopyrine method), and high-density lipoprotein cholesterol (direct method: immunoinhibition) were measured using the Olympus 2700/480 automated biochemistry analyser (Fullerton, CA, USA) from 2008 to 2015, and Beckman Coulter AU 680 clinical chemistry analyser (Fullerton, CA, USA) from 2016 to 2021.

Outcomes

Outcomes of interest were diabetes, prediabetes, dysglycaemia, hypertension, generalised obesity, abdominal obesity, and dyslipidaemia. Projection estimates for each of the metabolic NCDs were also reported for the year 2021. Self-reported or known diabetes was defined based on a physician diagnosis of diabetes or current (in the past 6 months) use of medications for diabetes (insulin or oral hypoglycaemic agents). Physician diagnosis of diabetes was checked against medical reports or prescription for validity, which also helped to define the date and year of diagnosis. In those without a self-reported diagnosis, diabetes and prediabetes (impaired fasting glucose [IFG] and impaired glucose tolerance [IGT]) were diagnosed using OGTT, HbA_{1c}, or a combination of OGTT and HbA_{1c}. For the OGTT, diabetes was defined as per the WHO consultation group report recommendations[19]—ie, fasting CBG of 126 mg/dL (7·0 mmol/L) or higher, or 2-h post-oral glucose load CBG of 220 mg/dL (12·2 mmol/L) or higher. Isolated IFG was diagnosed if individuals had a fasting CBG of 110 mg/dL (6·1 mmol/L) or higher but less than 126 mg/dL (7·0 mmol/L), and 2-h post-glucose CBG of less than 160 mg/dL (8·9 mmol/L).[20] Isolated IGT was diagnosed if individuals had a 2-h post-oral glucose load CBG of 160 mg/dL (8·9 mmol/L) or higher but less than 220 mg/dL (12·2 mmol/L), and fasting CBG of less than 110 mg/dL (6·1 mmol/L).[19] Prediabetes was defined as the presence of IFG, IGT, or both.[19,20] Dysglycaemia was defined as the presence of prediabetes or diabetes. We also assessed the prevalence of IFG using the American Diabetes Association (ADA) criteria[21]—ie, fasting CBG 100–125 mg/dL (5·6–6·9 mmol/L)—and of diabetes and prediabetes using HbA_{1c} cutoffs of 6·5% (48 mmol/mol) or higher and 5·7–6·4% (39–46 mmol/mol), respectively.[22]

Generalised obesity was defined as a BMI of 25 kg/m^2 or higher, and abdominal obesity was defined as a waist circumference of 90 cm or higher for men and 80 cm or higher for women (based on WHO Asia Pacific guidelines).[23] Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, or a diastolic blood pressure of 90 mm Hg or higher, or treatment with antihypertensive drugs (Eighth Joint National Committee criteria).[24] For defining dyslipidaemia, National Cholesterol Education Programme—Adult Treatment Panel III guidelines[25] were used as follows: hypercholesterolaemia—serum cholesterol concentrations of 200 mg/dL (5·2 mmol/L) or higher; hypertriglyceridaemia—serum triglyceride concentrations of 150 mg/dL (1·7 mmol/L)

or higher; low HDL cholesterol—HDL cholesterol concentrations of less than 40 mg/dL (1·04 mmol/L) for men and less than 50 mg/dL (1·3 mmol/L) for women; high LDL cholesterol—LDL cholesterol concentrations of 130 mg/dL (3·4 mmol/L) or higher calculated using the Friedewald equation.[26] The intra-assay and inter-assay coefficients of variation for biochemical assays conducted at the central laboratory ranged between 3·1% and 7·6%.

Statistical analysis

The sample size was calculated separately for urban and rural areas, as previous studies have shown large variations between urban and rural prevalence of diabetes. Assuming a prevalence of 10% in urban areas and 4% in rural areas, allowing for margin of error of 20% of prevalence, a non-response rate of 20%, and level of significance of 5%, the sample size was estimated to be 1200 in urban areas and 2800 in rural areas in each of the states studied, with a total of 4000 individuals per state (details in appendix pp 1–8). Estimates for continuous variables are shown as mean (SE) and for categorical variables as proportions (95% CI). Sampling weights were calculated to account for sampling at different levels within each state (appendix pp 1–10). We used the proc survey (frequency/mean) procedure, an approach that produces *n*-way tables from complex multistage survey designs with stratification, clustering, and weighting. To account for the multistage complex survey design of the study, all the key survey elements were used in the statistical analysis.[27] The primary sampling unit was accounted for as the cluster, the normalised weight was accounted for as the final study weight, and the state was accounted for as the stratum to estimate population means, variance, and proportions. To compare the mean and percentage of variables between two groups (urban and rural, and male and female), survey-adjusted linear regression and the Wald χ^2 test were applied, respectively.

For subgroup analysis, the Indian states were divided into six geographical zones: north (Chandigarh, Delhi, Haryana, Himachal Pradesh, Punjab, and Rajasthan), south (Andhra Pradesh, Telangana, Karnataka, Kerala, Puducherry, and Tamil Nadu), east (Bihar, Jharkhand, Odisha, and West Bengal), west (Goa, Gujarat, and Maharashtra), central (Chhattisgarh, Madhya Pradesh, Uttar Pradesh, and Uttarakhand), and northeast (Arunachal Pradesh, Assam, Manipur, Meghalaya, Mizoram, Nagaland, Sikkim, and Tripura).

To account for the different time periods of the survey, the analytical strategy we used is akin to standardising estimates according to age, sex, and region to obtain the current prevalence of cardiometabolic risk factors in each state. The information from the National Family Health Survey-5 (NFHS-5) was used for the standardisation.[28] Similar assumptions have been made by the International Diabetes Federation while making future projections for diabetes.[29] The purpose of this standardisation was to ensure that population ageing and other demographic trends were accounted for when estimating diabetes in states that were sampled in earlier time periods. Minimal assumptions were made about changes in the population that possibly affected diabetes prevalence during the study period. We therefore focus only on region, sex, and age, as these are known factors that contribute to diabetes prevalence that are themselves changing in the population, and therefore could drive secular changes in diabetes prevalence.

NFHS-5 study weights were computed for subgroups defined by region, sex, and age (10-year intervals) following the complex survey design. The weights assigned to each subgroup based on the NFHS-5 household dataset were multiplied by the weighted prevalence in the respective subgroup. The prevalence of each cardiometabolic risk factor in the specific state was calculated by adding the re-weighted prevalence of all subgroups. The weighting procedure using information from NFHS-5 is illustrated in detail in the appendix (pp 11–13).

The estimated adult population (≥20 years) of India for the year 2021 from the population projections published by the Ministry of Health and Family Welfare, Government of India,[30] was used for estimating the numbers of individuals with diabetes, prediabetes, dysglycaemia, hypertension, obesity, and dyslipidaemia. Projection estimates were calculated among adults aged 20 years or older by the direct method to the 2021 India Census projected population. For the direct method, we used the region, age, and sex standardised prevalence obtained from the pooled results from the 31 states and union territories and multiplied it by the 2021 India Census projected population. α was set at 0·05 to determine statistical significance. To analyse data, we used SAS (version 9.4).

Role of the funding source

This study was funded by Indian Council of Medical Research and Department of Health Research, Ministry of Health and Family Welfare, Government of India. Some members of the funding source provided scientific inputs for the study, were involved in quality control, and helped to revise the manuscript.

Results

Overall, from all 31 states and union territories, 119 022 individuals were assessed for eligibility, of whom 113 043 individuals (33 537 from urban areas and 79 506 from rural areas) participated in the study (response rate: 95·0%) between Oct 18, 2008 and Dec 17, 2020. A total of 5979 individuals were not included in the study due to the following reasons: refused to participate (n=3780), not available (n=1369), or their house was locked (n=830) during the survey period.

We have included data from the following numbers of individuals for analysis of various cardiometabolic risk factors: diabetes or prediabetes—107 119; hypertension—111 439; generalised obesity—110 368; abdominal obesity—108 665; and dyslipidaemia—18 492 (available only in every fifth participant).

The mean age of the 113 043 individuals studied was 43·0 years, 52 602 (46·5%) were male, and 30 119 (weighted proportion 26·9%) had no formal education (table 1). Compared with their rural counterparts, urban residents were significantly younger, and had higher BMI, waist circumference, diastolic blood pressure, and educational attainment. The glycaemic (urban *vs* rural: fasting blood glucose 105 mg/dL *vs* 100 mg/dL, p<0·0001) and lipid parameters (total cholesterol 175 mg/dL *vs* 167 mg/dL, p<0·0001; LDL cholesterol 104 mg/dL *vs* 99 mg/dL, p<0·0001) were significantly higher among urban residents. Males were older, were better educated, and had lower BMI but higher blood pressure, triglycerides, and HbA_{1c} compared with females.

The overall weighted prevalence of diabetes by OGTT was 11·4% (95% CI 10·2–12·5; 10 151 of 107 119 individuals), with significantly higher prevalence in urban compared with rural areas (urban areas 4272 [16·4%] of 31 560 individuals *vs* rural areas 5879 [8·9%] of 75 559, p<0·0001), and among males compared with females (males 4978 [12·1%] of 49 706 individuals *vs* females 5173 [10·7%] of 57 413, p<0·0001) (table 2). The weighted prevalence of diabetes was higher when diagnosed using HbA_{1c} (13·3% [10·4–16·2]; 2082 of 18 090 individuals) and highest when using a combination of OGTT and HbA_{1c} (21·1% [17·6–24·5]; 3368 of 18 366 individuals; appendix p 18).

The weighted prevalence of IFG (by WHO cutoff) was 10·1% (95% CI 9·0–11·2; 10 449 of 107 119 individuals) and that of IGT was 3·3% (2·6–4·0; 3276 of 107 119 individuals). IFG prevalence was significantly higher among females and IGT among males. Prevalence of IFG and IGT was similar in urban and rural areas. The overall weighted prevalence of prediabetes was 15·3% (13·9–16·6; 15 496 of 107 119 individuals; table 2). Sensitivity analysis using the ADA criteria[21] for diagnosing IFG (ie, fasting glucose 100–125 mg/dL) demonstrated a nearly three-fold increase in prevalence of IFG to 27·6% (26·0–29·3; 29 073 of 107 119 individuals). Using the ADA criteria, the overall prevalence of prediabetes was 32·8% (31·1–34·6; 34 120 of 107 119 individuals; appendix p 15). The weighted prevalence of prediabetes by HbA_{1c} was 21·0% (17·5–24·6; 3561 of 18 090 individuals) and by using a combination of OGTT and HbA_{1c} was 26·6% (22·8–30·4; 4733 of 18 366 individuals; appendix p 18).

	Urban (n=33 537)	Rural (n=79 506)	p value*	Male (n=52 602)	Female (n=60 441)	p value†	Overall (n=113 043)
Age, years	42·1 (0·15)	43·4 (0·10)	p<0·0001	44·0 (0·11)	42·1 (0·09)	p<0·0001	43·0 (0·09)
Education							
No formal schooling	16·2% (15·3–17·1)	32·0% (31·2–32·7	p<0·0001	17·2% (16·6–17·8)	35·3% (34·5–36·0)	p<0·0001	26·9% (26·3–27·5)
Primary school, high school, or higher secondary school	64·4% (63·4–65·3)	60·3% (59·6–61·0)	p<0·0001	67·5% (66·8–68·1)	56·6% (55·9–57·3)	p<0·0001	61·6% (61·1–62·2)
Technical, undergraduate, or postgraduate education	19·4% (18·3–20·5)	7·7% (7·3–8·1)	p<0·0001	15·3% (14·7–15·9)	8·1% (7·7–8·5)	p<0·0001	11·5% (11·0–11·9)
Anthropometry							
BMI, kg/m²	24·0 (0·06)	22·2 (0·03)	p<0·0001	22·5 (0·03)	23·1 (0·04)	p<0·0001	22·8 (0·03)
Waist circumference, cm	84·3 (0·17)	79·5 (0·11)	p<0·0001	82·5 (0·10)	79·8 (0·11)	p<0·0001	81·1 (0·10)
Blood pressure							
Systolic blood pressure, mm Hg	129 (0·24)	129 (0·15)	p=0·054	131 (0·14)	127 (0·15)	p<0·0001	129 (0·13)
Diastolic blood pressure, mm Hg	82 (0·15)	81 (0·09)	p<0·0001	82 (0·09)	80 (0·08)	p<0·0001	81 (0·07)
Glycaemic parameters							
Fasting blood glucose (mg/dL)	105 (0·34)	100 (0·18)	p<0·0001	101 (0·21)	102 (0·21)	p=0·016	102 (0·17)
2-h post-glucose blood glucose, mg/dL	123 (0·39)	118 (0·28)	p<0·0001	119 (0·29)	120 (0·26)	p=0·013	120 (0·23)
HbA_{1c}‡	5·8% (0·03)	5·5% (0·01)	p<0·0001	5·7% (0·02)	5·6% (0·02)	p=0·27	5·6% (0·01)
Lipid parameters‡							
Total serum cholesterol, mg/dL	175 (0·78)	167 (0·53)	p<0·0001	169 (0·57)	170 (0·59)	p<0·0001	170 (0·44)
Serum triglycerides, mg/dL	149 (2·05)	136 (1·07)	p<0·0001	153 (1·41)	128 (1·29)	p<0·0001	140 (0·98)
Serum HDL cholesterol, mg/dL	40·8 (0·22)	41·1 (0·14)	p=0·0011	39·7 (0·16)	42·3 (0·15)	p<0·0001	41·0 (0·12)
Serum LDL cholesterol, mg/dL	104 (0·70)	99 (0·43)	p<0·0001	99 (0·47)	103 (0·52)	p<0·0001	101 (0·37)
Total cholesterol to HDL cholesterol ratio	4·56 (0·03)	4·28 (0·02)	p<0·0001	4·52 (0·02)	4·21 (0·02)	p<0·0001	4·36 (0·02)

Data are mean (SE) or percentage (95% CI). *For urban *vs* rural residence. †For male *vs* female. ‡Data available only in a subset of the population (data collected in every fifth individual, HbA_{1c}, n=18 090; lipid parameters, n=18 492).

Table 1: Baseline characteristics of the study population

The overall weighted prevalence of dysglycaemia (by OGTT) was 26·6% (95% CI 25·0–28·3; 25 647 of 107 119 individuals) using the WHO criteria (table 2) and 44·2% (42·3–46·0; 44 271 of 107 119 individuals) using the ADA criteria (appendix p 15). The weighted prevalence of dysglycaemia by HbA_{1c} was 34·3% (30·3–38·4; 5643 of 18 090 individuals) and by using a combination of OGTT (by WHO criteria) and HbA_{1c} was 47·7% (43·5–51·8; 8101 of 18 366 individuals; appendix p 18).

The weighted prevalence of hypertension was 35·5% (95% CI 33·8–37·3; 35 172 of 111 439 individuals), which was higher in urban areas and among males. When sensitivity analysis was done using American College of Cardiology/American Heart Association (ACC/AHA) criteria[31] (≥130/80 mm Hg), the prevalence of hypertension nearly doubled to 66·3% (64·6–67·9%; 69 702 of 111 439 individuals). Generalised obesity and abdominal obesity were present in 28·6% (26·9–30·3; 29 861 of 110 368 individuals) and 39·5% (37·7–41·4; 40 121 of 108 665 individuals) of the population, respectively. Dyslipidaemia was found in 81·2% (77·9–84·5; 14 895 of 18 492 individuals), mainly driven by low HDL cholesterol (66·9%; 62·9–70·9; 12 411 of 18 492 individuals). Dyslipidaemia and generalised and abdominal obesity were significantly higher among urban compared with rural residents. Generalised obesity was significantly higher in females. Of the lipid parameters, only hypertriglyceridaemia was significantly higher in males, while hypercholesterolaemia, low HDL cholesterol, and high LDL cholesterol were significantly higher in females.

The state-wise weighted prevalence of diabetes ranged from 4·8% (154 of 3421 individuals; in Uttar Pradesh) to 26·4% (886 of 3744 individuals; in Goa) and that of prediabetes from 6·8% (236 of 4053 individuals) to 31·3% (1240 of 3925 individuals). Diabetes prevalence (figure 1A) was highest in the southern and northern regions of India, with urban areas having high prevalence throughout. The central and northeastern regions had lower prevalence. Conversely, prevalence of prediabetes (figure 1B) was highest in the central and northern regions of India and lowest in Punjab, Jharkhand, and some parts of the northeastern region. The prevalence of prediabetes was not significantly different between urban and rural areas. The ratio of diabetes to prediabetes was 1:2 or less in Arunachal Pradesh, Bihar, Madhya Pradesh, Meghalaya, Chhattisgarh, Rajasthan, Sikkim, and Uttar Pradesh (most of which are states with a lower human development index). The ratio was 1:1 or more in Chandigarh, Goa, Delhi, Kerala, Mizoram, Puducherry, Punjab, and Tamil Nadu (all states with a high human development index; appendix pp 19–22).

	Urban (n=33 537)	Rural (n=79 506)	p value*	Male (n=52 602)	Female (n=60 441)	p value†	Overall (n=113 043)
Dysglycaemia (diabetes and prediabetes)	9055/31 560 (31·8%; 29·4–34·2)	16 592/75 559 (24·1%; 22·7–25·4)	p<0·0001	11 948/49 706 (27·2%; 25·4–28·9)	13 699/57 413 (26·2%; 24·6–27·7)	p<0·0001	25 647/107 119 (26·6%; 25·0–28·3)
Diabetes	4272/31 560 (16·4%; 14·6–18·2)	5879/75 559 (8·9%; 8·1–9·7)	p<0·0001	4978/49 706 (12·1%; 10·9–13·3)	5173/57 413 (10·7%; 9·6–11·8)	p<0·0001	10 151/107 119 (11·4%; 10·2–12·5)
Prediabetes	4783/31 560 (15·4%; 13·6–17·2)	10 713/75 559 (15·2%; 14·1–16·3)	p=0·41	6970/49 706 (15·0%; 13·6–16·5)	8526/57 413 (15·5%; 14·2–16·7)	p=0·023	15 496/107 119 (15·3%; 13·9–16·6)
Impaired fasting glucose	3138/31 560 (9·9%; 8·4–11·5)	7311/75 559 (10·1%; 9·3–11·0)	p=0·32	4525/49 706 (9·4%; 8·3–10·6)	5924/57 413 (10·7%; 9·6–11·7)	p<0·0001	10 449/107 119 (10·1%; 9·0–11·2)
Impaired glucose tolerance	1030/31 560 (3·4%; 2·5–4·3)	2246/75 559 (3·3%; 2·7–3·8)	p=0·41	1668/49 706 (3·7%; 3·0–4·5)	1608/57 413 (2·9%; 2·3–3·5)	p<0·0001	3276/107 119 (3·3%; 2·6–4·0)
Hypertension	11 588/33 063 (40·7%; 38·2–43·2)	23 584/78 376 (33%; 31·6–34·3)	p<0·0001	17 768/51 801 (38·7%; 36·8–40·7)	17 404/59 639 (32·6%; 31·0–34·2)	p<0·0001	35 172/111 439 (35·5%; 33·8–37·3)
Generalised obesity (BMI ≥25 kg/m²)	12 135/32 784 (39·6%; 37·1–42·1)	17 726/77 584 (23·1%; 21·8–24·4)	p<0·0001	12 311/51 784 (25·4%; 23·7–27·1)	17 550/58 584 (31·6%; 30·0–33·3)	p<0·0001	29 861/110 368 (28·6%; 26·9–30·3)
Abdominal obesity (waist ≥90 cm [males], ≥80 cm [females])	15 566/32 293 (51·6%; 49·0–54·1)	24 555/76 372 (33·5%; 32·0–34·9)	p<0·0001	13 370/51 800 (28·8%; 27·0–30·7)	26 751/56 865 (49·6%; 47·8–51·4)	p<0·0001	40 121/108 665 (39·5%; 37·7–41·4)
Dyslipidaemia‡	4493/5415 (82·9%; 78·3–87·5)	10 402/13 077 (80·3%; 77·7–83·0)	p<0·0001	6954/9283 (75·1%; 71·3–79·0)	7941/9209 (86·8%; 84·0–89·6)	p<0·0001	14 895/18 492 (81·2%; 77·9–84·5)
Hypercholesterolaemia (≥200 mg/dL)	1367/5415 (27·4%; 21·6–33·3)	2701/13 077 (22·3%; 19·5–25·0)	p<0·0001	2023/9283 (23·2%; 19·5–26·9)	2045/9209 (24·8%; 20·9–28·6)	p=0·011	4068/18 492 (24·0%; 20·2–27·8)
Hypertriglyceridaemia (≥150 mg/dL)	1834/5415 (36·4%; 30·6–42·1)	3851/13 077 (30·0% (27·0–33·0)	p<0·0001	3347/9283 (37·5%; 33·4–41·6)	2338/9209 (27·1%; 23·4–30·8)	p<0·0001	5685/18 492 (32·1%; 28·2–36·0)
Low HDL cholesterol (<40 mg/dL [males]; <50 mg/dL [females])	3751/5415 (68·1%; 62·4–73·8)	8660/13 077 (66·3%; 63·1–69·4)	p=0·018	5298/9283 (56·3%; 51·9–60·7)	7113/9209 (76·8%; 73·2–80·4)	p<0·0001	12 411/18 492 (66·9%; 62·9–70·9)
High LDL cholesterol (≥130 mg/dL)	1191/5415 (23·5%; 17·9–29·1)	2369/13 077 (19·6%; 16·9–22·3)	p<0·0001	1690/9283 (19·4%; 15·9–22·9)	1870/9209 (22·3%; 18·6–26·1)	p<0·0001	3560/18 492 (20·9%; 17·3–24·5)

Data are n/N (weighted prevalence %; 95% CI). The absolute numbers (n/N) do not correspond exactly to the percentages, because the percentages represent weighted prevalences. *For urban vs rural residence. †For male vs female. ‡Data available only in a subset of the population (data collected in every fifth individual, n=18 492; urban, n=5415; rural, n=13 077; male, n=9283; female, n=9209).

Table 2: **Weighted prevalence of cardiometabolic risk factors among the study population**

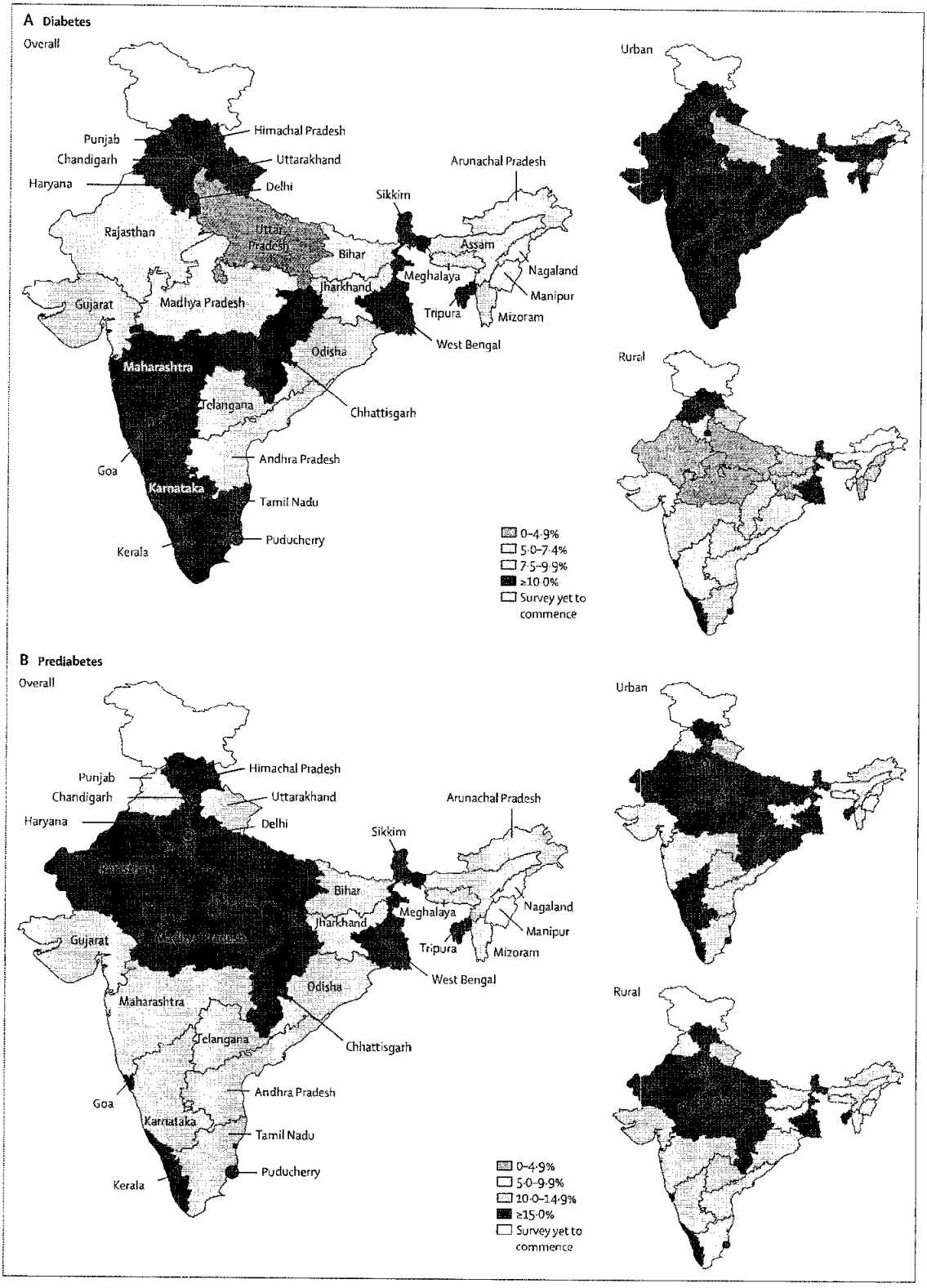
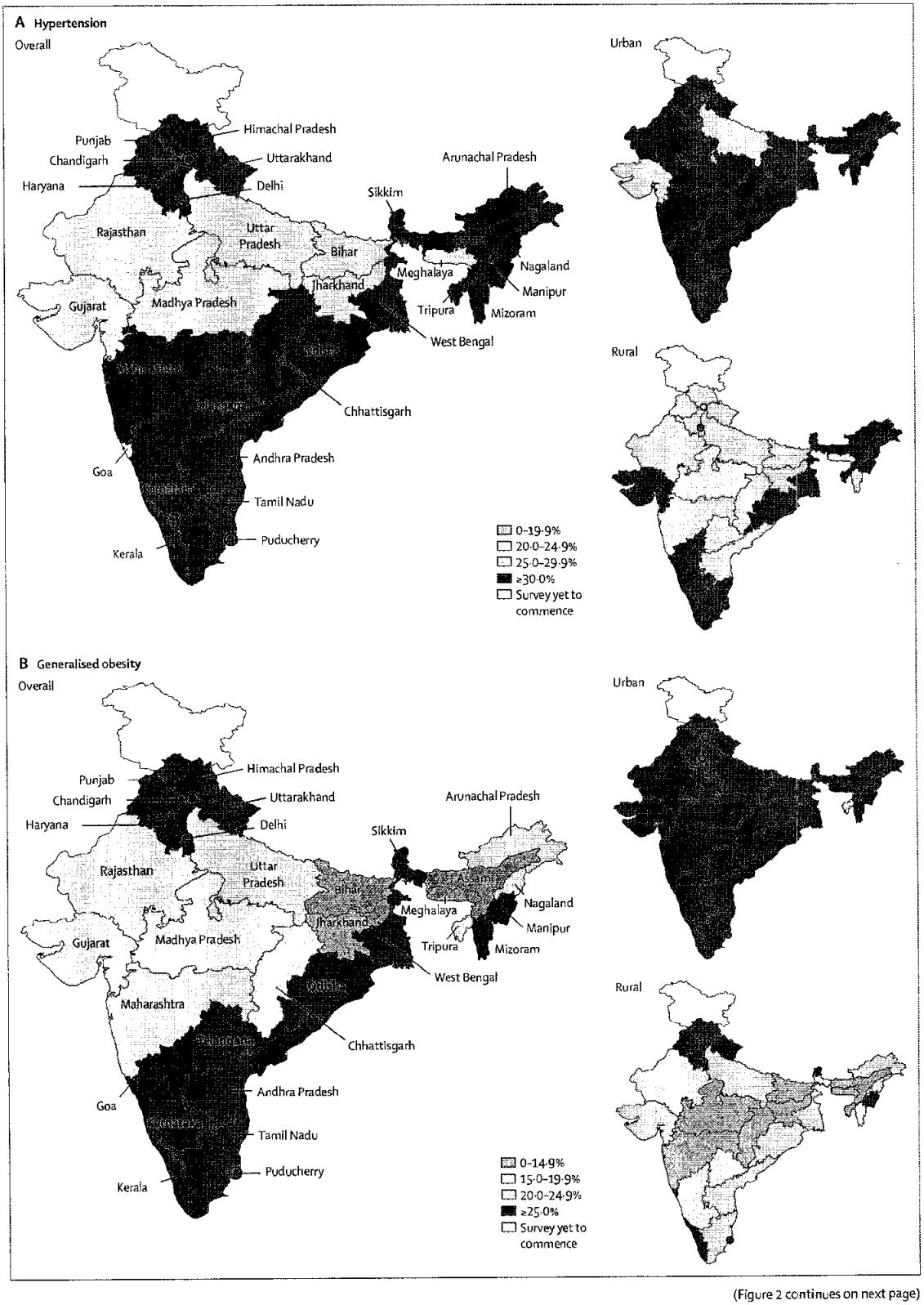


Figure 1: **Overall and area-wise weighted prevalence of diabetes and prediabetes**
(A) Diabetes. (B) Prediabetes.



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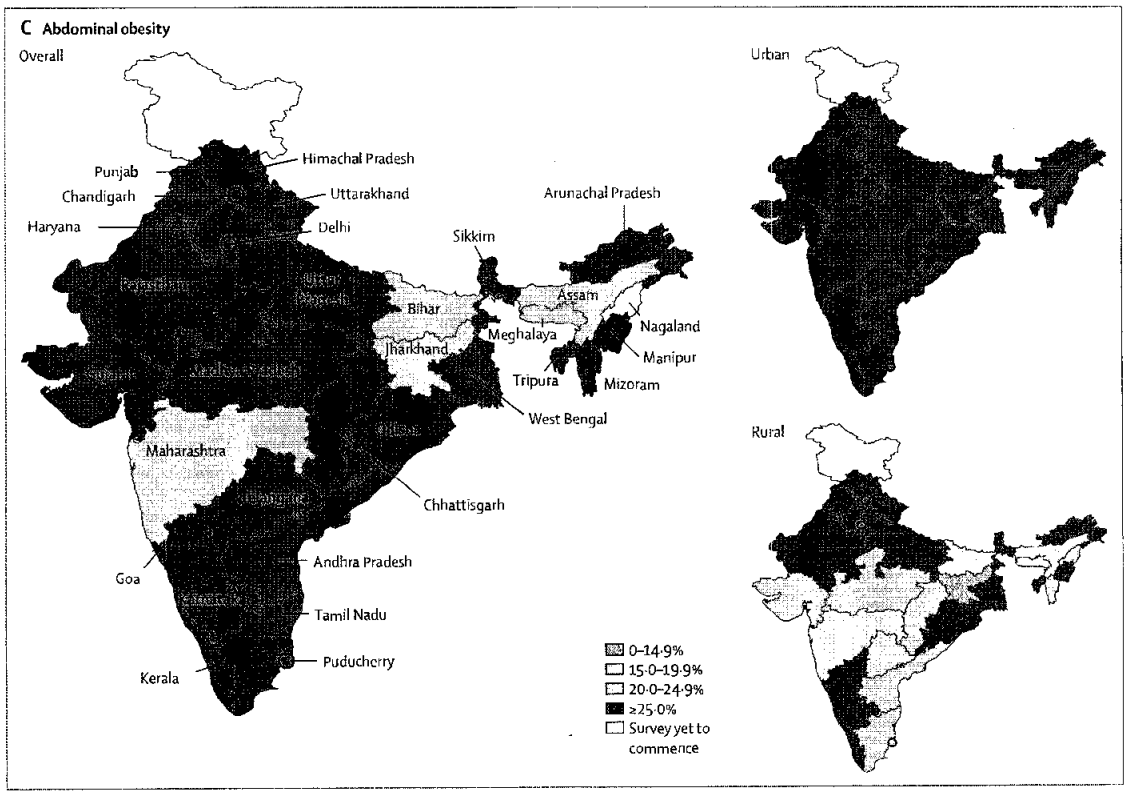


Figure 2: **Overall and area-wise weighted prevalence of hypertension, generalised obesity, and abdominal obesity**
(A) Hypertension. (B) Generalised obesity. (C) Abdominal obesity.

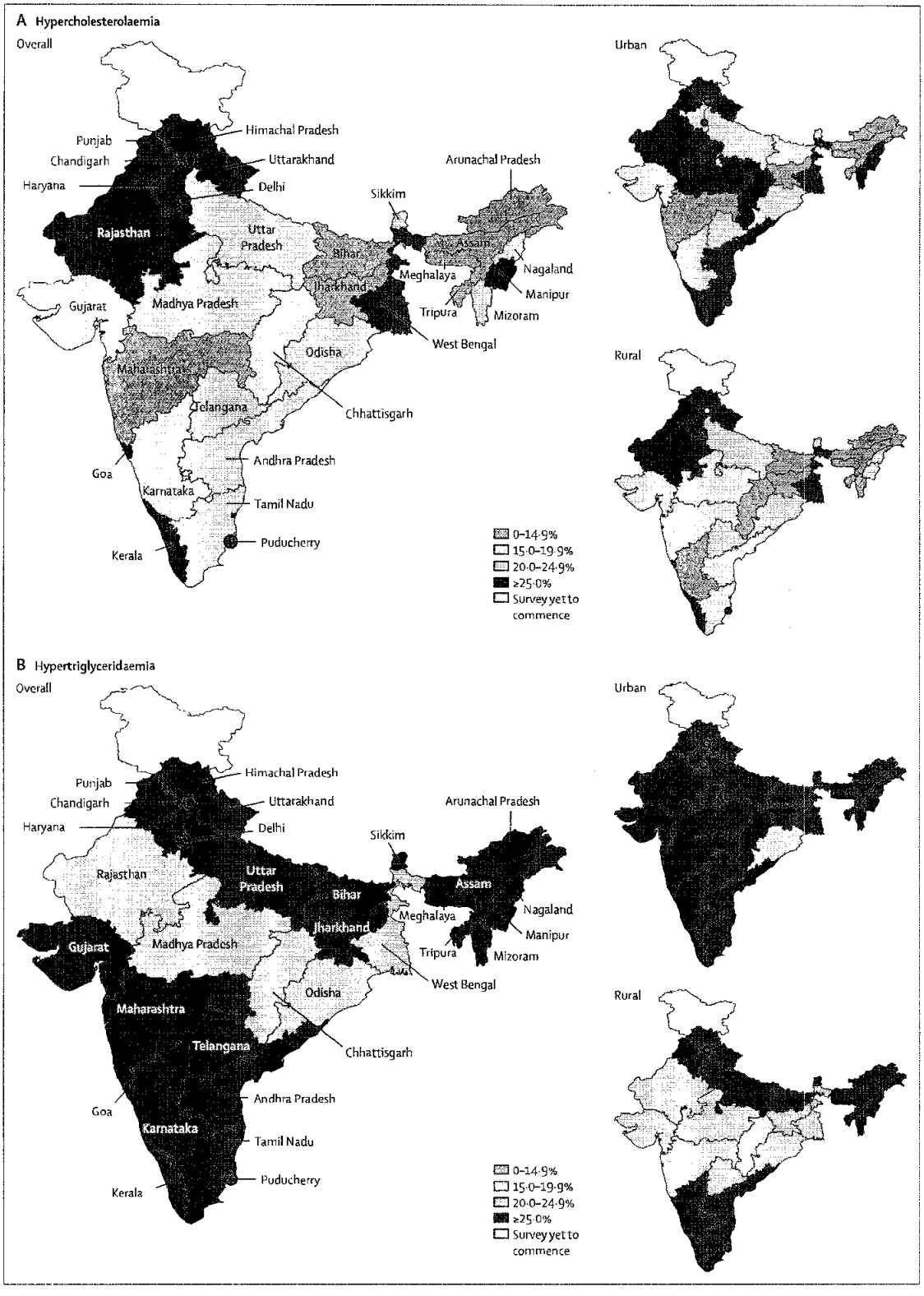
The state-wise weighted prevalence of hypertension ranged from 24·3% (851 of 3641 individuals) to 51·8% (1644 of 3709 individuals), generalised obesity from 11·6% (377 of 3219 individuals) to 53·3% (1741 of 3790 individuals), and abdominal obesity from 18·4% (541 of 3212 individuals) to 61·2% (1958 of 3781 individuals; appendix pp 19–20). Weighted prevalence of hypercholesterolaemia ranged from 4·6% (20 of 411 individuals) to 50·3% (289 of 579 individuals), hypertriglyceridaemia from 21·2% (135 of 661 individuals) to 47·9% (275 of 613 individuals), low HDL cholesterol from 51·8% (374 of 627 individuals) to 83·1% (488 of 650 individuals), and high LDL cholesterol from 3·2% (14 of 411 individuals) to 52·1% (303 of 579 individuals; appendix pp 21–22).

Overall, hypertension was highly prevalent throughout the country except in the central region, more so in the urban areas (figure 2A). High prevalence rates of both generalised and abdominal obesity were observed in urban areas compared with rural areas (figures 2B, C). Overall, abdominal obesity was high in all the regions of India, while generalised obesity was more prevalent in the south followed by the northern and eastern regions. The prevalence of hypertriglyceridaemia (figure 3B) and low HDL cholesterol (figure 3C) was high in all the regions of India with very little urban–rural difference, whereas hypercholesterolaemia (figure 3A) and high LDL cholesterol (figure 3D) showed wide interstate and inter-regional variability, with highest prevalence in the northern region, Kerala, and Goa.

Figure 4 presents the 2021 projections for cardiometabolic risk factors for the entire country. We estimated that in 2021, 101 million people had diabetes, and the number with prediabetes was 136 million. About 315 million people in India had hypertension, 254 million had generalised obesity, and 351 million had abdominal obesity. In addition, 213 million people had hypercholesterolaemia and 185 million had high LDL cholesterol.

Discussion

This report from the ICMR-INDIAB study highlights the enormous burden of NCDs faced by India. Our estimates of the prevalence of diabetes and prediabetes in India (101 million and 136 million, respectively) are much higher than earlier reported figures,[32] which have been collated from several sources, including an earlier report from ICMR-INDIAB.[10] This earlier report, however, included only 15 states of the country



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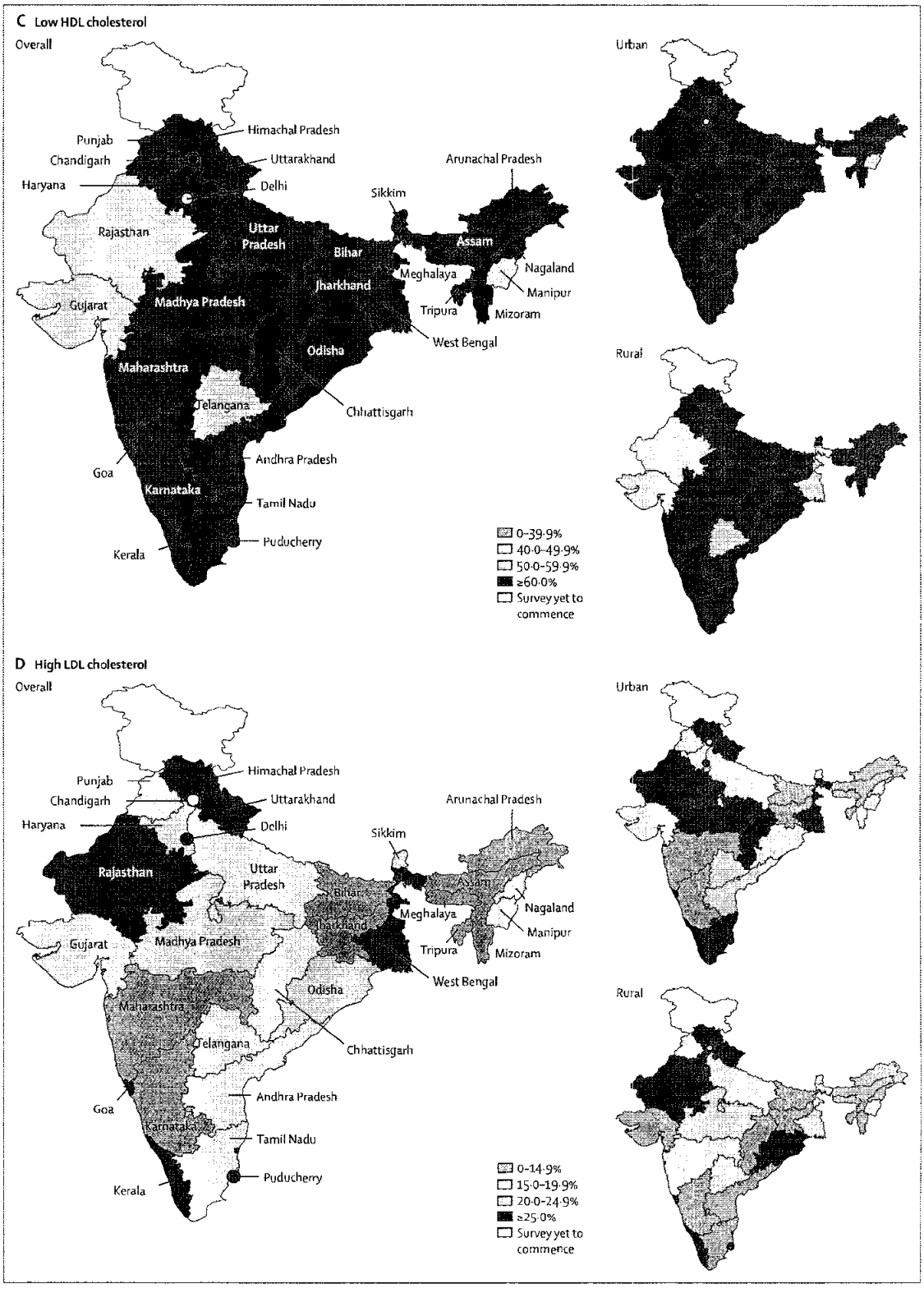
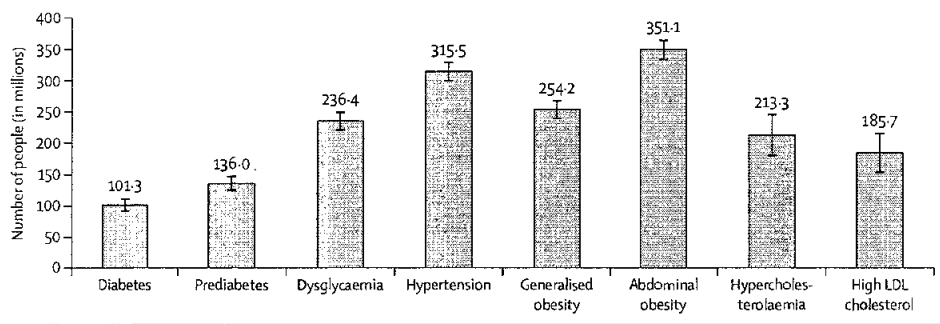


Figure 3: **Overall and area-wise weighted prevalence of hypercholesterolaemia, hypertriglyceridaemia, low HDL cholesterol, and high LDL cholesterol**
(A) Hypercholesterolaemia. (B) Hypertriglyceridaemia. (C) Low HDL cholesterol. (D) High LDL cholesterol.



	Projections (in millions)	95% CI
Diabetes	101·3	90·7–111·1
Prediabetes	136·0	123·5–147·5
Dysglycaemia	236·4	222·2–251·5
Hypertension	315·5	300·4–331·5
Generalised obesity	254·2	239·1–269·3
Abdominal obesity	351·1	335·1–367·9
Hypercholesterolaemia	213·3	179·5–247·1
High LDL cholesterol	185·7	153·8–217·7

Figure 4: Projections for metabolic disease prevalence in India

(including seven of the northeastern states with low prevalence of diabetes) and had not yet sampled some of the more socioeconomically developed states of India (eg, Kerala, Goa, and Puducherry), which could have led to the reported prevalence rates being lower.[10] The present report, on the other hand, uses data from all states of India which have been age-standardised for the current time period and, therefore, we believe that our estimates are a more accurate reflection of the actual numbers.

We also found that using HbA_{1c} in addition to OGTT for diagnosis led to nearly half the population being diagnosed with dysglycaemia. This has been reported in earlier studies also and has been attributed to the high prevalence of iron-deficiency anaemia in India.[33,34] National guidelines do not, therefore, recommend the use of HbA_{1c} as the sole diagnostic criterion for diabetes and prediabetes.[35] Similarly, use of the ADA cutoffs led to a near doubling of prevalence of prediabetes compared with the WHO criteria. Considering the relatively low risks of progression to diabetes and of cardiovascular disease among individuals diagnosed with prediabetes using the ADA criteria compared with the less stringent WHO criteria,[36] the Indian National Guidelines have recommended the use of the latter for diagnosing prediabetes.[35] We have therefore used the OGTT and the WHO criteria for estimating the prevalence of diabetes and prediabetes in India.

Our results also emphasise the interstate and inter-regional variations in diabetes prevalence in India, a phenomenon that has already been reported in earlier studies on NCDs from India, such as the Annual Health Survey and the District-Level Household Survey conducted between 2012 and 2014,[6] the NFHS-5 conducted between 2019 and 2021,[28] and the India State-Level Disease Burden Initiative published in 2018.[3]

With regard to other metabolic risk factors, we document the presence of dyslipidaemia in more than 80%, hypertension in more than one-third (nearly two-thirds if the ACC/AHA criteria are used), and obesity in nearly a third of the population. It is of interest that low HDL cholesterol accounted for the majority of the dyslipidaemia burden in the country, with an overall prevalence of 66·9%. Previous research has shown that low concentrations of HDL cholesterol are more common in Asian Indians or south Asians compared with other ethnic groups.[37–39] Gupta and colleagues[40] reported low HDL cholesterol in 54·9% of Asian Indian men and 64·4% women,[38] and an analysis from the INTERHEART study reported that low HDL cholesterol was present in over 80% of the Asian Indian participants studied,[41] a number comparable to our results. This phenomenon appears to be a component of the Asian Indian phenotype, which also includes low adiponectin concentrations, increased visceral fat, increased waist circumference, and increased insulin resistance. Both low HDL cholesterol and high triglycerides were uniformly prevalent across India in our study. On the other hand, the prevalence of high LDL cholesterol showed significant interstate variation. Whether ethnic differences or dietary patterns (eg, different cooking oils used) are responsible for the heterogeneity in hypercholesterolaemia needs further elucidation, and these studies are of particular importance given the pre-eminent role of LDL cholesterol in cardiovascular risk.

Our results, in general, are in line with those of other recent large studies on cardiometabolic risk factors in India. The prevalence of diabetes was 7·5% and that of hypertension 25·3% in a pooled analysis of data from the Annual Health Survey and the District-Level Household Survey.[6] Another recent analysis of the NFHS-5 data reported a diabetes prevalence of 6·5%.[42] However, this analysis used self-report and random blood glucose measurements for diagnosis of diabetes, with less than 1·5% of the population having a fasting capillary sample. NFHS-5 also showed a lower prevalence of obesity compared with our findings, perhaps due to the higher cutoffs used, and a lower prevalence of hypertension, probably on account of the younger age of the population studied.[28] Other large studies on the prevalence of hypertension in India have reported numbers similar to our results.[43,44] There is also sufficient evidence for an increasing trend in the prevalence of these risk factors in India; a series of five cross-sectional epidemiological studies from Jaipur,

India showed a secular trend of increase in BMI, hypertension, and total and non-HDL cholesterol over a 20-year period,[5,45] while clear increases in diabetes prevalence have been reported in serial studies from different parts of India using uniform diagnostic criteria.[46,47]

These results have multiple implications for the planning and provision of health care in India. There is a very high prevalence of diabetes and related NCDs in the country, which translates to a large population of individuals at risk of not only cardiovascular disease but also of chronic complications of diabetes such as kidney, foot, and eye disease, the costs of treating which are crippling to the individual, society, and country as a whole. Moreover, the high prevalence rates of obesity and prediabetes across the country (even in regions where the prevalence of diabetes is currently low) suggest that the epidemic will continue to accelerate, especially since Asian Indians tend to develop diabetes at lower levels of obesity, and to progress faster from prediabetes to diabetes compared with white Caucasians.[48,49] In particular, the uniformly high prevalence of prediabetes in rural areas is of grave concern since these areas, in general, lack the infrastructure to care for increasing numbers of people with diabetes and its complications.

Prevention, early diagnosis, and prompt treatment of hyperglycaemia, hypertension, and dyslipidaemia are the cornerstones of preventing morbidity and mortality due to cardiovascular disease and other chronic complications of diabetes. Unfortunately, only around 7% of people with previously diagnosed diabetes in India meet treatment targets for blood glucose, lipids, and blood pressure,[15] and the proportion is likely to be even lower among those with undiagnosed diabetes. Therefore, there needs to be a thorough reorientation of health-care priorities towards caring for individuals with metabolic NCDs, particularly in states where the disease burden is found to be high. As a significant proportion of India's population (particularly in rural areas) depends on the government for provision of health care, strengthening the public health-care system is an essential step towards improving diabetes and NCD care in these regions. The incorporation of NCD detection and control into the primary health-care system as part of the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (recently renamed as the National Programme for Prevention and Control of Non-Communicable Diseases [NP-NCD]),[50] and the provision of NCD care through setting up of Health and Wellness Centres under the Ayushman Bharat scheme by the Government of India, are therefore steps in the right direction.

For the Ayushman Bharat scheme see https://ab-hwc.nhp.gov.in/

Provision of health care is primarily the responsibility of state governments in India. As different states in India are at different stages in the trajectory of the diabetes pandemic, state-specific strategies are the need of the hour. States with a high prevalence of diabetes will need to put in place systems to ensure optimal risk factor control, so as to effectively prevent long-term complications. On the other hand, the ratio of diabetes to prediabetes is less than 1:2 in many of the less economically developed states, suggesting that these states can expect large increases in the prevalence of diabetes in the near future. Urgent measures are indicated to prevent or delay such an eventuality, since these states have limited availability of resources for provision of optimal diabetes care. There needs to be a focus on evidence-based approaches to prevent the progression of prediabetes to diabetes or even to reverse it to normal in these states.

There were multiple challenges in implementing such a large nationwide study on diabetes and other metabolic NCDs in India. These can be broadly classified under manpower and team cohesion, religious and cultural misconceptions, topography and climatic conditions, transporting biological samples, obtaining permissions, linguistic barriers, and safety and security threats. In each region, local manpower was recruited with the help of the state principal investigator. Field data collection challenges such as religious and cultural misconceptions among the participants were addressed with the help of religious leaders and community elders from the local communities in the surveyed regions. Participant unavailability and unwillingness to spend time were overcome through multiple visits to the primary sampling units to collect the data. Linguistic barriers were overcome through translating the study documents into 15 vernacular languages. The strategies devised with the assistance of the state principal investigators and health authorities enabled successful implementation of the study, obtaining response rates of more than 90% in every state.

Our study has a few limitations. Since the study is cross-sectional, causal implications cannot be drawn from it. The use of CBG, which has a greater coefficient of variation than venous plasma, is another limitation of this study. However, we have earlier shown good correlation between CBG and venous plasma estimations.[51] Also, our methodological approach did not allow us to differentiate between type 1 and type 2 diabetes. A further limitation of this study is that different phases of the study were conducted at different times, which is inevitable when sampling such a large country. To overcome this limitation, the current prevalence of cardiometabolic risk factors was estimated in each state by doing weighted analysis accounting for region-specific and sex-specific changes in age structure using 2019 population estimate information from NFHS-5. Nevertheless, our estimates did not account for potential long-term changes in lifestyle-based risk factors for diabetes. In particular, this means that states

measured in phases 1–3 might have even higher metabolic disease prevalence than what is reported here. The major strengths of the current study are that it was performed on a nationally representative sample that was geographically and ethnically diverse, and truly representative of the regions studied. This study is perhaps the first to specifically look at the prevalence of metabolic NCDs by studying all states and union territories of India. Compared with other recent large surveys, our study used robust methods for diagnosis of diabetes and prediabetes, such fasting blood glucose and OGTT. Moreover, HbA_{1c} was available in a subset of the population, which adds to the validity of the diagnosis. The learnings from this study with respect to field-level operational challenges and the means of overcoming them will provide impetus and direction to future nationwide epidemiological studies of such magnitude.

In summary, this report on India's metabolic health from the ICMR-INDIAB study reiterates the significant NCD burden in the country. While the diabetes epidemic seems to have peaked in some of the more developed states, most of the less developed states are still in the initial take-off phase. The prevalence of other cardiometabolic risk factors such as obesity, hypertension, and dyslipidaemia is uniformly high across the country, particularly in the urban areas. The focus should therefore be on implementing interventions to minimise the progression of prediabetes to diabetes in states where the diabetes epidemic has yet to peak, and providing optimal care to ensure comprehensive risk factor reduction in individuals with diabetes so as to prevent complications in those states where the epidemic has already stabilised.

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Contributors

RMA, RU, and VM conceived the study, designed it, and were involved in implementation of the study, training the team, designing quality assurance measures, and interpretation of the data. MD and RP were involved in the design and coordination of the study and interpretation of the data. NT, AKD, SB, PKJ, HKD, AK, VKD, AB, PVR, AD, SK, AG, RL, SVM, and SC were responsible for the supervision of the study in their respective states. SJ, TK, and RSD provided scientific input for the study, were involved in the quality control, and helped to revise the report. NE helped in the field coordination of the study. UV and RS were responsible for data management and statistical analyses. RMA, RU, MD, RP, and VM drafted the manuscript and all authors contributed to the critical revision of the manuscript for important intellectual content. RMA and VM take full responsibility for the overall content of this work. RMA is the guarantor of this work and, as such, takes responsibility for the integrity of the data and the accuracy of the data analysis. RMA, RU, MD, RP, UV, RS, and VM had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication. MD, RP, UV, and RS accessed and verified the data.

Declaration of interests

We declare no competing interests.

Data sharing

Raw data are available on reasonable request to the corresponding author. All data relevant to the study are included in this Article or the appendix.

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White Rice Intake and Incident Diabetes: A Study of 132,373 Participants in 21 Countries

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OBJECTIVE

Previous prospective studies on the association of white rice intake with incident diabetes have shown contradictory results but were conducted in single countries and predominantly in Asia. We report on the association of white rice with risk of diabetes in the multinational Prospective Urban Rural Epidemiology (PURE) study.

RESEARCH DESIGN AND METHODS

Data on 132,373 individuals aged 35–70 years from 21 countries were analyzed. White rice consumption (cooked) was categorized as <150, ≥150 to <300, ≥300 to <450, and ≥450 g/day, based on one cup of cooked rice = 150 g. The primary outcome was incident diabetes. Hazard ratios (HRs) were calculated using a multivariable Cox frailty model.

RESULTS

During a mean follow-up period of 9.5 years, 6,129 individuals without baseline diabetes developed incident diabetes. In the overall cohort, higher intake of white rice (≥450 g/day compared with <150 g/day) was associated with increased risk of diabetes (HR 1.20; 95% CI 1.02–1.40; *P* for trend = 0.003). However, the highest risk was seen in South Asia (HR 1.61; 95% CI 1.13–2.30; *P* for trend = 0.02), followed by other regions of the world (which included South East Asia, Middle East, South America, North America, Europe, and Africa) (HR 1.41; 95% CI 1.08–1.86; *P* for trend = 0.01), while in China there was no significant association (HR 1.04; 95% CI 0.77–1.40; *P* for trend = 0.38).

CONCLUSIONS

Higher consumption of white rice is associated with an increased risk of incident diabetes with the strongest association being observed in South Asia, while in other regions, a modest, nonsignificant association was seen.

Globally, 425 million people currently have diabetes and this number is expected to increase to 629 million by 2045 (1). China and India, two countries in Asia where rice is the staple food, are also the top two countries in terms of the number of people with diabetes in the world (2). Rapid urbanization and economic development, especially in developing countries of the world, have led to a dramatic change in nutrition and dietary intake as well as in physical inactivity, both of which are related to the obesity and diabetes epidemics (3).

Carbohydrate forms 70–80% of the calories consumed in many South Asian countries (4). Till the early 1970s, most of the traditional diets, especially in India and some other Asian countries, were less milled or polished as it was manually hand

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pounded (5,6). Undermilled rice (2% degree of polishing) is nutritionally superior (higher in fiber, γ-oryzanol, other polyphenols, and vitamin E) than the fully milled white rice (7). The polishing process strips the grains of dietary fiber by removing the bran and alters the structure of the grain kernel (8). Interestingly, during the last four to five decades of replacing hand-pounded or undermilled rice with highly milled white rice, the prevalence of diabetes in urban areas in India increased from 2% in the 1970s to 25% in 2015 and in rural areas from 1% to 14–16% (9,10). Undoubtedly, this secular trend in the increase in the diabetes rates cannot be solely attributed to increased intake of polished white rice as several other diabetogenic factors (e.g., a marked decrease in physical activity [PA] and increase in obesity rates) also occurred during this period, due to the improved socioeconomic status and lifestyle modification of the people. Thus, rice (carbohydrate) consumption was possibly only one of the many factors contributing to the diabetes epidemic.

It is known that consumption of foods high in glycemic index (GI) and glycemic load (GL) leads to elevated postprandial blood glucose levels (11). A meta-analysis of cohort studies from Western countries showed that diets high in GI and GL, mostly from carbohydrate sources, were associated with higher risk of type 2 diabetes (12). In contrast, reports from a study conducted in eight European countries show that carbohydrate intake was not associated with diabetes risk (13).

Specifically, consumption of high amounts of white rice has been shown to increase the risk of diabetes in some studies (14–18) but not all (19–22). In their meta-analysis that pooled results from four studies in China, Japan, U.S., and Australia, Hu et al. (14) showed that each extra serving of white rice increased the risk for diabetes by 11%. By contrast, a large prospective cohort study of >45,000 participants from Singapore reported that higher consumption of white rice (above 500 g/day) did not substantially increase the risk of incident diabetes (19). Two different cohort studies from Iran also showed opposing results with one showing an increased risk while the other did not (21). Many of these studies were conducted in single countries and predominantly in Asia where consumption of white rice is higher than most other regions of the world. Our aim was to assess the association of white rice consumption with risk of diabetes in the large multiethnic, multinational Prospective Urban Rural Epidemiology (PURE) study with data on 132,373 individuals, enrolled from 21 counties, representing different geographies and continents.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The design and methods of the PURE study have been described previously (23,24). In this report, we include data on 132,373 individuals who had complete information on diet from 21 countries (Argentina, Bangladesh, Brazil, Canada, Chile, China, Colombia, India, Iran, Malaysia, occupied Palestine territory, Pakistan, Philippines, Poland, South Africa, Saudi Arabia, Sweden, Tanzania, Turkey, United Arab Emirates, and Zimbabwe) and who had completed at least one follow-up visit. Data were collected at the community, household, and individual levels using standardized questionnaires. Standard case-report forms were used to record data on health outcomes during follow-up. For the current analysis, we included all outcome events (i.e., incident diabetes) until 3 July 2019.

Procedures

In the PURE study, the participants' habitual food intake was recorded using country-specific validated food frequency questionnaires (FFQs) at baseline. For countries where a validated FFQ was not available, we developed and validated FFQs using a standard method (Supplementary Table 1). For validation of FFQ, we followed the Hu et al. (25) classification and classified starchy foods as refined grains (which included white rice when we started the PURE study in 2005) and whole grains. Deattenuated correlation coefficients of nutrient and food intake are presented in Supplementary Table 2. Participants were asked "during the past year, on average, how often have you consumed the following foods or drinks" and were asked to select their response from a list of food items. The format of the FFQ was the same for all countries, and the frequency of consumption of each food item varied

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from "never" to "more than six times per day." Standard serving sizes were assigned to each food item. The reported frequency of consumption for each food item was converted to daily intake and was then multiplied by the portion size (U.S. Department of Agriculture) to calculate the daily intake of that particular food. For the present analysis, rice was not included in the refined grains group, and it was computed separately. Mixed dishes prepared with rice (such as rice with beans, rice with vegetables, and so on) were disaggregated into their constituents, and a proportional weight was assigned to the white rice component, which was included in the white rice definition. The list of FFQ validation studies is provided in the supplementary material (Supplementary Table 1). Regarding types of rice, during the FFQ development, we collected a 24-h dietary recall from 100 participants residing in urban and rural areas of each country. The most commonly reported food items were compiled as a food list and predefined portion sizes were assigned for each food item. To ensure face and content validity of the short FFQ, two expert nutritionists (M.D. and a local nutritionist) checked the food list, and if nutrient-rich or discriminating foods were missing, those foods were added to the list. Then, they structured the food list as a short FFQ. Brown rice was reported as a commonly consumed food only in very few countries, e.g., Brazil, and hence it was not included in the list.

Outcome

The main outcome of this study was incident diabetes. Incident diabetes was deemed to have occurred in those who had no diabetes at baseline but subsequently, on follow-up, reported having a diagnosis of diabetes made by a physician, used oral antidiabetic agents or insulin, or had a documented fasting plasma glucose level of ≥7.0 mmol/L (126 mg/dL) (26). Of the 6,129 cases of incident diabetes, 5,563 (90.7%) were diagnosed based on documented evidence of the use of hypoglycemic agents or insulin and/or a documented elevated plasma glucose level, while in 566 (9.3%), it was based on self-reported diabetes.

Statistical Analysis

One cup of cooked white rice is roughly equivalent to 150 g, and hence white rice consumption was categorized into the following groups: <150 g/day, ≥150 to <300 g/day, ≥300 to <450 g/day, and ≥450 g/day (equivalent to less than one cup, one to two cups, two to three cups, and greater than three cups of cooked rice), with the lowest intake group, i.e., <150 g/day, used as the reference group. We estimated the median intakes of white rice consumption across these four different categories of white rice intake. We examined the association between white rice intake and incident diabetes in the entire PURE cohort and examined it separately in South Asia (India, Bangladesh, Pakistan), the rest of the world (South East Asia, Middle East, South America, North America/Europe, and Africa), and China.

We calculated the hazard ratios (HRs) for incident diabetes using multivariable Cox frailty model with random intercepts to account for center clustering (which also adjusts for region and country) and evaluated the association of white rice consumption with incident diabetes. Multivariable models were adjusted for age, sex, BMI, waist-to-hip ratio, family history of diabetes, smoking, location, wealth index, education, PA, energy intake, whole grains and refined grains, vegetable and fruit intake, and study center as random effect.

Location refers to urban/rural area. PA was assessed using the long form International Physical Activity Questionnaire and was calculated as a total of occupation, transportation, housework, and recreational activity reported in metabolic equivalents (MET) × minutes per week. Total PA was then categorized into physically inactive (<600 MET × minutes per week) or physically active (>600 MET × minutes per week), corresponding to <150 min per week or >150 min per week of moderate intensity PA.

RESULTS

Dietary information was recorded in 148,858 individuals in the PURE study. After excluding participants who had baseline diabetes (n = 16,485), 132,373 individuals were included in the analysis. The overall mean age of participants was 50 ± 9 years. Baseline characteristics of participants across regions and in South Asia, the rest of the world, and China are presented in Supplementary Tables 3 and 4.

Overall, the median (interquartile range [IQR]) consumption of white rice was 128 (36–400) g/day among all PURE participants. The highest median (IQR) consumption of white rice was seen in South Asia at 630 (103–952) g/day, followed by South East Asia at 239 (115–389) g/day, and China at 200 (57–600) g/day (Fig. 1).

Table 1 shows the characteristics of participants with different levels of white rice consumption. Those who consumed ≥450 vs. <150 g/day were younger, had

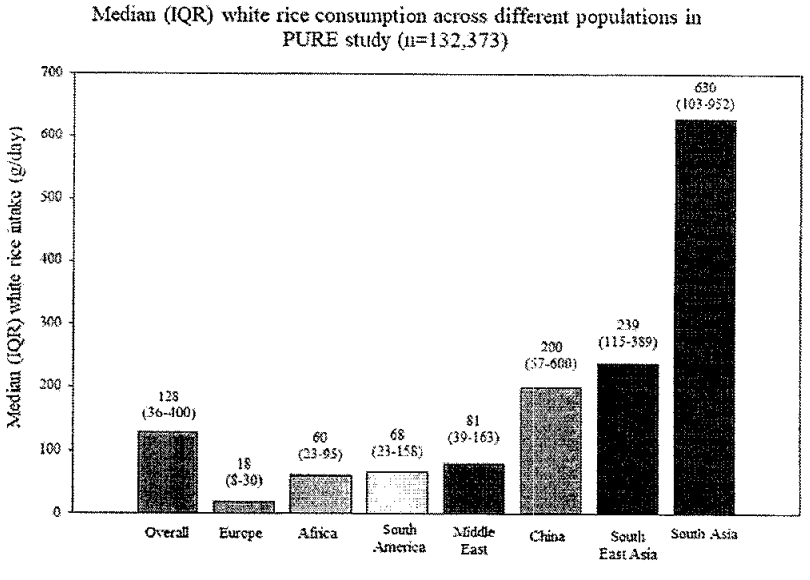

Figure 1—Consumption of white rice (g/day) in different geographic regions. South Asia includes India, Pakistan, and Bangladesh. South East Asia includes Malaysia, Philippines.

Table 1—Characteristics of study participants by levels of white rice consumption in 132,373 participants

	White rice intake (g/day)			
	<150 g/day (*n* = 71,914)	≥150 to <300 g/day (*n* = 16,976)	≥300 to <450 g/day (*n* = 14,010)	≥450 g/day (*n* = 29,473)
Median intake (g/day)	42.8 (18.7–82.6)	200 (171.9–233.5)	395 (341.0–400)	900 (609.8–991.4)
Age (years)	50.3 (10.0)	50.3 (9.7)	50.8 (9.8)	48.8 (9.8)
BMI (kg/m^2)	26.5 ± 5.4	25.9 ± 4.6	25.3 ± 4.5	23.1 ± 4.3
Men	29,192 (40.3)	6,693 (40.5)	5,547 (39.6)	13,470 (45.7)
Urban	40,509 (56.0)	9,993 (60.5)	7,737 (55.2)	10,621 (36.0)
Physical inactivity	11,474 (17.4)	2,780 (17.7)	2,035 (15.3)	5,182 (18.4)
Current smoker	10,811 (15.0)	1,374 (8.4)	1,555 (11.2)	1,431 (4.9)
Fasting plasma glucose (mmol/L)	4.9 ± 0.8	4.9 ± 0.8	4.9 ± 0.7	5.0 ± 0.7
Diet components				
Energy intake (kcal)	1,963 (1,497–2,546)	2,048 (1,579–2,619)	2,065 (1,586–2,658)	2,120 (1,693–2,741)
%E from carbohydrate	57.6 (50.0–66.1)	58.2 (52.6–64.6)	61.8 (56.0–68.2)	71.4 (63.3–78.5)
%E from fat	26.7 (19.4–32.4)	25.9 (20.0–30.6)	22.4 (16.9–27.7)	15.2 (9.6–23.5)
%E from protein	15.7 (13.6–17.9)	16.2 (14.0–18.2)	15.5 (13.2–17.5)	12.0 (10.5–14.2)
Fiber intake (g/day)	24.2 (15.6–34.5)	21.1 (14.3–29.4)	16.9 (10.4–24.9)	10.8 (7.8–14.7)
Refined wheat products (g/day)	146 (66–300)	171 (88–279)	102 (56–182)	43 (12–107)
Whole wheat products (g/day)	27 (0–125)	15 (0–71)	11 (0–33)	7 (0–33)
Red meat (g/day)	42.8 (14.4–87.8)	51.4 (16.4–108.7)	48.0 (16.4–107.7)	15 (2.0–52.4)
White meat (g/day)	39.0 (12.1–74.8)	39.9 (13.9–82.7)	44.4 (18.8–79.8)	26.2 (6.9–67.2)
Processed meat (g/day)	2.8 (0–12.1)	0 (0–6)	1.9 (0–9.6)	0 (0–3.3)
Fish (g/day)	11.4 (0–26)	12.8 (2.8–36.7)	11.3 (0–28.7)	8.6 (0–39.7)
Dairy products (g/day)	145.3 (29.5–290.0)	137.1 (13.1–289.9)	97.8 (4–252.9)	15.7 (0–118.6)

Data are median (IQR), mean ± SD, or n (%). E, energy.

lower BMI (23.1 ± 4.3 vs. 26.5 ± 5.4 kg/m^2), and lower smoking rates (4.9% vs. 15.0%). These clinical characteristics probably reflect the profile of Asians, particularly South Asians who consume the maximum amount of rice. The higher category of rice consumers also consumed lower amounts of most other foods, such as whole and refined wheat products, fiber, red meat, and dairy products. Additionally, those who consumed ≥450 g/day of white rice consumed the highest percentage of their energy from carbohydrate and a lower percentage from fat and protein.

During mean follow-up of 9.5 years, 6,129 cases of incident diabetes were recorded. Table 2 shows the association of white rice consumption with incident diabetes. In the overall PURE cohort, after adjusting for lifestyle and dietary factors, higher consumption of white rice (≥450 vs. <150 g/day) was significantly associated with an increased risk of incident diabetes (HR 1.20; 95% CI 1.02–1.40; *P* for trend = 0.003). The subgroup analysis by regions showed that the association was most pronounced in South Asia (HR 1.61; 95% CI 1.13–2.30; *P* for trend = 0.02) followed by the rest of the world, which includes South East Asia, Middle East, South America, North America, Europe, and Africa (HR 1.41; 95% CI 1.08–1.86; *P* for trend = 0.01). However, in China, the effect was minimal and did not reach statistical significance (HR 1.04; 95% CI 0.77–1.40; *P* for trend = 0.38).

The association between rice intake and incident diabetes was seen even when stratified based on family history of diabetes, PA, BMI, or waist-to-hip ratio, particularly in South Asia (Supplementary Tables 5*A*, 5*B*, 5*C*, and 5*D*). Further subgroup analysis by different regions showed the direction of association to be similar in South East Asia, Middle East, and South America, but the results did not reach statistical significance. In North America, Europe, and Africa, the amount of white rice consumed was much less, and therefore the model did not provide meaningful results (Supplementary Table 6). A pooled analysis showed no significant heterogeneity between the regions (I^2 = 7.7%; *P* = 0.369) (Supplementary Fig. 1).

CONCLUSIONS

Data from this large multinational prospective cohort study of 21 countries show that in the overall PURE cohort, higher consumption of white rice is associated with an increased risk of diabetes, which was most marked and driven by the strong association seen in South Asia. In other regions, like South East Asia, Middle East, South America, North America, Europe, and Africa, the association was in a similar direction, but it did not reach statistical significance except when pooled. In China, there was no significant association between white rice consumption and incident diabetes.

Overall, our findings are consistent with results from some of the previous studies conducted in Asia and Europe and North America (14–18), but not all (19–22). A meta-analysis by Hu et al. (14), which included data on 352,384 participants with 13,284 incident diabetes from four studies in China, Japan, U.S., and Australia, showed that each extra serving of white rice (equivalent to about 150 g of cooked rice) increased the risk for diabetes by 11%. The Shanghai Women's Health Study, one of the earliest studies conducted on 64,227 Chinese women, showed a relative risk of 1.78 among women who consumed 750 g of cooked white rice compared with 500 g/day (15). A similar association was seen in a Japanese study among women, where women consuming >437 g of white rice had a 1.65 times higher risk of diabetes than those consuming <200 g/day (16). It is important to note that in the meta-analysis by

Table 2—Association of white rice consumption with incident diabetes in the overall PURE cohort, China, South Asia, and the rest of the world

	White rice intake (g/day)				
	<150 g/day	≥150 to <300 g/day	≥300 to <450 g/day	≥450 g/day	*P* for trend
Overall PURE cohort (*N* = 132,373)	*n* = 71,914	*n* = 16,976	*n* = 14,010	*n* = 29,473	
Median intake (g/day)	42.8 (18.7–82.6)	200 (171.9–233.5)	395 (341.0–400.0)	900 (609.8–991.4)	
Diabetes events	2,960 (4.1)	922 (5.4)	628 (4.5)	1,619 (5.5)	
Minimally adjusted model	1.00	1.13 (1.03–1.24)	1.22 (1.09–1.37)	1.19 (1.05–1.34)	0.001
Fully adjusted model*	1.00	1.12 (1.01–1.24)	1.25 (1.10–1.43)	1.20 (1.02–1.40)	0.003
South Asia (*N* = 26,419)†	*n* = 7,227	*n* = 1,672	*n* = 2,046	*n* = 15,474	
Median intake (g/day)	34 (15–64)	200 (173–246)	356 (328–395)	379 (694–1,099)	
Diabetes events	343 (4.8)	114 (6.8)	139 (6.8)	1,243 (8.0)	
Minimally adjusted model	1.00	1.19 (0.93–1.52)	1.17 (0.90–1.53)	1.23 (0.98–1.55)	0.12
Fully adjusted model*	1.00	1.26 (0.86–1.86)	1.70 (1.14–2.52)	1.61 (1.13–2.30)	0.02
Rest of the world (*N* = 64,227)‡	*n* = 46,798	*n* = 8,004	*n* = 7,137	*n* = 2,288	
Median intake (g/day)	42 (19–79)	187 (158–234)	395 (327–395)	675 (550–786)	
Diabetes events	2,097 (4.5)	577 (7.2)	317 (4.4)	108 (4.7)	
Minimally adjusted model	1.00	1.21 (1.07–1.36)	1.18 (1.00–1.38)	1.46 (1.16–1.83)	0.0006
Fully adjusted model*	1.00	1.19 (1.04–1.36)	1.13 (0.95–1.35)	1.41 (1.08–1.86)	0.01
China (*N* = 41,727)	*n* = 17,889	*n* = 7,300	*n* = 4,827	*n* = 11,711	
Median intake (g/day)	57 (20–86)	200 (200–228)	400 (400–402)	800 (600–905)	
Diabetes events	520 (2.91)	231 (3.2)	172 (3.6)	268 (2.3)	
Minimally adjusted model	1.00	1.02 (0.86–1.21)	1.42 (1.15–1.74)	0.99 (0.79–1.23)	0.53
Fully adjusted model*	1.00	0.97 (0.80–1.17)	1.34 (1.05–1.70)	1.04 (0.77–1.40)	0.38

Data are median (IQR) or n (%). *The fully adjusted model includes the following: adjusted for age, sex, BMI, waist-to-hip ratio, family history of diabetes, smoking, location, education, wealth index, PA, energy intake, whole grains, refined grains, fruits and vegetables, and study center as random effect. †South Asia includes India, Pakistan, and Bangladesh. ‡The rest of the world includes South East Asia, Middle East, South America, North America, Europe, and Africa.

Hu et al. (14), however, a direct association of risk was observed only in one study, the Nurses' Health Study II, which showed a higher risk (odds ratio 1.40; 95% CI 1.09–1.80; $P = 0.01$). The Japanese study reported an effect only in women and not in men (16). Prospective data from a south Indian cohort with a follow-up of 10 years showed a doubling in the rate of incident diabetes with increasing quartiles (416 vs. 222 g/day) of white rice consumption (18).

There are also some studies that do not corroborate our results (19–22). The Singapore Chinese Health Study of 45,411 Chinese participants followed up for 11 years, with 5,207 cases of incident diabetes, reported no increase in the risk of diabetes (HR 0.98; 95% CI 0.90–1.08), although the median intake in the lowest and highest quartile was substantial (236 vs. 649 g/day) (19). Another study from China showed that a diet high in white rice was associated with a lower prevalence of diabetes in certain parts of China (20). In the current study also, in China, there was no significant association between rice intake and incident diabetes. It is possible that the type of rice is different in China (sticky rice), that the vegetables, pulses, or meat consumed with the rice blunts the GL of the rice, or that the consumption of rice itself has decreased in China in recent times.

Data from two prospective studies from Iran reported opposing results (21). While data from Tehran showed significantly higher risk for >250 g/day of white rice, the Golestan Cohort Study showed no significant increase in risk at 210 g/day intake of white rice (21). A lack of association between white rice intake and incident diabetes was also reported in a study conducted in southern Spain (22). However, this again is not a predominantly rice-eating region, and the comparison was between rice consumed two to three times per week and rice consumed once a week. Hence, this would not compare with the predominantly rice-eating populations, like South Asia, that we have reported in our study. Unmeasured confounding caused by other dietary factors, characteristics of the population and ethnicity could also explain the discrepancy in these findings. Finally, the inconsistent reports from these different studies could also be attributed to different amounts of white rice consumed among the different study population.

What could be the possible mechanism by which excess rice intake leads to diabetes?

It is known that excess rice consumption leads to postprandial glucose spikes that, in turn, lead to compensatory hyperinsulinemia to maintain euglycemia (27,28). Over time, β-cells become exhausted, leading to β-cell failure and diabetes. There are some reports that suggest that rice consumption leads to high arsenic exposure due to the arsenic-contaminated groundwater that is used for rice cultivation (29–31). Some authors believe that this is an alternative explanation for the link between rice intake and diabetes, as arsenic is known to damage β-cells (32) or to act as an endocrine disruptor (33). However, further studies are needed to look at this hypothesis by measuring the arsenic content of soil and water and the risk of diabetes.

Traditional diets earlier consisted of mainly hand-pounded rice and other coarse grains like barley, rye, and maize. These have now been replaced by highly polished white rice in several Asian countries (34). It has been shown that replacing white rice with unpolished brown rice decreases the glycemic response by 23% and the fasting insulin response by 57% in overweight Asian Indians (35). However, the consumer acceptance of brown rice is poor (36). Longer cooking duration,

decreased visual appeal, and greater difficulty in chewing the grain are some of the barriers for the wider acceptance of brown rice (36,37).

One of the earliest studies on GI showed that the GI of rice was higher or similar to white bread (38). Consumption of white bread has also been associated with an increased risk of diabetes (39). A recent study showed that a unique high-fiber white rice variety had a significantly higher dietary fiber and lower GI than regular polished white rice (40). Further, a continuous glucose monitoring study assessing 24-h glycemic responses showed that this high-fiber white rice had a 34% lower 24-h glucose response and a 30% reduction in adjusted mean plasma insulin levels (41). While replacing white rice with other cereals, such as wheat or millets, may not be an acceptable option due to taste preferences in some cultures, modifying the diet quality by replacing the staple white rice with less polished brown rice (36) or healthier varieties of rice may be viable options in countries where highly polished white rice constitutes the bulk (>70%) of the calories in the diet. All legumes, as a class, have a low GI (42) and, thus, adding legumes to rice not only increases the fiber and protein content but also lowers the GI of the rice-containing meal (28,35).

Our study has several strengths. This is the largest prospective study on rice and incident diabetes, and it covers 21 countries from five continents, with a broad range of white rice consumption. Second, several potential confounders have been included in the multivariable analysis. Third, the sample size is large, and there is a fairly long period of follow-up. However, there are also limitations of our study, which include the following: measurement of diet was done only at baseline and changes in diet and other lifestyle factors could have subsequently occurred. Despite extensive adjustment for confounding factors, residual confounding due to unmeasured dietary factors, such as alcohol use, or the newly emerging risk factors like air pollution (43) or use of pesticides (44) cannot be completely ruled out. Third, the costs and logistics involved in carrying out glucose tolerance tests or A1C tests in all participants is prohibitive in a large, multinational study such as this, and hence these tests could not be done. Nevertheless, the majority of the participants in the study (97.3%) were tested for diabetes using fasting blood glucose. Fourth, information on different types of white rice would have further enhanced the results of this study, for example, whether parboiled rice or raw rice was used, as there are nutritional differences between the two. However, unfortunately, this information was not collected at the time of baseline data collection as country-specific FFQs were used, which did not have this level of granularity. Obviously, these unanswered questions provide opportunities for further research in this field.

In conclusion, we report that consumption of higher amounts of white rice was associated with increased risk of incident diabetes with the risk being most pronounced in South Asia, while in other regions the risk was modest and failed to reach statistical significance, the most notable example of this being China. Replacing highly polished white rice with other cereals or healthier varieties of rice or by adding adequate legumes and pulses may not only help to reduce the GI of the meal but also, possibly, to reduce the actual quantity of white rice consumed. These may be important public health strategies to be adopted in South Asian and other populations with rice as the staple food, which, if combined with measures to increase PA, could help to slow down the rapidly rising epidemic of type 2 diabetes in these regions.

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Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study

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Summary

Background The relationship between macronutrients and cardiovascular disease and mortality is controversial. Most available data are from European and North American populations where nutrition excess is more likely, so their applicability to other populations is unclear.

Methods The Prospective Urban Rural Epidemiology (PURE) study is a large, epidemiological cohort study of individuals aged 35–70 years (enrolled between Jan 1, 2003, and March 31, 2013) in 18 countries with a median follow-up of 7·4 years (IQR 5·3–9·3). Dietary intake of 135 335 individuals was recorded using validated food frequency questionnaires. The primary outcomes were total mortality and major cardiovascular events (fatal cardiovascular disease, non-fatal myocardial infarction, stroke, and heart failure). Secondary outcomes were all myocardial infarctions, stroke, cardiovascular disease mortality, and non-cardiovascular disease mortality. Participants were categorised into quintiles of nutrient intake (carbohydrate, fats, and protein) based on percentage of energy provided by nutrients. We assessed the associations between consumption of carbohydrate, total fat, and each type of fat with cardiovascular disease and total mortality. We calculated hazard ratios (HRs) using a multivariable Cox frailty model with random intercepts to account for centre clustering.

Findings During follow-up, we documented 5796 deaths and 4784 major cardiovascular disease events. Higher carbohydrate intake was associated with an increased risk of total mortality (highest [quintile 5] *vs* lowest quintile [quintile 1] category, HR 1·28 [95% CI 1·12–1·46], p_{trend}=0·0001) but not with the risk of cardiovascular disease or cardiovascular disease mortality. Intake of total fat and each type of fat was associated with lower risk of total mortality (quintile 5 *vs* quintile 1, total fat: HR 0·77 [95% CI 0·67–0·87], p_{trend}<0·0001; saturated fat, HR 0·86 [0·76–0·99], p_{trend}=0·0088; monounsaturated fat: HR 0·81 [0·71–0·92], p_{trend}<0·0001; and polyunsaturated fat: HR 0·80 [0·71–0·89], p_{trend}<0·0001). Higher saturated fat intake was associated with lower risk of stroke (quintile 5 *vs* quintile 1, HR 0·79 [95% CI 0·64–0·98], p_{trend}=0·0498). Total fat and saturated and unsaturated fats were not significantly associated with risk of myocardial infarction or cardiovascular disease mortality.

Interpretation High carbohydrate intake was associated with higher risk of total mortality, whereas total fat and individual types of fat were related to lower total mortality. Total fat and types of fat were not associated with cardiovascular disease, myocardial infarction, or cardiovascular disease mortality, whereas saturated fat had an inverse association with stroke. Global dietary guidelines should be reconsidered in light of these findings.

Funding Full funding sources listed at the end of the paper (see Acknowledgments).

Introduction

Cardiovascular disease is a global epidemic with 80% of the burden of disease in low-income and middle-income countries.[1] Diet is one of the most important modifiable risk factors for cardiovascular disease and other non-communicable diseases and current guidelines recommend a low-fat diet (<30% of energy) and limiting saturated fatty acids to less than 10% of energy intake by replacing them with unsaturated fatty acids.[2] However, recommendations on lowering saturated fatty acids are largely based on one ecological study[3] and observational studies done in European and North American countries such as Finland, where the intake of saturated fatty acids (about 20% of total energy intake) and cardiovascular disease mortality were both very high.[4] Furthermore, dietary recommendations are based on the assumption of a linear association between saturated fatty acid intake and LDL cholesterol, and then the association between LDL cholesterol and cardiovascular disease events. However, this assumption does not consider the effect of saturated fatty acids on other lipoproteins (eg, HDL cholesterol), ratio of total

Research in context

Evidence before this study

We did a systematic search in PubMed for relevant articles published between Jan 1, 1960, and May 1, 2017, restricted to the English language. Our search terms included "carbohydrate", "total fat", "saturated fatty acid", "monounsaturated fatty acid", "polyunsaturated fatty acid", "total mortality", and "cardiovascular disease". We searched published articles by title and abstract to identify relevant studies. We also hand-searched reference lists of eligible studies. We considered studies if they evaluated association between macronutrient intake and total mortality or cardiovascular disease. The studies cited in this report are not an exhaustive list of existing research. Existing evidence on the associations of fats and carbohydrate intake with cardiovascular disease and mortality are mainly from North America and Europe.

Added value of this study

Current guidelines recommend a low fat diet (<30% of energy) and limiting saturated fatty acids to less than 10% of energy intake by replacing them with unsaturated fatty acids. The recommendation is based on findings from some North American and European countries where nutrition excess is of concern. It is not clear whether this can be extrapolated to other countries where undernutrition is common. Moreover, North American and European populations consume a lower carbohydrate diet than populations elsewhere where most people consume very high carbohydrate diets mainly from refined sources. Consistent with most data, but in contrast to dietary guidelines, we found fats, including saturated fatty acids, are not harmful and diets high in carbohydrate have adverse effects on total mortality. We did not observe any detrimental effect of higher fat intake on cardiovascular events. Our data across 18 countries adds to the large and growing body of evidence that increased fats are not associated with higher cardiovascular disease or mortality.

Implications of all the available evidence

Removing current restrictions on fat intake but limiting carbohydrate intake (when high) might improve health. Dietary guidelines might need to be reconsidered in light of consistent findings from the present study, especially in countries outside of Europe and North America.

cholesterol to HDL cholesterol, or on apolipoproteins (which could be a better marker of cardiovascular disease risk)[5,6] and blood pressure, which also affect the risk of cardiovascular disease.[7]

Recently, several meta-analyses of randomised trials and prospective cohort studies[8–10] and ecological studies,[11] largely done in European and North American countries, showed either no association or a lower risk between saturated fatty acid consumption with total mortality and cardiovascular disease events.[12,13] The uncertainty regarding the effect of saturated fatty acids on clinical outcomes in part might be due to the fact that most observational cohort studies have been done in high-income countries[8,9] where saturated fatty acid intake is within a limited range (about 7–15% of energy). Furthermore, it is not known whether findings obtained from European and North American countries where nutritional excess is more common, can be extrapolated to other regions of the world where nutritional inadequacy might be more common. The Prospective Urban Rural Epidemiology (PURE) study provides a unique opportunity to study the impact of diet on total mortality and cardiovascular disease in diverse settings, such as those where overnutrition is common and where undernutrition is of greater concern. In this study, our primary aim was to assess the association of fats (total, saturated fatty acids, and unsaturated fats) and carbohydrate with total mortality and cardiovascular disease events. The secondary aim was to examine associations between these nutrients and myocardial infarction, stroke, cardiovascular disease mortality, and non-cardiovascular disease mortality.

Methods

Study design and participants

The design and methods of the PURE study have been described previously.[1,14–16] PURE recruitment occurred between Jan 1, 2003, and March 31, 2013, and included individuals aged 35–70 years from 18 low-income, middle-income, and high-income countries on five continents. We aimed to include populations that varied by socioeconomic factors while ensuring feasibility of long-term follow-up when selecting the participating countries. We included three high-income (Canada, Sweden, and United Arab Emirates), 11 middle-income (Argentina, Brazil, Chile, China, Colombia, Iran, Malaysia, occupied Palestinian territory, Poland, South Africa, and Turkey) and four low-income countries (Bangladesh, India, Pakistan, and Zimbabwe), based on gross national income per capita from the World Bank classification for 2006 when the study was initiated. Additional countries have joined PURE, but since follow-up in these countries is incomplete, they are not included in the present analyses. The study was coordinated by the Population Health Research Institute (PHRI; Hamilton Health Sciences, Hamilton, ON, Canada). More details of the sampling and recruitment strategy used in PURE are detailed in the Article by Miller and colleagues[17] and an earlier report.[18]

Procedures

Data were collected at the community, household, and individual levels. Within participating communities, our goal was to enrol an unbiased sample of households. Households were eligible if at least one member was

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See Online for appendix

between 35 and 70 years of age, and the household intended to stay in the current address for another 4 years. Standardised questionnaires were used to collect information about demographic factors, socioeconomic status (education, income, and employment), lifestyle (smoking, physical activity, and alcohol intake), health history, and medication use. Physical activity was assessed using the International Physical Activity Questionnaire.[19] History of diabetes was self-reported. Physical assessment included weight, height, waist and hip circumferences, and blood pressure. Detailed follow-up occurred at 3, 6, and 9 years and repeated measures of selected risk factors, causes of death, other health outcomes, and community data were collected. Standardised case-report forms were used to record data on major cardiovascular events and mortality during follow-up, which were adjudicated centrally in each country by trained physicians using standard definitions (appendix pp 8–17). Data were electronically transferred to the PHRI where quality control checks were undertaken.

Participants' habitual food intake was recorded using country-specific (or region-specific in India) validated food frequency questionnaires (FFQs) at baseline. Where a validated FFQ was not available (ie, Argentina), we developed and validated FFQs using a standard method.[20–30] Multiple 24-h dietary recalls were used as the reference method to validate the FFQs in about 60–250 participants from each country (appendix p 18). To convert food into nutrients, country-specific nutrient databases were constructed with information on 43 macronutrients and micronutrients. The nutrient databases are primarily based on the United States Department of Agriculture food composition database (release 18 and 21), modified with reference to local food composition tables, and supplemented with recipes of local mixed dishes.[31] However, for Canada, China, India, Malaysia, South Africa, Sweden, and Turkey we used the nutrient databases that were used for validation of the FFQs. The FFQ was administered together with other questionnaires at the baseline.

For the current analysis, we included all outcome events known to us until March 31, 2017. 148723 participants completed the FFQ, of which 143934 participants had plausible energy intake (500–5000 kcal per day) and had no missing values on age and sex. We excluded 1230 participants (0·8% of the cohort) because follow-up information was not available and 7369 participants with a history of cardiovascular disease (5·0% of the cohort). The remaining 135335 individuals were included in this analysis (appendix p 19).

Outcomes

The primary outcomes were total mortality and major cardiovascular events (fatal cardiovascular disease, non-fatal myocardial infarction, stroke, and heart failure). Secondary outcomes were all myocardial infarctions, stroke, cardiovascular disease mortality, and non-cardiovascular disease mortality. The numbers of cases of heart failure were too few to be analysed separately.

The follow-up period varied based on the date when recruitment began at each site or country. During the follow-up period contact was made with every participant on an annual basis either by telephone or by a face-to-face interview with the local research team. The median duration of follow-up was 7·4 years (IQR 5·3–9·3), which varied across countries (appendix p 22).

Statistical analysis

Continuous variables were expressed as means (SDs) and categorical variables as percentages. Education was categorised as none, primary school (first 6 years), or secondary school (7–11 years) and college, trade school, or university (>11 years). Smoking was categorised as never, former, or current smoker. Physical activity was categorised based on the metabolic equivalent of task (MET) per min per week into low (<600 MET min per week), moderate (600–3000 MET min per week), and high (>3000 MET min per week) activity. Waist-to-hip ratio (waist circumferences [cm]/hip circumferences [cm]) was used as a continuous variable. Since food patterns are culture dependent and dietary patterns are generally related to geographical region rather than income region, we categorised countries into seven regions. Regions included China, south Asia (Bangladesh, India, and Pakistan), North America, Europe (Canada, Poland, and Sweden), South America (Argentina, Brazil, Chile, and Colombia), Middle East (Iran, occupied Palestinian territory, Turkey, and United Arab Emirates), southeast Asia (Malaysia), and Africa (South Africa and Zimbabwe). For the overall analysis, participants were categorised into quintiles of nutrient intake (carbohydrate, fats, and protein) based on percentage of energy (% E) provided by nutrients, which was computed by dividing energy from the nutrient by the total daily energy intake (eg, for carbohydrate, %E=([carbohydrate (g)×4]/total energy intake [kcal])×100). To assess the shape of associations between nutrients and events we used restricted cubic splines, fitting a restricted cubic spline function with three knots. We calculated hazard ratios (HRs) using a multivariable Cox frailty model with random intercepts to account for centre clustering (which also adjusts for region and country). Estimates of HRs and 95% CIs are presented for percentage of energy from carbohydrate, total protein, total fat, and types of fat. All models were adjusted for age and sex. Additionally, all multivariable models were adjusted for education, smoking, physical activity, waist-to-hip ratio, history of diabetes, urban or rural location, and total energy intake.

In subgroup analyses, since higher carbohydrate (but lower fat) consumption is more common in Asian countries[32,33] and lower carbohydrate intake (and higher fat) in non-Asian countries[11] we examined whether the

effect of carbohydrate and fats on outcomes were consistent in these two regions. The countries in Asia included Bangladesh, China, India, Malaysia, and Pakistan; the remaining countries were considered to be non-Asian countries. We used this approach for two main reasons: to assess the consistency of the associations across regions representing different levels of nutrient intake, with Asian countries characterising higher carbohydrate (and lower fat) consumption and non-Asian countries capturing lower carbohydrate intake (and higher fat); and to maximise the power within regions (compared with examining effects within smaller geographical regions with fewer people and relatively few events). Participants were categorised into region-specific quintile categories of nutrient intake based on the intake distribution of participants in Asian and non-Asian countries, with the lowest quintile category used as reference group within regions (we did not do further region subgroup analyses due to low statistical power to detect subgroup interactions). Since the impact of macronutrient intake on outcome events might or might not occur through changes in waist-to-hip ratio, we excluded waist-to-hip ratio from the multivariable models in secondary analyses to assess the impact on estimates.

The effect of isocaloric replacement (as 5% of energy) of carbohydrate with saturated and unsaturated fats and protein was estimated using multivariable nutrient density models.[34] In this modelling approach, the percentage of energy intake from saturated and unsaturated fats and protein were included as exposures with total energy as a covariate. The coefficients in this model indicate change in outcomes by replacement of carbohydrate (as 5% of energy) by other nutrients. For all analyses, the criterion for statistical significance was α=0·05. Statistical analyses were done with SAS software, version 9.3. Spline curves were generated with the SAS LGTPHCURV9 Macro.

	Overall (n=135 335)	China (n=42 152)	South Asia (n=29 560)	Europe and North America (n=14 916)	South America (n=22 626)	Middle East (n=11 485)	Southeast Asia (n=10 038)	Africa (n=4558)
Age (years)	50·29 (9·92)	50·58 (9·82)	48·18 (10·24)	53·01 (9·18)	51·13 (9·69)	48·57 (9·23)	51·47 (9·96)	49·98 (10·35)
Male	56 422 (41·7%)	17 575 (41·7%)	12 887 (43·6%)	6567 (44·0%)	8685 (38·4%)	4930 (42·9%)	4323 (43·1%)	1455 (31·9%)
Urban location	71 300 (52·7%)	20 170 (47·9%)	14 224 (48·1%)	10 488 (70·3%)	12 896 (57·0%)	6526 (56·8%)	4841 (48·2%)	2155 (47·3%)
Systolic blood pressure (mm Hg)	130·9 (22·2)	132·9 (22·2)	125·8 (21·2)	132·0 (20·4)	131·7 (22·7)	127·1 (20·3)	135·2 (23·1)	138·9 (27·5)
Waist-to-hip ratio	0·87 (0·08)	0·86 (0·07)	0·87 (0·09)	0·88 (0·09)	0·890 (0·08)	0·89 (0·09)	0·83 (0·08)	0·84 (0·087)
Current smoker	28 410/134 449 (21·1%)	9588/41 670 (23·0%)	6799/29 468 (23·1%)	2256/14 888 (15·2%)	4709/22 548 (20·9%)	2178/11 485 (19·0%)	1532/9943 (15·4%)	1348/4447 (30·3%)
Education								
Pre-secondary school	57 438/134 981 (42·6%)	14 113/42 036 (33·6%)	15 135/29 432 (51·4%)	1138/14 903 (7·6%)	13 298/22 565 (58·9%)	6935/11 485 (60·4%)	4263/10 032 (42·5%)	2556/4528 (56·5%)
Secondary school	51 730/134 981 (38·3%)	21 853/42 036 (52·0%)	10 239/29 432 (34·8%)	4649/14 903 (31·2%)	5471/22 565 (24·3%)	3114/11 485 (27·1%)	4551/10 032 (45·4%)	1853/4528 (40·9%)
Post-secondary school	25 813/134 981 (19·1%)	6070/42 036 (14·4%)	4058/29 432 (13·8%)	9116/14 903 (61·2%)	3796/22 565 (16·8%)	1436/11 485 (12·5%)	1218/10 032 (12·1%)	119/4528 (2·6%)
Physical activity								
Low (<600 MET per min per week)	22 022/125 945 (17·5%)	6424/41 534 (15·5%)	5588/25 999 (21·5%)	826/13 628 (6·1%)	2889/21 567 (13·4%)	2452/11 342 (21·6%)	3315/9428 (35·2%)	528/2447 (21·6%)
Moderate (600–3000 MET per min per week)	47 850/125 945 (38·0%)	17 518/41 534 (42·2%)	8903/25 999 (34·2%)	4757/13 628 (34·9%)	6944/21 567 (32·2%)	5290/11 342 (46·6%)	3336/9428 (35·4%)	1102/2447 (45·0%)
High (>3000 MET per min per week)	56 073/125 945 (44·5%)	17 592/41 534 (42·4%)	11 508/25 999 (44·3%)	8045/13 628 (59·0%)	11 734/21 567 (54·4%)	3600/11 342 (31·7%)	2777/9428 (29·5%)	817/2447 (33·4%)
History of diabetes	9634 (7·1%)	1610 (3·8%)	2723 (9·2%)	785 (5·3%)	1530 (6·8%)	1405 (12·2%)	1351 (13·5%)	230 (5·1%)
Energy from carbohydrate (%)	61·2% (11·6)	67·0% (9·8)	65·4% (11·3)	52·4% (8·1)	57·6% (11·4)	53·5% (7·5)	53·9% (8·2)	63·3% (11·5)
Energy from fat (%)	23·5% (9·3)	17·7% (7·8)	22·7% (10·4)	30·5% (6·0)	25·2% (7·7)	30·3% (6·1)	29·2% (5·9)	22·8% (8·3)
Energy from protein (%)	15·2% (3·6)	15·3% (2·3)	11·6% (1·9)	16·7% (2·7)	17·5% (3·8)	16·9% (2·8)	17·1% (3·2)	13·4% (3·0)
Energy from saturated fatty acids (%)	8·0% (4·1)	5·7% (2·7)	8·4% (5·2)	10·9% (3·7)	8·9% (3·4)	10·2% (2·9)	9·2% (2·1)	5·9% (2·8)
Energy from monounsaturated fatty acids (%)	8·1% (3·7)	6·8% (2·9)	5·9% (3·1)	11·2% (2·6)	9·0% (3·2)	10·2% (3·0)	11·8% (3·9)	7·2% (3·2)
Energy from polyunsaturated fatty acids (%)	5·3% (3·0)	4·2% (2·8)	6·2% (4·0)	4·8% (1·3)	4·4% (1·6)	7·0% (1·9)	8·2% (2·0)	6·0% (2·9)
Energy from protein (%)	15·2% (3·6)	15·3% (2·8)	11·7% (1·9)	16·7% (2·7)	17·5% (3·8)	16·9% (2·8)	17·2% (3·2)	13·4% (3·0)
Energy from animal protein (%)	6·4% (4·5)	5·6% (3·4)	1·9% (1·9)	9·3% (3·0)	10·5% (4·9)	8·9% (3·0)	7·3% (3·1)	5·2% (3·1)
Energy from plant protein (%)	8·8% (2·2)	9·7% (1·5)	9·8% (2·1)	7·4% (2·0)	7·0% (2·3)	8·0% (1·3)	9·8% (2·2)	7·5% (1·4)

Data are mean (SD), n (%), or n/N (%). MET=metabolic equivalents.

Table 1: Characteristics of the study participants at baseline by region and overall

Role of the funding sources

The funders and sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; in the preparation, review, or approval of the manuscript; or in the decision to submit the manuscript for publication. MD, AM, XZ, SR, SIB, SSA, and SY had full access to the data and were responsible for the decision to submit for publication.

Results

During a median follow-up of 7·4 years (IQR 5·3–9·3), 5796 individuals died and 4784 had a major cardiovascular disease event (2143 myocardial infarctions and 2234 strokes).

	Incidence (per 1000 person-years; 95% CI)					Hazard ratio (95% CI)				p_{trend}
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Quintile 2 vs quintile 1	Quintile 3 vs quintile 1	Quintile 4 vs quintile 1	Quintile 5 vs quintile 1	
Percentage energy from carbohydrate										
Median (IQR)	46·4% (42·6–49·0)	54·6% (52·9–56·2)	60·8% (59·3–62·3)	67·7% (65·7–69·7)	77·2% (74·4–80·7)	..	..	..	..	..
Total mortality	4·1 (3·8–4·3)	4·2 (3·9–4·5)	4·5 (4·2–4·8)	4·9 (4·6–5·2)	7·2 (6·9–7·5)	1·07 (0·96–1·20)	1·06 (0·94–1·19)	1·17 (1·03–1·32)	1·28 (1·12–1·46)	0·0001
Major cardiovascular disease	3·9 (3·6–4·2)	4·2 (3·9–4·5)	4·2 (3·9–4·5)	4·6 (4·3–4·8)	5·1 (4·8–5·4)	1·00 (0·90–1·12)	1·02 (0·91–1·14)	1·08 (0·96–1·22)	1·01 (0·88–1·15)	0·62
Myocardial infarction	2·0 (1·8–2·2)	2·2 (2·0–2·4)	2·0 (1·8–2·2)	1·8 (1·6–2·0)	2·1 (1·9–2·3)	0·93 (0·80–1·09)	0·92 (0·78–1·09)	0·99 (0·83–1·18)	0·90 (0·73–1·10)	0·40
Stroke	1·4 (1·3–1·6)	1·6 (1·4–1·7)	1·8 (1·6–2·0)	2·4 (2·2–2·6)	2·7 (2·5–2·9)	1·03 (0·86–1·22)	1·09 (0·91–1·31)	1·21 (1·01–1·45)	1·11 (0·92–1·35)	0·10
Cardiovascular disease mortality	1·3 (1·1–1·4)	1·6 (1·4–1·7)	1·4 (1·3–1·6)	1·3 (1·2–1·5)	1·7 (1·5–1·9)	1·18 (0·97–1·43)	1·02 (0·83–1·26)	1·11 (0·88–1·38)	1·13 (0·89–1·44)	0·50
Non-cardiovascular disease mortality	2·5 (2·3–2·7)	2·3 (2·1–2·5)	2·7 (2·5–2·9)	3·2 (3·0–3·5)	5·1 (4·8–5·4)	1·00 (0·87–1·15)	1·09 (0·94–1·27)	1·22 (1·05–1·42)	1·36 (1·16–1·60)	<0·0001
Percentage energy from total fat										
Median (IQR)	10·6% (8·1–12·6)	18·0% (16·3–19·7)	24·2% (22·8–25·5)	29·1% (27·9–30·3)	35·3% (33·3–38·3)	..	..	..	..	..
Total mortality	6·7 (6·4–7·0)	5·1 (4·7–5·4)	4·6 (4·3–5·0)	4·3 (4·0–4·6)	4·1 (3·9–4·4)	0·90 (0·82–0·98)	0·81 (0·73–0·90)	0·80 (0·71–0·90)	0·77 (0·67–0·87)	<0·0001
Major cardiovascular disease	5·3 (5·0–5·6)	4·3 (4·0–4·6)	4·2 (3·9–4·5)	4·0 (3·8–4·3)	4·1 (3·8–4·4)	1·01 (0·92–1·11)	1·01 (0·90–1·13)	0·95 (0·84–1·07)	0·95 (0·83–1·08)	0·33
Myocardial infarction	2·1 (1·9–2·3)	1·6 (1·4–1·8)	2·0 (1·8–2·2)	2·0 (1·8–2·2)	2·3 (2·1–2·6)	1·02 (0·87–1·20)	1·08 (0·90–1·29)	0·97 (0·80–1·18)	1·12 (0·92–1·37)	0·40
Stroke	3·0 (2·7–3·2)	2·3 (2·1–2·6)	1·6 (1·5–1·8)	1·6 (1·4–1·8)	1·3 (1·2–1·5)	1·05 (0·93–1·19)	0·91 (0·78–1·06)	0·95 (0·79–1·13)	0·82 (0·68–1·00)	0·05
Cardiovascular disease mortality	1·6 (1·4–1·8)	1·3 (1·2–1·5)	1·5 (1·3–1·6)	1·4 (1·3–1·6)	1·5 (1·3–1·7)	0·89 (0·74–1·06)	0·92 (0·75–1·12)	0·88 (0·70–1·10)	0·92 (0·72–1·16)	0·50
Non-cardiovascular disease mortality	4·7 (4·4–5·0)	3·4 (3·1–3·6)	2·9 (2·6–3·1)	2·6 (2·3–2·8)	2·3 (2·1–2·5)	0·91 (0·82–1·01)	0·78 (0·69–0·89)	0·78 (0·67–0·90)	0·70 (0·60–0·82)	<0·0001
Percentage energy from total protein										
Median (IQR)	10·8% (9·9–11·5)	13·1% (12·6–13·6)	15·0% (14·5–15·5)	16·9% (16·4–17·4)	19·7% (18·8–21·4)	..	..	..	..	..
Total mortality	8·5 (8·1–8·9)	5·4 (5·1–5·7)	3·7 (3·5–4·0)	3·2 (2·9–3·4)	3·6 (3·3–3·9)	1·05 (0·96–1·15)	0·92 (0·82–1·03)	0·85 (0·75–0·96)	0·88 (0·77–1·00)	0·0030
Major cardiovascular disease	5·0 (4·7–5·3)	4·6 (4·3–4·9)	4·4 (4·1–4·7)	4·2 (3·9–4·5)	3·7 (3·5–4·0)	1·02 (0·91–1·13)	1·08 (0·96–1·22)	1·09 (0·97–1·24)	0·96 (0·84–1·10)	0·86
Myocardial infarction	2·8 (2·5–3·0)	2·0 (1·8–2·2)	1·7 (1·5–1·9)	1·7 (1·5–1·9)	1·7 (1·5–1·9)	1·04 (0·89–1·20)	1·01 (0·85–1·20)	1·11 (0·92–1·33)	1·02 (0·83–1·24)	0·67
Stroke	1·8 (1·6–2·0)	2·2 (2·0–2·4)	2·4 (2·1–2·6)	2·1 (1·9–2·3)	1·6 (1·4–1·8)	1·01 (0·86–1·19)	1·14 (0·96–1·36)	1·11 (0·92–1·33)	0·90 (0·74–1·09)	0·47
Cardiovascular disease mortality	2·4 (2·2–2·6)	1·7 (1·5–1·9)	1·0 (0·9–1·2)	0·9 (0·8–1·1)	1·1 (0·9–1·2)	1·09 (0·93–1·29)	0·89 (0·73–1·10)	0·92 (0·74–1·16)	0·90 (0·71–1·15)	0·26
Non-cardiovascular disease mortality	5·5 (5·2–5·8)	3·3 (3·1–3·6)	2·5 (2·2–2·7)	2·0 (1·8–2·2)	2·3 (2·1–2·5)	1·02 (0·91–1·15)	0·92 (0·80–1·05)	0·79 (0·68–0·93)	0·85 (0·73–0·99)	0·0022

Hazard ratios and 95% CIs are adjusted for age, sex, education, waist-to-hip ratio, smoking, physical activity, diabetes, urban or rural location, and energy intake. Centre was also included as a random effect and frailty models were used. Major cardiovascular disease=fatal cardiovascular disease+myocardial infarction+stroke+heart failure.

Table 2: **Association between percentage energy from macronutrients and clinical outcomes (n=135 335)**

1649 died due to cardiovascular disease and 3809 died due to non-cardiovascular disease. There were 338 deaths due to injury, which were not included in non-cardiovascular disease mortality because these were considered to be unlikely to be associated with diet. Among non-cardiovascular disease mortality, in all regions except Africa, the most common cause of mortality was cancer followed by respiratory diseases. In Africa, infectious disease was the first and respiratory disease was the second most common cause of non-cardiovascular disease mortality.

The characteristics of participants and data on macronutrient intake are presented in table 1.

Carbohydrate intake was higher in China, south Asia, and Africa compared with other regions. In south Asia about

	Incidence (per 1000 person-years; 95% CI)					Hazard ratio (95% CI)				p_{trend}
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Quintile 2 vs quintile 1	Quintile 3 vs quintile 1	Quintile 4 vs quintile 1	Quintile 5 vs quintile 1	
Percentage energy from saturated fatty acids										
Median (IQR)	2·8% (2·0–3·4)	4·9% (4·4–5·5)	7·1% (6·5–7·7)	9·5% (8·9–10·2)	13·2% (11·9–15·1)	..	..	..	..	..
Total mortality	7·1 (6·7–7·4)	5·2 (4·9–5·5)	4·3 (4·0–4·6)	3·9 (3·6–4·2)	4·4 (4·1–4·7)	0·96 (0·88–1·05)	0·92 (0·83–1·02)	0·85 (0·75–0·95)	0·86 (0·76–0·99)	0·0088
Major cardiovascular disease	5·2 (4·9–5·5)	4·7 (4·4–5·1)	4·1 (3·8–4·4)	3·9 (3·6–4·2)	4·1 (3·8–4·4)	1·13 (1·02–1·25)	1·06 (0·95–1·18)	1·03 (0·91–1·17)	0·95 (0·83–1·10)	0·49
Myocardial infarction	2·1 (1·9–2·3)	1·8 (1·6–2·0)	1·7 (1·5–1·9)	1·9 (1·7–2·1)	2·5 (2·3–2·7)	1·28 (1·08–1·51)	1·20 (1·00–1·44)	1·16 (0·95–1·41)	1·17 (0·94–1·45)	0·40
Stroke	2·7 (2·5–2·9)	2·6 (2·3–2·8)	1·9 (1·7–2·1)	1·5 (1·4–1·7)	1·3 (1·1–1·4)	1·10 (0·97–1·25)	1·01 (0·87–1·17)	0·93 (0·78–1·11)	0·79 (0·64–0·98)	0·0498
Cardiovascular disease mortality	1·7 (1·6–1·9)	1·5 (1·4–1·7)	1·3 (1·1–1·4)	1·4 (1·2–1·5)	1·4 (1·2–1·6)	1·04 (0·87–1·24)	0·95 (0·78–1·17)	0·99 (0·79–1·23)	0·83 (0·65–1·07)	0·20
Non-cardiovascular disease mortality	4·9 (4·6–5·2)	3·4 (3·1–3·6)	2·8 (2·5–3·0)	2·3 (2·1–2·5)	2·6 (2·4–2·8)	0·94 (0·84–1·04)	0·91 (0·81–1·03)	0·78 (0·68–0·91)	0·86 (0·73–1·01)	0·0108
Percentage energy from monounsaturated fatty acids										
Median (IQR)	3·4% (2·4–4·0)	5·4% (5·0–5·9)	7·3% (6·8–7·8)	9·5% (8·9–10·1)	12·5% (11·5–13·8)	..	..	..	..	..
Total mortality	7·5 (7·2–7·9)	5·6 (5·3–5·9)	4·4 (4·1–4·7)	3·7 (3·4–4·0)	3·7 (3·4–3·9)	1·02 (0·93–1·11)	0·91 (0·82–1·00)	0·81 (0·72–0·91)	0·81 (0·71–0·92)	<0·0001
Major cardiovascular disease	5·2 (4·9–5·5)	4·6 (4·3–4·9)	4·5 (4·2–4·8)	3·9 (3·6–4·2)	3·8 (3·6–4·1)	1·04 (0·94–1·15)	1·06 (0·95–1·18)	1·02 (0·90–1·15)	0·95 (0·84–1·09)	0·54
Myocardial infarction	2·4 (2·2–2·7)	2·0 (1·8–2·2)	1·9 (1·7–2·1)	1·8 (1·6–2·0)	1·9 (1·7–2·1)	1·09 (0·93–1·28)	1·13 (0·95–1·34)	1·04 (0·86–1·25)	1·12 (0·92–1·38)	0·40
Stroke	2·5 (2·3–2·7)	2·3 (2·1–2·5)	2·1 (1·9–2·3)	1·6 (1·5–1·8)	1·5 (1·3–1·6)	1·03 (0·90–1·18)	1·00 (0·86–1·16)	0·99 (0·83–1·17)	0·85 (0·70–1·03)	0·10
Cardiovascular disease mortality	1·9 (1·7–2·1)	1·7 (1·5–1·8)	1·4 (1·3–1·6)	1·3 (1·1–1·4)	1·1 (0·9–1·2)	1·07 (0·90–1·26)	0·98 (0·81–1·18)	0·90 (0·73–1·12)	0·85 (0·66–1·09)	0·10
Non-cardiovascular disease mortality	5·2 (4·9–5·5)	3·5 (3·3–3·8)	2·6 (2·4–2·8)	2·2 (2·0–2·4)	2·4 (2·1–2·6)	1·00 (0·90–1·11)	0·86 (0·76–0·97)	0·77 (0·67–0·89)	0·79 (0·68–0·93)	0·0003
Percentage energy from polyunsaturated fatty acids										
Median (IQR)	2·1% (1·6–2·5)	3·3% (3·1–3·6)	4·4% (4·1–4·7)	5·7% (5·4–6·2)	8·5% (7·5–10·4)	..	..	..	..	..
Total mortality	5·8 (5·5–6·2)	4·8 (4·5–5·1)	4·6 (4·3–4·9)	5·0 (4·6–5·3)	4·9 (4·6–5·2)	0·92 (0·84–1·01)	0·87 (0·79–0·96)	0·85 (0·77–0·94)	0·80 (0·71–0·89)	<0·0001
Major cardiovascular disease	5·4 (5·1–5·8)	3·9 (3·6–4·2)	4·0 (3·7–4·3)	4·2 (3·9–4·5)	4·7 (4·4–5·0)	1·01 (0·91–1·11)	0·99 (0·89–1·10)	0·97 (0·87–1·09)	1·01 (0·90–1·14)	0·94
Myocardial infarction	2·2 (2·0–2·4)	1·6 (1·4–1·8)	1·7 (1·6–1·9)	2·0 (1·8–2·2)	2·7 (2·4–2·9)	1·02 (0·86–1·21)	1·05 (0·88–1·25)	0·98 (0·82–1·17)	1·12 (0·93–1·34)	0·40
Stroke	3·0 (2·8–3·2)	1·9 (1·7–2·1)	1·7 (1·6–1·9)	1·7 (1·5–1·9)	1·6 (1·5–1·8)	0·96 (0·84–1·09)	0·94 (0·81–1·08)	0·95 (0·81–1·11)	0·92 (0·78–1·09)	0·30
Cardiovascular disease mortality	1·5 (1·3–1·6)	1·3 (1·1–1·5)	1·3 (1·2–1·5)	1·4 (1·2–1·6)	1·9 (1·7–2·1)	0·99 (0·82–1·19)	0·88 (0·72–1·07)	0·81 (0·67–0·99)	0·94 (0·76–1·15)	0·20
Non-cardiovascular disease mortality	4·0 (3·7–4·3)	3·2 (3·0–3·5)	3·0 (2·7–3·2)	3·2 (3·0–3·5)	2·6 (2·4–2·8)	0·90 (0·80–1·00)	0·86 (0·76–0·96)	0·88 (0·78–0·99)	0·75 (0·65–0·86)	0·0002

Hazard ratios and 95% CIs are adjusted for age, sex, education, waist-to-hip ratio, smoking, physical activity, diabetes, urban or rural location, and energy intake. Centre was also included as a random effect and frailty models were used. Major cardiovascular disease=fatal cardiovascular disease+myocardial infarction+stroke+heart failure.

Table 3: Association between percentage energy from types of different fat and clinical outcomes (n=135 335)

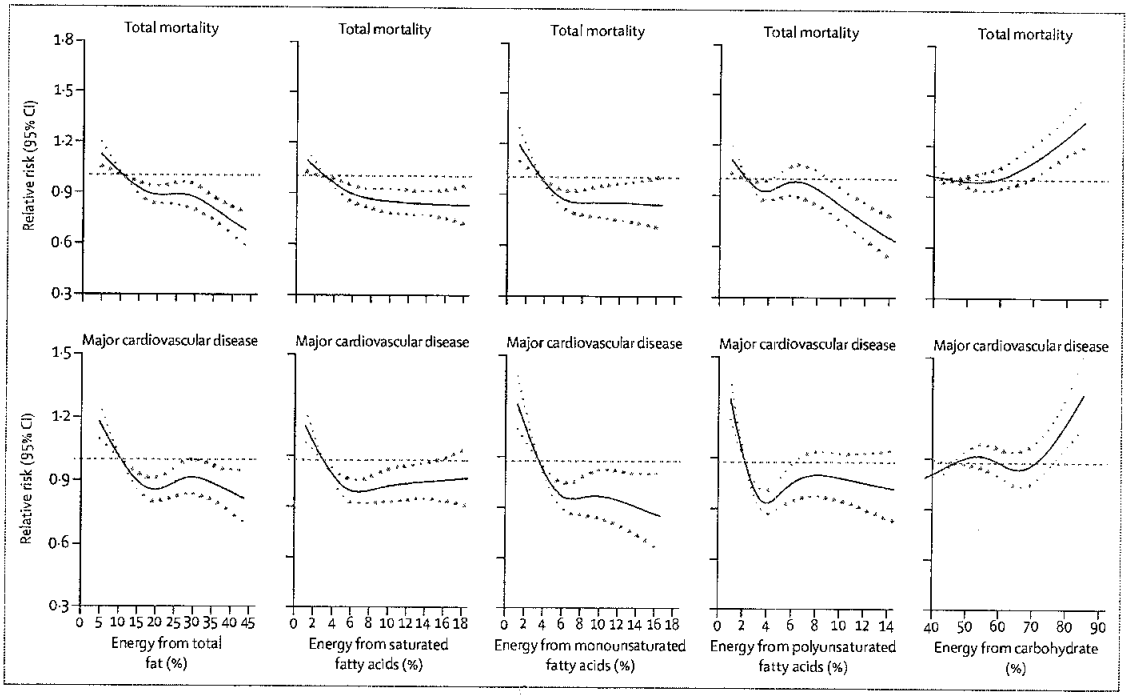

Figure 1: **Association between estimated percentage energy from nutrients and total mortality and major cardiovascular disease (n=135 335)**
Adjusted for age, sex, education, waist-to-hip ratio, smoking, physical activity, diabetes, urban or rural location, centre, geographical regions, and energy intake. Major cardiovascular disease=fatal cardiovascular disease+myocardial infarction+stroke+heart failure.

65% of the population consume at least 60% of energy from carbohydrate and 33% consume at least 70% of energy from carbohydrate, and in China the corresponding percentages are 77% and 43% (appendix p 33). The highest amount of fat consumed was in North America and Europe, Middle East, and southeast Asia. Intake of protein was highest in South America and southeast Asia.

Tables 2 and 3 show nutrient intake and risk of total mortality and cardiovascular disease events. Higher carbohydrate intake was associated with higher risk of total mortality (quintile 5 *vs* quintile 1, HR 1·28 [95% CI 1·12–1·46]; p_{trend}=0·0001) and non-cardiovascular disease mortality (quintile 5 *vs* quintile 1, HR 1·36 [1·16–1·60]; p_{trend}<0·0001), after multivariable adjustment for covariates (table 2). No significant associations between carbohydrate intake and major cardiovascular disease, myocardial infarction, stroke, and cardiovascular disease mortality were recorded (table 2).

In comparisons between quintile 5 and quintile 1, total fat intake was associated with lower risks of total mortality (HR 0·77 [95% CI 0·67–0·87]; p_{trend}<0·0001), stroke (HR 0·82 [0·68–1·00]; p_{trend}=0·0562), and non-cardiovascular disease mortality (HR 0·70 [0·60–0·82]; p_{trend}<0·0001). No significant associations between total fat intake and major cardiovascular disease, myocardial infarction, and cardiovascular disease mortality were found. Similarly, total protein intake was inversely associated with risks of total mortality (HR 0·88 [95% CI 0·77–1·00]; p_{trend}=0·0030) and non-cardiovascular disease mortality (HR 0·85 [0·73–0·99]; p_{trend}=0·0022; table 2). Animal protein intake was associated with lower risk of total mortality and no significant association was observed between plant protein and risk of total mortality.

In comparisons between quintile 5 and quintile 1, a higher intake of saturated fatty acids was inversely associated with risk of total mortality (HR 0·86 [95% CI 0·76–0·99]; p_{trend}=0·0088), stroke (HR 0·79 [0·64–0·98]; p_{trend}=0·0498), and non-cardiovascular disease mortality (HR 0·86 [0·73–1·01]; p_{trend}=0·0108; table 3). Higher saturated fatty acid intake was not associated with major cardiovascular disease, myocardial infarction, or cardiovascular disease mortality. Similarly, monounsaturated fatty acid intake was associated with lower risk of total mortality (HR 0·81 [95% CI 0·71–0·92]; p_{trend}<0·0001), a non-significant trend for lower risk of stroke (HR 0·85 [0·70–1·03]; p_{trend}=0·10), and lower risk of non-cardiovascular disease mortality (HR 0·79 [0·68–0·92]; p_{trend}=0·0003). Intake of polyunsaturated fatty acids was associated with lower risk of total mortality (HR 0·80 [95% CI 0·71–0·89]; p_{trend}<0·0001) and non-cardiovascular disease mortality (HR 0·75 [0·65–0·86]; p_{trend}=0·0002). Intakes of monounsaturated fatty acids and polyunsaturated fatty acids were not significantly associated with major cardiovascular disease, myocardial infarction, and cardiovascular disease mortality.

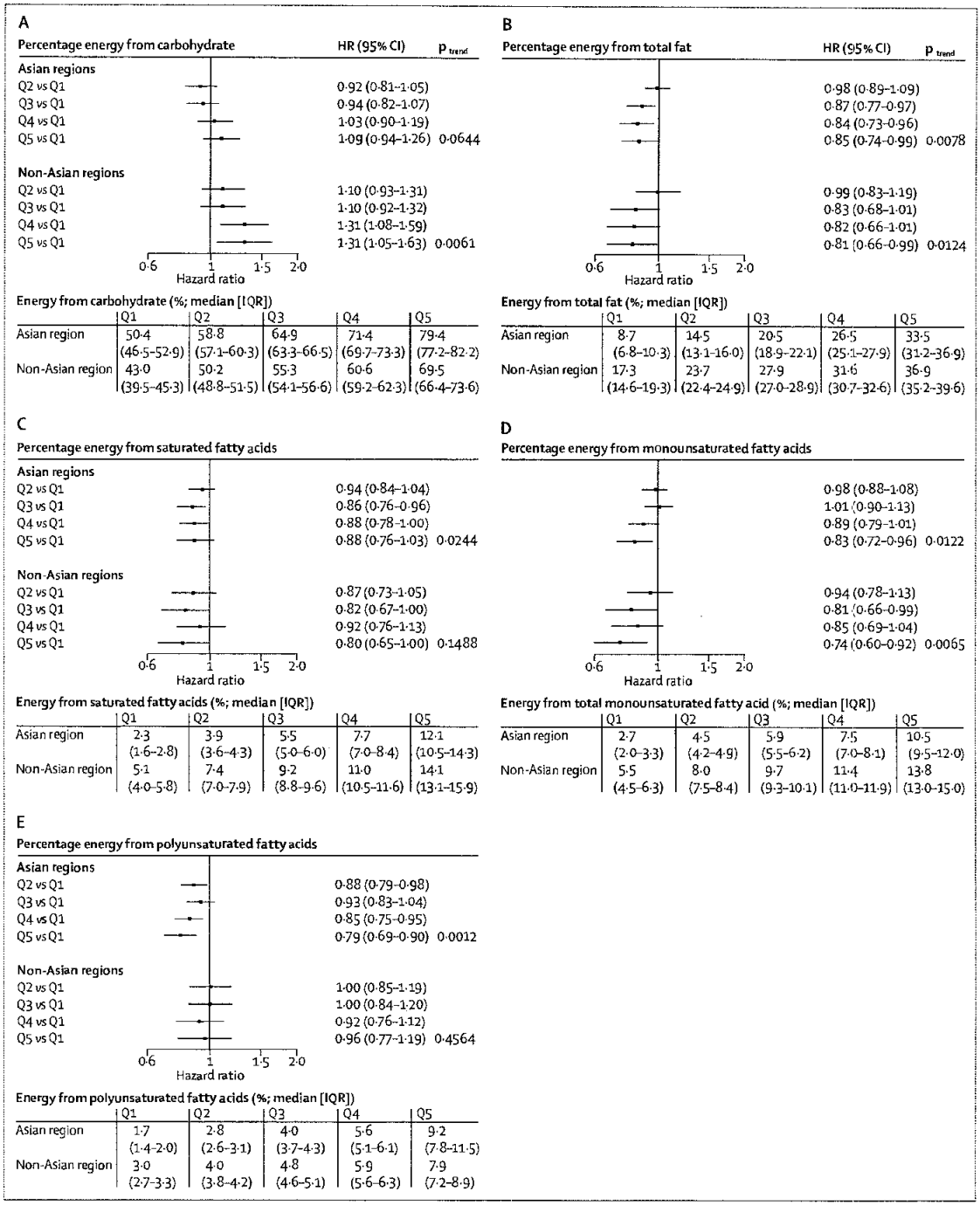

Figure 2: **Associations between (A) carbohydrate, (B) total fat, (C) saturated fatty acids, (D) monounsaturated fatty acids, and (E) polyunsaturated fatty acids with risk of total mortality in Asia and other regions**

Hazard ratios (HRs) and 95% CIs are adjusted for age, sex, education, waist-to-hip ratio, smoking, physical activity, diabetes, urban or rural location, and energy intake. Centre was also included as a random effect and frailty models were used (p for heterogeneity >0·2 for total fat and >0·5 for carbohydrate, saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids). Q1–Q5=quintiles 1–5.

Restricted multivariable cubic spline plots for total mortality and major cardiovascular disease and other outcomes are shown in figure 1 and the appendix (pp 20, 21). Multivariable splines for total fats and subtypes

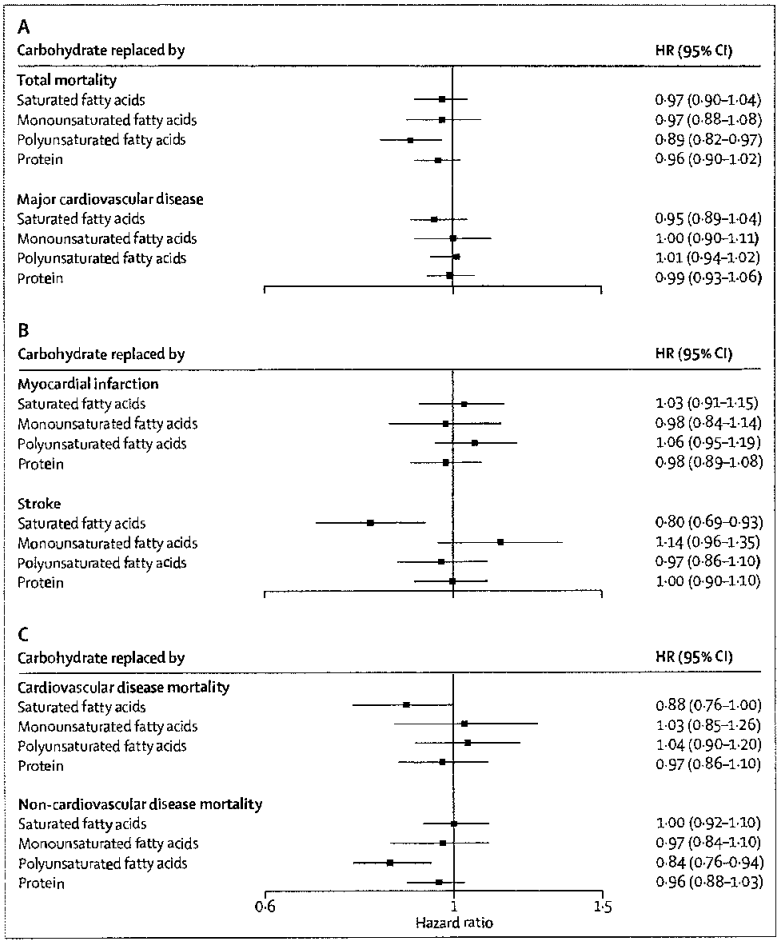

Figure 3: **Risk of clinical outcomes associated with isocaloric (5% of energy) replacement of carbohydrate with other nutrients (n=135 335)**

Hazard ratios (HRs) and 95% CIs are adjusted for age, sex, education, waist-to-hip ratio, smoking, physical activity, diabetes, urban or rural location, and energy intake. Centre was also included as a random effect and frailty models were used. Major cardiovascular disease=fatal cardiovascular disease+myocardial infarction+stroke+heart failure.

showed non-linear, decreasing trends in total mortality and major cardiovascular disease outcomes with increasing nutrients. However, multivariable splines for carbohydrate had a non-linear increasing trend in risks of total mortality and major cardiovascular disease (figure 1) and non-cardiovascular disease mortality (appendix p 21). The rise appeared to occur among those who consumed more than 60% (mid estimate from the spline) when energy intake from carbohydrate exceeded 70% energy (where the lower CI is above a HR of 1).

We investigated the influence of socioeconomic status and poverty using four different measures of socioeconomic status to adjust in the analysis of the associations between different nutrient intakes and total mortality and cardiovascular disease events. These were household wealth, household income, education, and economic level of the country subdivided by urban and rural locations. When we included education in the models, the estimates of association were robust. Additionally, we adjusted for study centre as a random effect which takes into account socioeconomic factors and clustering by community. When we reanalysed the data using household income, household wealth, or economic level of the country our results were unchanged (appendix p 34).

Higher carbohydrate intake was associated with higher risk of total mortality in both Asian countries and non-Asian countries (figure 2A). Conversely, higher intake of total fat and individual types of fat were each associated with lower total mortality risk in Asian countries and non-Asian countries (figure 2B–E).

Isocaloric (5% of energy) replacement of carbohydrate with polyunsaturated acids was associated with an 11% lower risk of mortality (HR 0·89 [95% CI 0·82–0·97]), whereas replacement of carbohydrate with saturated fatty acids, monounsaturated acids, or protein was not significantly associated with risk of total mortality. Replacement of carbohydrate with different types of fat or with protein was not significantly associated with major cardiovascular disease. Replacement of carbohydrate with saturated fatty acids was associated with a 20% lower risk of stroke (HR 0·80 [95% CI 0·69–0·93]). No significant associations with stroke risk were found for replacement of carbohydrate with other fats and protein. Replacement of carbohydrate with polyunsaturated fatty acids was associated with 16% lower risk of non-cardiovascular disease mortality (HR 0·84 [95% CI 0·76–0·94]; figure 3A–C).

Discussion

In this large prospective cohort study from 18 countries in five continents, we found that high carbohydrate intake (more than about 60% of energy) was associated with an adverse impact on total mortality and non-cardiovascular disease mortality. By contrast, higher fat intake was associated with lower risk of total mortality, non-cardiovascular disease mortality, and stroke. Furthermore, higher intakes of individual types of fat were associated with lower total mortality, non-cardiovascular disease mortality, and stroke risk and were not associated with risk of major cardiovascular disease events, myocardial infarction, or cardiovascular disease mortality. Our findings do not support the current recommendation to limit total fat intake to less than 30% of energy and saturated fat intake to less than 10% of energy. Individuals with high carbohydrate intake might benefit from a reduction in carbohydrate intake and increase in the consumption of fats.

For decades, dietary guidelines have focused on reducing total fat and saturated fatty acid intake, based on the presumption that replacing saturated fatty acids with carbohydrate and unsaturated fats will lower LDL cholesterol and should therefore reduce cardiovascular disease events. This focus is largely based on selective emphasis on some observational and clinical data,

despite the existence of several randomised trials and observational studies that do not support these conclusions.[9,35–37] Moreover, many studies that report higher risk of coronary heart disease deaths with higher saturated fatty acid intake were from North American and European populations (with relatively high intakes of total and saturated fats) where in the past cardiovascular disease was the major cause of deaths[38] and their applicability to other populations is uncertain.

In our study more than half of the participants (52%) consumed a high carbohydrate diet (at least 60% of energy) and about a quarter derive more than 70% of their energy from carbohydrate. This value is higher than most previous studies done in North America and Europe (appendix p 33). Furthermore, our study population represented a broad range of carbohydrate intake (mean intake of 46–77% of energy). This might explain the stronger association between carbohydrate intake and total mortality in our study compared with previous studies, which generally included participants with lower mean consumption of carbohydrate and a relatively narrower range of carbohydrate intake (35–56% of energy).[39–41] Moreover, in our study most participants from low-income and middle-income countries consumed a very high carbohydrate diet (at least 60% of energy), especially from refined sources (such as white rice and white bread), which have been shown to be associated with increased risk of total mortality and cardiovascular events.[42] Therefore, recommending lowering carbohydrate might be particularly applicable to such settings if replacement foods from fats and protein are available and affordable. It is also noteworthy that the spline plots showed a non-linear increasing trend in total mortality with a carbohydrate intake and the rise seems to occur among those who consumed more than 60% of energy from carbohydrate (ie, based on the midpoint of the estimate, with the lower CI showing an HR >0·1 when more than 70% of energy came from carbohydrates). Additionally, higher carbohydrate intakes increase some forms of dyslipidaemia (ie, higher triglycerides and lower HDL cholesterol), apolipoprotein B (ApoB)-to-apolipoprotein A1 (ApoA1) ratios and increased small dense LDL (the most atherogenic particles)[43,44] and increased blood pressure[45] (see Mente and colleagues[45]). However, the absence of association between low carbohydrate intake (eg, <50% of energy) and health outcomes does not provide support for very low carbohydrate diets. Importantly, a certain amount of carbohydrate is necessary to meet short-term energy demands during physical activity and so moderate intakes (eg, 50–55% of energy) are likely to be more appropriate than either very high or very low carbohydrate intakes.

A high carbohydrate diet is usually accompanied by a low fat intake. Our findings show a higher risk of total mortality, non-cardiovascular disease mortality, and stroke by lower fat consumption. The health benefit of replacing total fat with carbohydrate has been debated. Previous studies showed that replacement of fat with carbohydrate was not associated with lower risk of coronary heart disease and a pooled analysis of two large cohort studies (the Health Professionals Follow up and the Nurses' Health Study)[46] showed an inverse association between total fat and total mortality. Furthermore, higher glycaemic load was shown to be associated with a higher risk of ischaemic stroke in the Nurses' Health Study.[47] Our findings indicate that limiting total fat consumption is unlikely to improve health in populations, and a total fat intake of about 35% of energy with concomitant lowering of carbohydrate intake might lower risk of total mortality.

For individual fats, we found an inverse association between saturated fatty acid intake, total mortality, non-cardiovascular disease mortality, and stroke risk without any evidence of an increase in major cardiovascular disease, myocardial infarction, and cardiovascular disease mortality. Our spline showed a non-linear association between saturated fatty acid intake and outcomes and this suggests that the nature of the relationship is more complex than previously assumed and the risks might depend on the amount of nutrient consumed. This is the first large study to describe the association between low level saturated fatty acid intake (eg, <7% of energy) and total mortality and cardiovascular disease events. Two large prospective cohort studies (the Health Professionals Follow up and the Nurses' Health Study) did not find significant associations between saturated fatty acid intake and risk of cardiovascular disease when replacement nutrients were not taken into account.[38,39,48,49] Randomised controlled trials of saturated fatty acid reduction (replaced by polyunsaturated fatty acids) have also not shown a statistically significant impact on total mortality.[9,35–37] Unlike previous studies from North American and European countries, our study covers a much broader range of saturated fatty acid intake including a large number of people in the lower range of intake (ie, 50% of participants consumed less than 7% of energy and 75% of participants consumed less than 10% of energy from saturated fatty acids compared with 50% of participants with greater than 10% of energy in studies of North American and European countries). The larger number of people (75%) with lower saturated fatty acids consumption in PURE allows us to examine the associations of low saturated fatty acids with total mortality and cardiovascular disease events. Our findings of an inverse association between saturated fatty acid intake and risk of stroke are consistent with some previous cohort studies.[50] Collectively, the available data[9] do not support the recommendation to limit saturated fatty acids to less than 10% of intake and that a very low intake (ie, below about 7% of energy) might even be harmful.

We found an inverse association between monounsaturated fatty acid intake and total mortality. Consistent with our findings, two large cohort studies of the Health Professionals Follow up and the Nurses' Health Study showed lower total mortality by higher monounsaturated fatty acid intake.[46] Furthermore, our

findings are consistent with randomised trials of the Mediterranean diet that have shown reduced risk of total mortality and cardiovascular disease among those consuming higher amounts of olive oil and nuts.[51] Higher polyunsaturated fatty acid intake was associated with lower total mortality rates and a modest lower risk of stroke. This finding is consistent with the lower total mortality among US men and women (the Health Professionals Follow up and the Nurses' Health Study) and Japanese men,[52] as well as a meta-analysis of randomised clinical trials.[53] Extensive adjustment for socioeconomic status using four different approaches (education, household income, household wealth, and income level of the country, with subdivision by rural and urban location) did not alter our results. Despite this, it is possible that high consumption of carbohydrate and low consumption of animal products might simply reflect lower incomes; residual confounding as a potential reason for our results cannot be completely excluded.

In our replacement analyses, the strongest association on total mortality was observed when carbohydrate was replaced with polyunsaturated fatty acids, which is consistent with the pooled analyses of the Health Professionals Follow up and the Nurses' Health Study.[46] We found a lower risk of stroke when carbohydrate was replaced with saturated fatty acids, which is consistent with previous work showing that refined carbohydrate intake is associated with increased risk of stroke.[7,47]

Mente and colleagues[45] relate the intake of total fat, types of fat, and carbohydrate to blood lipids and observed patterns of associations that were consistent with previous studies (eg, higher intakes of saturated fatty acids are associated with higher LDL cholesterol, but also with higher HDL cholesterol, lower triglycerides, lower total cholesterol-to-HDL cholesterol ratio, and lower ApoB-to-ApoA1 ratio). By contrast, increased carbohydrate intake is associated with lower LDL cholesterol but also with lower HDL cholesterol and higher triglycerides, total cholesterol-to-HDL cholesterol ratio, and ApoB-to-ApoA1 ratio. The latter is particularly noteworthy as ApoB-to-ApoA1 ratio is the strongest lipid predictor of myocardial infarction and ischaemic strokes; this might provide a mechanistic explanation for the higher risk of events seen with high carbohydrate intake and the generally lower risk of cardiovascular disease with greater saturated fatty acid intake. The lipid findings not only confirm the validity of the FFQs that we used in the PURE study, but also show that nutrients have varying effects on different lipid fractions. This suggests that predicting the net clinical effect based on considering only the effects of nutrient intake on LDL cholesterol is not reliable in projecting the effects of diet on cardiovascular disease events or on total mortality.

Our study is the first to our knowledge that used country-specific FFQs and nutrient databases in a large number of individuals from countries in diverse regions with varying food habits. The standardised dietary method enabled a direct comparison of nutrients and foods within each region included in the study and standardised methods to collect and adjudicate events. However, our study had some limitations. First, we used FFQs to estimate participants' dietary intake which is not a measure of absolute intake, but is suited for classifying individuals into intake categories and is the most commonly used approach for assessing intake in epidemiological studies. Measurement error in reporting might lead to random errors that could dilute real associations between nutrients and clinical events. Second, dietary intakes were measured only at baseline, and it is possible that dietary changes might have occurred during the follow-up period. Even if major dietary changes occurred after the baseline assessment, they probably would have weakened the observed associations. Third, there is potential for social desirability bias and individuals who are health conscious might also adopt other healthy lifestyles. However, if this were the case, we would not expect to see different associations for the different outcomes. Fourth, as with any observational cohort study, observed associations might be in part due to residual confounding (eg, differences in the ability to afford fats and animal proteins, which are more expensive than carbohydrates) despite extensive adjustment for known confounding factors. Furthermore, while high-carbohydrate and low-fat diets might be a proxy for poverty or access to health care, all of our models adjusted for education and study centre (which tracks with country income and urban or rural location) and would be expected to account for differences in socioeconomic factors across intake categories. Additional analyses adjusting for other measures of socioeconomic status (household wealth or income) did not alter the results. Despite this, it is possible that high consumption of carbohydrate and low consumption of animal products might reflect lower incomes and residual confounding of our results cannot be completely excluded. We were unable to quantify separately the types of carbohydrate (refined *vs* whole grains) consumed. However, carbohydrate consumption in low-income and middle-income countries is mainly from refined sources. Fifth, we were unable to measure trans-fat intake which might affect our results, especially our replacement analyses. Lastly, our FFQ assessed polyunsaturated fatty acid intake mainly from foods, rather than from vegetable oils, which might have different health effects than those observed in our study.

In conclusion, we found that a high carbohydrate intake was associated with an adverse impact on total mortality, whereas fats including saturated and unsaturated fatty acids were associated with lower risk of total mortality and stroke. We did not observe any detrimental effect of fat intakes on cardiovascular disease events. Global dietary guidelines should be reconsidered in light of the consistency of findings from the present study, with the conclusions from meta-analyses of other observational studies[8,10,54] and the results of recent randomised controlled trials.[36]

Contributors

MD coordinated the entire nutrition component of PURE, wrote the analysis plans, and had the primary responsibility for writing the paper. SY designed and supervised the PURE study, interpreted the data, and reviewed and commented on all drafts. AM reviewed and commented on the data analysis and drafts. XZ did the analysis and reviewed and commented on drafts. SSA reviewed and commented on the data analysis and drafts. SIB reviewed and commented on the data analysis. SR coordinated the worldwide study and reviewed and commented on drafts. All other authors coordinated the study in their respective countries and provided comments on drafts of the manuscript.

Declaration of interests

We declare no competing interests.

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Novel subgroups of type 2 diabetes and their association with microvascular outcomes in an Asian Indian population: a data-driven cluster analysis: the INSPIRED study

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ABSTRACT

Introduction Type 2 diabetes is characterized by considerable heterogeneity in its etiopathogenesis and clinical presentation. We aimed to identify clusters of type 2 diabetes in Asian Indians and to look at the clinical implications and outcomes of this clustering.

Research design and methods From a network of 50 diabetes centers across nine states of India, we selected 19 084 individuals with type 2 diabetes (aged 10–97 years) with diabetes duration of less than 5 years at the time of first clinic visit and performed k-means clustering using the following variables: age at diagnosis, body mass index, waist circumference, glycated hemoglobin, serum triglycerides, serum high-density lipoprotein cholesterol and C peptide (fasting and stimulated). This was then validated in a national epidemiological data set of representative individuals from 15 states across India.

Results We identified four clusters of patients, differing in phenotypic characteristics as well as disease outcomes: cluster 1 (Severe Insulin Deficient Diabetes, SIDD), cluster 2 (Insulin Resistant Obese Diabetes, IROD), cluster 3 (Combined Insulin Resistant and Deficient Diabetes, CIRDD) and cluster 4 (Mild Age-Related Diabetes, MARD). While SIDD and MARD are similar to clusters reported in other populations, IROD and CIRDD are novel clusters. Cox proportional hazards showed that SIDD had the highest hazards for developing retinopathy, followed by CIRDD, while CIRDD had the highest hazards for kidney disease.

Conclusions Compared with previously reported clustering, we show two novel subgroups of type 2 diabetes in the Asian Indian population with important implications for prognosis and management. The coexistence of insulin deficiency and insulin resistance seems to be peculiar to the Asian Indian population and is associated with an increased risk of microvascular complications.

Significance of this study

What is already known about this subject?

- Recently five distinct 'clusters' of individuals with diabetes with significantly different characteristics have been identified in a Scandinavian population.
- The unique Asian Indian phenotype predisposes them to young-onset type 2 diabetes (T2D).

What are the new findings?

- For the first time in India (and South Asia), clustering was done on 19 084 individuals with T2D using eight clinically relevant variables (age at diagnosis, body mass index, waist circumference, glycated hemoglobin, triglycerides, high-density lipoprotein cholesterol, and C peptide fasting and stimulated).
- Four replicable clusters were identified, two of which were unique to the Asian Indian population.
- The novel cluster 'Combined Insulin Resistant and Deficient Diabetes' is of particular importance as it is characterized by difficult-to-control hyperglycemia and increased hazards of kidney disease and retinopathy.

How might these results change the focus of research or clinical practice?

- Classifying Asian Indians with T2D into phenotypic clusters provides insights into the pathophysiological processes driving diabetes in this ethnic group, which could help in predicting the risk of complications and in focusing attention to individuals with the highest risk of morbidity and mortality.

BACKGROUND

Global estimates suggest that 463 million individuals have diabetes as of 2019 and that this number will increase to 700 million by 2045.[1] More than 90% of these individuals have type 2 diabetes, a condition that is characterized by considerable heterogeneity in its etiopathogenesis and clinical presentation. This heterogeneity has significant implications on the treatment and prognosis of patients with this condition.

Recently, distinct 'clusters' or subgroups of individuals with type 2 diabetes have been identified in a Scandinavian population of 8980 individuals, based on five parameters representing the clinical presentation as well as the presence of insulin resistance and beta-cell dysfunction.[2] These five subgroups have been termed severe autoimmune diabetes, severe insulin deficient diabetes, severe insulin resistant diabetes, mild obesity-related diabetes and mild age-related diabetes. Further analyses of these subgroups have shown that such clustering might have implications with respect to the risk of diabetes complications as well as selection of the most appropriate treatment. However, as the above study has been performed on a white Caucasian population, there is still no clarity on whether this classification is applicable to individuals with diabetes belonging to other ethnic groups.

Asian Indians (South Asians) represent an ethnic group with high predilection for developing type 2 diabetes; indeed, some of the largest increases in diabetes prevalence have been reported from the South Asian region. Type 2 diabetes in Asian Indians differs from that in white Caucasians in a number of significant ways. They tend to develop diabetes at a younger age and at lower levels of obesity than do white Caucasians. They also tend to progress faster from stages of 'pre-diabetes' to frank diabetes than members of other ethnic groups. The 'Asian Indian phenotype', characterized by high levels of abdominal fat and increased insulin resistance even at low levels of body mass index (BMI), has been postulated as a reason for this increased propensity to develop type 2 diabetes.[3] However, recent studies suggest that beta-cell dysfunction occurs quite early and rapidly in Asian Indians.[4] Type 2 diabetes in Asian Indians therefore appears to have a slightly different pathophysiology, with severe insulin deficiency being the primary defect in contrast to white Caucasians, in whom the main driver of diabetes is obesity and consequent insulin resistance.

It is therefore possible due to the above and the well-known younger age at diagnosis that clusters of type 2 diabetes identified in Asian Indians based on parameters used in the Western population might not behave exactly in the same manner with respect to treatment outcomes and risk of complications. In this paper, we attempt to identify distinct clusters of type 2 diabetes in Asian Indians and to look at the clinical implications and outcomes of this clustering. This study is part of the INdia-Scotland Partnership for pRecision mEdicine in Diabetes (INSPIRED) project.

RESEARCH DESIGN AND METHODS

Study population

Data for this analysis were obtained from the electronic medical records of a tertiary care center for diabetes, which has 50 branches spread across nine states of India. Clinical data of more than 400 000 patients have been captured and stored in the common diabetes electronic medical records (DEMR) system of the center,[5] which represents one of the largest databases of patients with diabetes in the world. Each patient is provided a unique identification number at the time of their first registration, and clinical, anthropometric and biochemical data are updated in the system at each subsequent visit. Patients undergo a comprehensive evaluation for classification of diabetes, assessment of control and presence of chronic complications at the time of their index visit, and these tests are repeated subsequently at regular intervals based on prespecified protocols.

The following examinations and investigations are performed for every patient during their clinic visits. Height, weight and waist circumference are measured using standardized techniques and the BMI calculated as weight (in kilograms) divided by the square of height (in meters). Blood pressure is recorded to the nearest 2 mm Hg from the right arm in a sitting position with a mercury sphygmomanometer (Diamond Deluxe BP Apparatus, Pune, India).

Blood samples are collected for the measurement of various parameters including fasting and postprandial plasma glucose, lipid profile, kidney and liver function tests, glycated hemoglobin (HbA1c), and C peptide (fasting and stimulated), while Glutamic Acid Decarboxylase (GAD) autoantibodies are measured in a selected subset of patients. Fasting plasma glucose (FPG), serum cholesterol, serum triglycerides and high-density lipoprotein (HDL) cholesterol are measured using Hitachi 912 Autoanalyzer (Hitachi, Mannheim, Germany). Fasting C peptide levels and stimulated (postbreakfast) C peptide levels are estimated by the electrochemiluminescence method on an Elecsys 2010 machine (Hitachi). To obtain the C peptide values, a fasting blood sample is obtained after an overnight fast of at least 8 hours and a postprandial sample after 90 min of a standard South Indian breakfast (above 250 calories).[6] HbA1c is measured by high-performance liquid chromatography using the Variant machine (Bio-Rad, Hercules, California, USA).

Diabetes is diagnosed if the FPG level is ≥126 mg/dL (7.0 mmol/L) and/or 2-hour postload glucose level is ≥200 mg/dL (11.1 mmol/L) and/or if the patient has been prescribed pharmacotherapy for diabetes by a physician.[7]

Type 2 diabetes is diagnosed by absence of ketosis, good beta-cell reserve as shown by fasting C peptide assay >0.6 pmol/mL, absence of pancreatic calculi (on abdominal radiograph), and response to oral hypoglycemic agents for at least 2 years.[8]

Assessment of complications is done as follows:

Retinopathy

A detailed retinal (fundus) examination is done by both direct and indirect ophthalmoscopy by a retinal specialist. Fundus photography is done using four-field stereo color retinal photography (Model FF 450 plus camera, Carl Zeiss, Jena, Switzerland). An Early Treatment Diabetic Retinopathy Study grading system that has been modified

and standardized in other population-based studies is used for the diagnosis of retinopathy.[9 10]

Nephropathy

Microalbuminuria is diagnosed if the albumin excretion was between 30 and 299 µg/mg and macroalbuminuria if albumin excretion is ≥300 µg/mg.[11] Nephropathy is defined as the presence of either microalbuminuria or macroalbuminuria.

Chronic kidney disease (CKD) is defined as an estimated glomerular filtration rate of less than 60 mL/min/1.73m^2 as calculated by the CKD-Epi formula.

Diabetic kidney disease is defined as the presence of CKD and/or albuminuria.

Homeostasis Model Assessment of beta-cell function (HOMA-B) and insulin resistance (HOMA-IR) are assessed based on C peptide concentrations and plasma glucose using the HOMA calculator (University of Oxford, Oxford, UK).[12]

From the DEMR, we selected 373 000 individuals aged 10–97 years who had a diagnosis of type 2 diabetes. From these, we further selected 55 429 individuals who had baseline data available for the variables of interest, namely age at diagnosis, BMI, waist circumference, HbA1c, serum triglycerides, serum HDL cholesterol, and C peptide (fasting and stimulated). Of these, we selected 20 850 individuals with reported duration of diabetes less than 5 years at first clinic visit (mean 1.74±1.4 years). After merging the HOMA-B and HOMA-IR and removing individuals with HOMA-B >500 and HOMA-IR <20 (n=1512), removing outliers for the remaining variables by the 5SD method (n=188) and excluding individuals who had a positive test for GAD autoantibodies (n=66), we had a final sample size of 19 084.

Cluster analysis

The k-means clustering method was done with k value of 4 using k-means function (max iteration=10 000) in R V.3.6.0. Cluster forming tendency of the data was validated by the Hopkins statistic value. The optimal number of clusters was determined based on silhouette width. Cluster-wise stability was computed by Jaccard bootstrap method through resampling of the data set 2000 times. A stable cluster generally yields Jaccard similarity index of greater than 0.75.[13] Cluster analysis was performed on scaled and centered values. Cluster labels were assigned based on the phenotype characteristics of individual cluster mean values of the variables.

Sensitivity analysis was done using three time periods for duration of diabetes <1 year, <3 years, and <5 years. Clustering tendency of the three different baseline diabetes duration data was found to have Hopkins statistic values of 0.19, 0.18, and 0.16, indicating that there were no significant differences in the cluster groups. Reclustering was done on men and women separately to validate the clustering and avoid the sex-dependent stratification effect on the phenotype variables. The minimum silhouette width was similar in both genders (male and female).

Statistical models

The risk of development of diabetes complications was calculated using Cox regression models with covariate as a cluster label and adjusted for age at diagnosis and sex, after excluding individuals who already had complications at their first visit to the clinic. Cluster-wise time to reaching target goal was analyzed by Cox regression model. Cox proportional hazards assumptions were tested using R V.3.6.0.

Validation of clustering in a nationally representative epidemiological data set (ICMR-INDIAB study)

In order to validate the applicability of this clinic-based clustering to the general population, we attempted to replicate the clustering in the data set derived from the nationally representative Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study. ICMR-INDIAB is a nationwide population-based study on diabetes and related non-communicable diseases being carried out in all 29 states and 2 of the Union Territories of India based on a representative sample of each state. The detailed methodology of ICMR-INDIAB has been published elsewhere.[14] Data from ICMR-INDIAB on the prevalence of diabetes in 15 states of India have been published.[15]

For purposes of this validation study, we selected 3851 individuals with type 2 diabetes from the INDIAB study population in 15 states of India and clustering was performed using the following six variables: age at diagnosis, BMI, waist circumference, HbA1c, serum triglycerides and serum HDL cholesterol. We excluded C peptide from the analysis as we did not have data on this variable in the population-based sample. After excluding 1521 individuals who did not have data on all our variables of interest as well as 88 outliers (5SD), we had a final sample size of 2204 individuals for the analysis. The k-means clustering was applied with k value as 4 (max iteration=10 000) in R V.3.6.0. The optimal cluster number was determined based on the silhouette width method.

Comparison with the Scandinavian clusters

Using the same five variables (age at onset, BMI, HbA1c, HOMA-B and HOMA-IR) reported by Ahlqvist *et al*,[2] we then attempted to assess whether the clusters identified in the Scandinavian population are replicable in the DEMR-derived Asian Indian clinic population. We applied the k-means clustering (k=4) on the Asian Indian population (N=19 084) based on these five variables and analyzed the optimal cluster number based on the silhouette width method.

We were unable to perform the Scandinavian clustering in the population-based INDIAB sample as we did not have information on variables such as HOMA-B and HOMA-IR in the epidemiological data set.

RESULTS

Using cluster analysis based on eight clinically relevant variables (age at diagnosis, BMI, waist circumference,

Table 1 Clinical and biochemical characteristics of the various subgroups of type 2 diabetes

	Cluster 1 (SIDD)	Cluster 2 (IROD)	Cluster 3 (CIRDD)	Cluster 4 (MARD)
n	5009	4934	2313	6828
Frequency, %	26.2	25.9	12.1	35.8
Men, %	65.8	59.8	73.7	58.6
Age at diagnosis, years	42.5 (10.8)	46.5 (10.4)	42.1 (9.8)	50.2 (10.3)
BMI, kg/m^2	24.9 (3.5)	32.6 (4.1)	26.5 (3.1)	25.9 (2.9)
Waist circumference, cm	90 (8.8)	108 (8.9)	94.9 (8.1)	92.4 (7.4)
Glycated hemoglobin, %	10.7 (2.1)	8.3 (1.8)	9.1 (1.9)	7.2 (1.2)
Glycated hemoglobin, mmol/mol	93.0	67.0	76.0	55.0
Serum triglycerides, mg/dL	149 (59)	155 (59)	351 (102)	136 (50)
HDL cholesterol, mg/dL	40 (9)	38 (8)	36 (8)	42 (9)
C peptide fasting, pmol/mL	0.8 (0.3)	1.5 (0.4)	1.2 (0.4)	1.1 (0.3)
C peptide stimulated, pmol/mL	1.7 (0.6)	3.3 (0.8)	2.6 (0.8)	3 (0.7)
HOMA-B	38.8 (26.9)	100.8 (51.5)	64.5 (37.7)	94.1 (43.1)
HOMA-IR	2.8 (1.6)	4.1 (1.5)	3.8 (1.9)	2.6 (0.8)
WHR	0.93 (0.06)	0.97 (0.08)	0.96 (0.06)	0.94 (0.07)
Systolic blood pressure, mm Hg	123 (16)	128 (16)	127 (17)	127 (17)
Diastolic blood pressure, mm Hg	79 (9)	82 (9)	81 (10)	79 (9)
Serum cholesterol, mg/dL	188 (43)	176 (40)	206 (44)	177 (41)
LDL cholesterol, mg/dL	118 (37)	107 (35)	106 (38)	108 (35)
Insulin at registration, %	24.9	10.6	15.0	5.3
Metformin at registration, %	38.4	71.3	50.9	63.4
Sulfonylureas at registration, %	32.8	44.1	38.0	39.7
Statin at registration, %	30.2	37.8	37.3	37.8
ACE inhibitor at registration, %	2.4	3.5	2.9	3.4

Variables in bold are those used for clustering.
ACE, angiotensin converting enzyme; BMI, body mass index; CIRDD, Combined Insulin Resistant and Deficient Diabetes; HDL, high-density lipoprotein; HOMA-B, homeostasis model assessment of beta-cell function; HOMA-IR, homeostasis model assessment of insulin resistence; IROD, Insulin Resistant Obese Diabetes; LDL, low-density lipoprotein; MARD, Mild Age-Related Diabetes; SIDD, Severe Insulin Deficient Diabetes; WHR, waist hip ratio.

HbA1c, serum triglycerides, serum HDL cholesterol, and C peptide fasting and stimulated), we were able to identify four replicable clusters of patients with type 2 diabetes in this Asian Indian population. The optimal number of clusters was based on silhouette width obtained from both the DEMR and the national ICMR-INDIAB data sets (online supplementary figure S1A,B). Table 1 shows the clinical and biochemical characteristics of these four clusters with respect to the eight variables used for clustering and compares other clinically relevant variables across these clusters. The Jaccard similarity index was greater than 0.75, which confirmed that the cluster allocations were stable.

Cluster 1, referred to as Severe Insulin Deficient Diabetes (SIDD), included 26.2% of clustered patients and was characterized by the lowest BMI and waist circumference, as well as the lowest C peptide (fasting and stimulated) levels. HOMA-B and HOMA-IR were both low in this cluster. These individuals had the highest HbA1c values and were more likely to be using insulin compared with the other clusters.

Cluster 2 is a novel cluster which we refer to as Insulin Resistant Obese Diabetes (IROD). This comprised 25.9% of clustered patients. These individuals had the highest BMI and waist circumference and the highest C peptide levels. HOMA-B and HOMA-IR were also the highest for this cluster. Metabolic control was intermediate and individuals were more likely to be on metformin.

Cluster 3, another novel group identified in this population, is referred to asCombined Insulin Resistant and Deficient Diabetes (CIRDD) and constitutes 12.1% of the study population. This group was characterized by the lowest age at onset. BMI and waist circumference were intermediate between SIDD and IROD. CIRDD had the highest triglyceride and lowest HDL cholesterol levels of all the four groups. C peptide levels were higher than SIDD, but lower than IROD. HOMA-B and HOMA-IR values were also intermediate between SIDD and IROD, indicating coexistence of insulin deficiency and insulin resistance. Metabolic control tended to be poor; however, only 15% were on insulin.

Table 2 Cox HR for microvascular complications across clusters

	Labels	Events (%)	HR (95% CI)*	P value
Retinopathy	SIDD	4.9	1.56 (1.22 to 1.98)	**<0.001**
	IROD	2.7	0.99 (0.79 to 1.24)	0.95
	CIRDD	4.1	1.31 (1.01 to 1.71)	**<0.05**
	MARD	2.9	1	–
Nephropathy	SIDD	6.4	1.18 (0.96 to 1.45)	0.1094
	IROD	6.3	1.03 (0.87 to 1.23)	0.672
	CIRDD	6.2	1.23 (1.05 to 1.46)	**<0.0001**
	MARD	5.7	1	–
CKD	SIDD	1.5	1.30 (0.94 to 1.78)	0.1031
	IROD	1.8	1.48 (1.12 to 1.97)	**<0.001**
	CIRDD	2.2	2.30 (1.61 to 3.26)	**<0.001**
	MARD	2	1	–
DKD	SIDD	6	1.03 (0.88 to 1.20)	0.7002
	IROD	6.3	1.20 (0.98 to 1.47)	0.0732
	CIRDD	5.7	1.22 (1.03 to 1.45)	**<0.05**
	MARD	5.9	1	–

The bold values denote the differences that have attained statistical significance.
*Adjusted for age, sex, HbA1c and blood pressure, using MARD as the reference group, HR=1.0.
CIRDD, Combined Insulin Resistant and Deficient Diabetes; CKD, chronic kidney disease; DKD, diabetic kidney disease; HbA1c, glycated hemoglobin; IROD, Insulin Resistant Obese Diabetes; MARD, Mild Age-Related Diabetes; SIDD, Severe Insulin Deficient Diabetes.

Cluster 4, referred to as Mild Age-Related Diabetes (MARD), represented the most frequent cluster in this population (35.8%) and was characterized by later age at onset than other clusters. They were characterized by the highest HDL cholesterol, fairly preserved C peptide values and the best metabolic control of all the four groups. This group had the least use of insulin.

The characteristics of the clusters did not differ when split by gender (online supplementary table S1, online supplementary figure S2A,B) and duration of diabetes (online supplementary table S2).

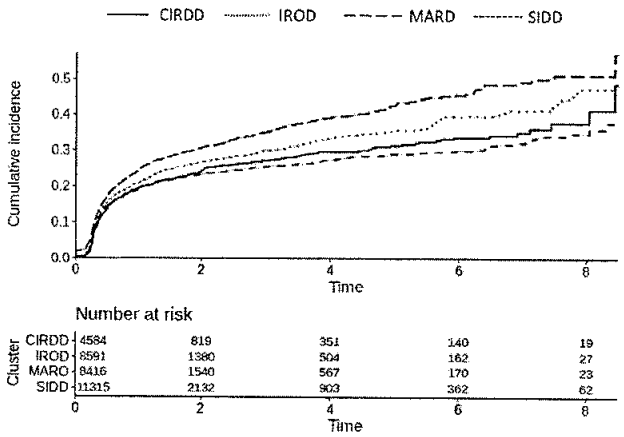

Figure 1 Reaching treatment goal (glycated hemoglobin <7% (53 mmol/mol)). CIRDD, Combined Insulin Resistant and Deficient Diabetes; IROD, Insulin Resistant Obese Diabetes; MARD, Mild Age-Related Diabetes; SIDD, Severe Insulin Deficient Diabetes.

Online supplementary table S3 shows the clustering without including HbA1c in the model. It was observed that the cluster characteristics are similar even without including HbA1c. In this model, SIDD was the most frequent cluster (32.7%), followed by MARD (31.9%), IROD (21.9%) and CIRDD (13.5%).

Table 2 shows the Cox proportional HR for various microvascular complications of diabetes among the clusters. SIDD had the highest hazards for developing retinopathy, followed by CIRDD ($p<0.05$), while CIRDD had the highest hazards for kidney disease (both CKD ($p<0.05$) and proteinuria) after adjusting for age, gender, HbA1c and blood pressure.

Figure 1 shows the time to reach treatment goal (HbA1c <7% (53 mmol/mol)) for various clusters. MARD showed the shortest time to reach goal, and CIRDD and SIDD the longest (online supplementary table S4).

Results from the validation with INDIAB data

Results from the validation study with the INDIAB data show that the clusters identified in the clinic population are replicable in this nationally representative data set (table 3).

In the INDIAB population, MARD was the most frequent cluster (34.8%), followed by IROD (30.3%), SIDD (24.7%) and CIRDD (7.6%). SIDD had the lowest BMI and waist circumference and highest HbA1c. IROD had the highest BMI and waist circumference

Table 3 Validation of cluster in nationally representative ICMR-INDIAB data (n=2204)

	Cluster 1 (SIDD)	Cluster 2 (IROD)	Cluster 3 (CIRDD)	Cluster 4 (MARD)
n	603	667	167	767
%	27.4	30.3	7.6	34.8
Men, %	54.6	52.0	63.5	57.5
Age at diagnosis, years	40.1 (9.8)	48.2 (9.6)	45.4 (10.2)	55.5 (9.8)
BMI, kg/m^2	22.7 (3.1)	29.9 (3.6)	25 (2.9)	23.4 (2.8)
Waist circumference, cm	82.8 (9.2)	102.5 (8.0)	90.4 (8.9)	86.1 (8.9)
Glycated hemoglobin, %	10.0 (2.1)	7.9 (1.8)	9.0 (2.0)	6.7 (1.2)
Glycated hemoglobin, mmol/mol	86.0	63.0	75.0	50.0
Serum triglycerides, mg/dL	180.6 (84.0)	187.8 (82.3)	414.0 (48.3)	151.1 (72.8)
HDL cholesterol, mg/dL	40.9 (10.5)	37.3 (8.9)	31.6 (8.1)	39.0 (10.3)
Serum cholesterol, mg/dL	183.5 (47.8)	178.3 (41.1)	218.9 (56.6)	171.7 (42.0)
Systolic blood pressure, mm Hg	135.1 (21.3)	141.6 (23.4)	139.6 (21)	142.4 (24.1)
Diastolic blood pressure, mm Hg	82.6 (11.1)	83.7 (12.6)	86 (11.3)	82.2 (12.2)

Variables in bold are those used for clustering.
BMI, body mass index; CIRDD, Combined Insulin Resistant and Deficient Diabetes; HDL, high-density lipoprotein; ICMR-INDIAB, Indian Council of Medical Research-India Diabetes; IROD, Insulin Resistant Obese Diabetes; MARD, Mild Age-Related Diabetes; SIDD, Severe Insulin Deficient Diabetes.

and intermediate metabolic control. Individuals in the CIRDD cluster had BMI intermediate between SIDD and IROD, the highest triglycerides and lowest HDL, and high HbA1c and diastolic blood pressure. MARD had the highest age at diagnosis, the highest HDL levels, the lowest diastolic blood pressure and the best metabolic control. In all these respects, the clusters derived from the ICMR-INDIAB population behaved similar to those derived from the DEMR.

Results of comparison with the Scandinavian clusters

We then undertook the clustering based on the five variables used by Ahlqvist *et al*.[2] We found that there were considerable differences between the clusters obtained in the Scandinavian population and the Asian Indian population (online supplementary tables S5 and S6). The insulin deficient cluster in the Asian Indian population was similar to SIDD in the Scandinavian population, as was the mild age-related subgroup to MARD (although with a lower age); however, the severely insulin resistant group in our population was also characterized by poor beta-cell function and higher levels of obesity (unlike severe insulin resistant diabetes in the Scandinavian population), while the mild obesity-related diabetes cluster could not be clearly defined in our population.

CONCLUSIONS

In this analysis of around 20 000 individuals with type 2 diabetes from South India, we were able to identify four clusters of patients, differing in phenotypic characteristics as well as disease outcomes with respect to diabetes control and risk of complications. These findings replicated in a population-based study in India across 15 Indian states. Two of these subgroups (SIDD and MARD) correspond to the clusters identified by Ahlqvist *et al*[2] in the Scandinavian populations,while the other two are novel subgroups (CIRDD and IROD) with certain unique phenotypic and biochemical characteristics.

One of these novel subgroups, which we have termed CIRDD, comprises a minority of patients with type 2 diabetes in our population, but represents a more aggressive phenotype in that the age of onset is lower and their metabolic control is almost as poor as those of the severe insulin deficient (SIDD) group. Also, they took almost as long as those in the SIDD cluster to reach treatment goals. It is likely that the presence of dual pathophysiology renders these individuals at high risk of developing diabetes at younger ages and predisposes them to poorer glycemic control. These individuals also had the highest serum triglyceride levels among all the clusters, possibly on account of accelerated lipolysis, secondary to insulin resistance. The insulin deficiency in these individuals could, in part, be attributed to beta-cell damage due to lipotoxicity. Patients with CIRDD also had the highest hazards of developing kidney disease and the second highest hazards for retinopathy. More aggressive therapy with a combination of agents targeting multiple pathophysiologies of type 2 diabetes may be indicated in these patients (perhaps as early as at the time of diagnosis) so as to help them develop a favorable 'legacy effect' and thus help prevent long-term complications. They also need to be screened more aggressively for complications, particularly nephropathy and retinopathy. All these of course have to be tested prospectively through well-planned randomized clinical trials.

Individuals with the second novel subgroup, IROD, had better metabolic control than either SIDD or CIRDD, implying that they have sufficient beta-cell function to at

least partially compensate for the obesity-related insulin resistance. However, they also had high risk of developing kidney disease. The higher risk of kidney disease in the two insulin resistant phenotypes (CIRDD and IROD) can be explained by the association of insulin resistance with increased salt sensitivity, glomerular hypertension and hyperfiltration.[16] The excess risk of kidney disease in CIRDD over and above that in IROD can likely be explained by the poorer glycemic control in the former, on account of concomitant insulin deficiency.

The SIDD phenotype is similar to that described by Ahlqvist *et al*[2] and had the worst metabolic control and took the longest time to reach treatment goal among the four subgroups. Similar to the Scandinavian population, the risk of retinopathy was highest in this insulin deficient phenotype, underlying the pivotal role played by hyperglycemia secondary to insulin deficiency in the development of this microvascular complication. Enabling timely attainment of glycemic goals in these individuals would require more intensive use of insulin therapy, patient education and adoption of technologies than has been the case thus far.

Individuals in the MARD subgroup formed the most frequent cluster in our population and behaved similar to the corresponding cluster in the Scandinavian population. They had the best metabolic control and the lowest risk of complications of all the four subgroups. However, these individuals had a significantly lower age of onset of diabetes (50.2 years) compared with those in the Scandinavian MARD cluster (67.3 years). This is likely explained by the lower age of onset of diabetes in the Asian Indian population in general. We cannot be certain whether our patients with MARD will continue to exhibit features of a mild phenotype of diabetes for the remainder of their lifespan; regular follow-up and monitoring is therefore essential even in this seemingly benign subgroup of type 2 diabetes.

Recent attempts to replicate the subclassification of type 2 diabetes in the US and Chinese population applying similar variables to those applied in the Scandinavian population have suggested that this European-oriented classification is generalizable to other ethnic groups.[17] In contrast, when we adopted the same approach in our Asian Indian population, we found that two of the subgroups could not be defined as described by Ahlqvist *et al*.[2] We postulate that our novel clustering approach (using variables that have been shown to be associated with the Asian Indian phenotype) will be more clinically relevant to our population. While we did use C peptide in our clustering in order to prove the existence of beta-cell deficiency, we were able to replicate the clusters even without the C peptide values. In resource-constrained settings, the use of C peptide may not be feasible. It is therefore gratifying that the model works even without C peptide, which would help to scale up the use of these clusters to smaller clinics in remote areas; however, the predictive accuracy will be slightly lower if this approach is used. Similarly, the cluster characteristics remained stable even if HbA1c was not used, but considering that the clinical accuracy is much improved when HbA1c is used, we prefer that HbA1c stays in the model. Moreover, HbA1c is now part of the standard of care for diabetes in India, as in the rest of the world.

The strengths of our study include the use of a very large database on diabetes and identification of clusters based on phenotypic variables appropriate to the Asian Indian phenotype. However, the study does have a few limitations. Our institution being a private, pay-for-service clinic, data on all the variables of interest were not available for every patient due to financial constraints. Similarly, as our institution is also a tertiary referral center for diabetes, only the more severe or advanced cases of diabetes tend to visit the clinic, and this could have introduced an element of bias into our results. Our results, however, show that these clusters are replicable when applied to a nationally representative population derived from a large epidemiological study, suggesting that they are generalizable to the Asian Indian population with diabetes.

In conclusion, we show that type 2 diabetes in the Asian Indian population can be classified into four phenotypic clusters with important implications for prognosis and management. While two of these clusters correspond to those reported in the white Caucasian population, the other two are novel and unique to the Asian Indian population. Of the four clusters, CIRDD is of particular importance as it represents a more aggressive phenotype of type 2 diabetes characterized by difficult-to-control hyperglycemia and markedly increased hazards of kidney disease and retinopathy. We acknowledge that categorizing patients into subtypes will have less power to predict complications than using the continuous data,[18] but conceptually we believe it is important to recognize that patients in India differ phenotypically and this phenotypic variation impacts on their risk of complications. Risk prediction either based on allocation to subgroups or using the continuous traits in clinical practice will help physicians tailor their treatment strategies such that individuals receive the most appropriate therapy right from the time of diagnosis.

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VB, SJ, MKS and ATNN were involved in data retrieval and statistical analyses. RU, RP and CP were involved in the interpretation of data and provided comments on drafts of the manuscript. All authors contributed to revision of the manuscript and approved the final submitted version. VM 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.

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The Stepwise Approach to Diabetes Prevention: Results From the D-CLIP Randomized Controlled Trial

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OBJECTIVE

This study tests the effectiveness of expert guidelines for diabetes prevention: lifestyle intervention with addition of metformin, when required, among people with prediabetes.

RESEARCH DESIGN AND METHODS

The Diabetes Community Lifestyle Improvement Program (D-CLIP) is a randomized, controlled, translation trial of 578 overweight/obese Asian Indian adults with isolated impaired glucose tolerance (iIGT), isolated impaired fasting glucose (iIFG), or IFG+IGT in Chennai, India. Eligible individuals were identified through community-based recruitment and randomized to standard lifestyle advice (control) or a 6-month, culturally tailored, U.S. Diabetes Prevention Program–based lifestyle curriculum plus stepwise addition of metformin (500 mg, twice daily) for participants at highest risk of conversion to diabetes at ≥4 months of follow-up. The primary outcome, diabetes incidence, was assessed biannually and compared across study arms using an intention-to-treat analysis.

RESULTS

During 3 years of follow-up, 34.9% of control and 25.7% of intervention participants developed diabetes (P = 0.014); the relative risk reduction (RRR) was 32% (95% CI 7–50), and the number needed to treat to prevent one case of diabetes was 9.8. The RRR varied by prediabetes type (IFG+IGT, 36%; iIGT, 31%; iIFG, 12%; P = 0.77) and was stronger in participants 50 years or older, male, or obese. Most participants (72.0%) required metformin in addition to lifestyle, although there was variability by prediabetes type (iIFG, 76.5%; IFG+IGT, 83.0%; iIGT, 51.3%).

CONCLUSIONS

Stepwise diabetes prevention in people with prediabetes can effectively reduce diabetes incidence by a third in community settings; however, people with iIFG may require different interventions.

Randomized controlled trials have shown the efficacy of lifestyle interventions or metformin for reducing diabetes conversion among individuals with impaired glucose tolerance (IGT) (1–5). The American Diabetes Association (ADA) and the International Diabetes Federation recommend stepwise diabetes prevention (lifestyle modification plus metformin when risk remains elevated) for individuals with any form of prediabetes, defined as isolated IGT (iIGT), isolated impaired fasting glucose

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(iIFG), or IFG+IGT (6,7). However, no large diabetes prevention trial has compared the effects of diabetes prevention across the prediabetes spectrum, and no study has tested the effectiveness of the stepwise diabetes prevention recommendations.

The incredible diabetes burden reflects our failure to translate proven evidence for prevention into action on a wider scale. Worldwide, 415 million people have diabetes, and this number will reach 642 million by 2040 (8). Most individuals with diabetes, 75%, live in low- and middle-income countries (LMICs) (8), where the condition has especially marked effects on health and economic prosperity.

The Diabetes Community Lifestyle Improvement Program (D-CLIP) (9) is a randomized controlled, diabetes prevention trial in adults with iIGT, iIFG, or IFG+IGT in which standard of care is compared with a culturally tailored lifestyle education curriculum based on the U.S. Diabetes Prevention Program (DPP) plus stepwise addition of metformin when needed. D-CLIP was conducted in Asian Indians, a population at elevated risk for developing diabetes even at younger ages and lower BMIs (10–13) and possibly with dual susceptibility to insulin resistance and early β-cell dysfunction (14,15). In this study we tested the effectiveness of guideline-based, stepwise diabetes prevention by comparing the incidence of diabetes between control and intervention participants and by determining whether intervention effects differ across baseline prediabetes type, HbA_{1c} level, age, sex, BMI level, or family history of diabetes.

RESEARCH DESIGN AND METHODS

D-CLIP is a randomized, controlled translational research study. Detailed study methods are described elsewhere (9), and details pertinent to this analysis are discussed below. The Emory University Institutional Review Board (IRB-00016503) and the Madras Diabetes Research Foundation Ethics Committee approved the study procedures and materials.

Participants

D-CLIP included overweight or obese (World Health Organization Asian-specific cut points: BMI 23 to <27.5 kg/m^2 for overweight, BMI ≥27.5 kg/m^2 for obese and/or waist circumference ≥90 cm for men or ≥80 cm for women) (16) adults aged 20–65 years with prediabetes (IFG: fasting plasma glucose [FPG] 5.6–6.9 mmol/L and/or IGT: 2-h, postload glucose of 7.8–11.0 mmol/L) (17). Individuals with diabetes, major health conditions impeding participation in an unsupervised lifestyle change program, or current pregnancy or breastfeeding were excluded.

Individuals provided written informed consent before screening and randomization. A detailed discussion of recruitment and enrollment is available elsewhere (18). Briefly, two-step screening included:*1*) community-based screening camps at housing/apartment blocks, worksites, schools, and churches and during community health events (e.g., World Diabetes Day health screening) with a short demographic questionnaire and anthropometry and finger-stick, random capillary glucose measurements; and *2*) clinic-based screening with questionnaires, anthropometric measurements, blood pressure measurement, a fasting blood draw, and a 2-h oral glucose tolerance test (OGTT) for individuals found in step 1 to be at risk for having prediabetes (initially, random capillary glucose ≥6.1 mmol/L, although this was later changed to ≥5.6 mmol/L to improve the pace of recruitment). A smaller sample of individuals with probable or known prediabetes, identified from clinic referrals, attended only clinic-based screening (step 2 above). Figure 1 details inclusion and exclusion at each step of enrollment.

A brief run-in period followed screening, whereby noncompliant individuals (never attended the first intervention class or the control group education class) were removed from the study. The baseline characteristics between noncompliant individuals and participants

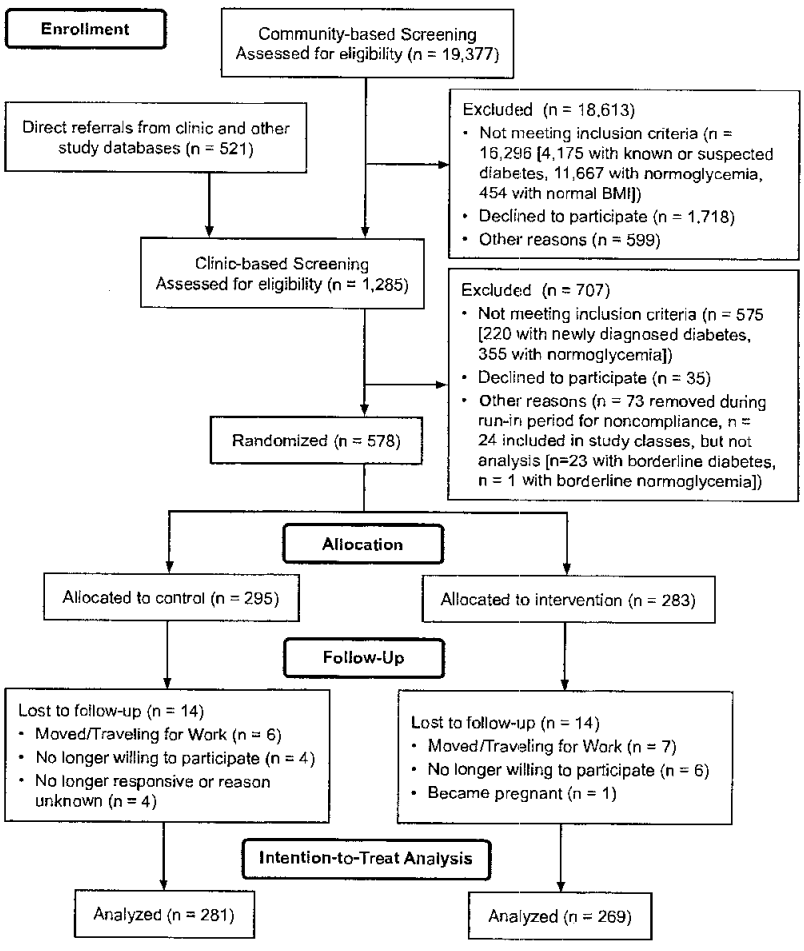

Figure 1—D-CLIP trial profile.

remaining in the study were not significantly different. The study enrolled 24 individuals, 12 per study arm, with borderline glucose levels (0.06–0.28 mmol/L outside the ADA cutoffs for diabetes [n = 23] or normoglycemia [n = 1]) who were not included in the analysis. The study physicians requested that these individuals be allowed to participate in the study because they felt that lifestyle education would be beneficial. A sensitivity analysis was conducted comparing the primary end point with and without these individuals.

Randomization and Masking

The study site coordinator (R.H.) provided a list of eligible study identifiers to the U.S.-based coordinator (M.B.W., who had no interaction with study participants) weekly for randomization using a random-number list created in SAS software (SAS Institute, Inc., Cary, NC). The study site coordinator then informed participants of their allocation group. Because of the nature of the trial and the inclusion of group-specific questions in the study questionnaire, study participants, staff, and investigators could not be blinded to group allocation.

Interventions

Control and intervention activities were conducted at the study site, a diabetes care and research institution in Chennai, India, with extensive experience in diabetes treatment and prevention. Classes and data collection visits were designed to fit within participants' schedules, with most activities occurring on weekends. Control arm participants received the study site's standard of care for prediabetes: a single day with one-on-one visits with a physician, a dietitian, and a fitness trainer and one group class on diabetes prevention (e.g., following a low-fat diet rich in complex carbohydrates and fresh fruits and vegetables, increasing physical activity). Metformin prescription for diabetes prevention is not standard of care at the study site, so no control arm participants received metformin. Aside from follow-up data collection visits, control participants had no additional contacts with study staff.

The stepwise intervention included lifestyle classes plus metformin when needed. The lifestyle curriculum was based on the DPP, with lessons modified to be group-based and culturally appropriate. Weekly classes included 16 core intervention classes in months 0–4 on active lifestyle changes, followed by 8 maintenance classes in months 5–6. Like the DPP, participants had two study goals: ≥7% weight loss and ≥150 min weekly of moderate-intensity exercise. Participants were trained on improving diet quality and reducing dietary intake through keeping weekly food diaries, adhering to individual goals for total fat intake, reducing portion sizes, and increasing intake of fiber-rich foods. A trained lifestyle modification team, including a health coach, a fitness instructor, and a community volunteer peer leader taught each cohort of 8–24 participants (18 total cohorts; median cohort size, 16). At 4 months or later (after the core lifestyle curriculum was completed), intervention participants were prescribed metformin at a dose of 500 mg twice daily if they were considered at high risk of converting to diabetes, defined as having IFG+IGT or IFG+ HbA_{1c} ≥5.7% (39 mmol/mol). After the lifestyle classes ended, intervention participants had minimal contacts with study staff (phone calls every 6 months to schedule study testing visits and LISTSERV postings for holidays).

Study Testing and Outcome Measures

Testing visits occurred at the study site at baseline, postcore intervention (month 4), postmaintenance (month 6), and every 6 months until study closeout and included study questionnaires, anthropometric measurements, blood pressure testing, and fasting blood draws. Three-sample (0, 30, and 120 min) 75-g OGTTs were performed annually.

The primary outcome, diabetes incidence, was diagnosed on the basis of a single, annual OGTT or the semiannual FPG test. Diagnostic cut points for diabetes were based on ADA criteria, FPG ≥7.0 mmol/L or 2-h glucose ≥11.1 mmol/L (17). Secondary outcomes included weight, waist circumference, FPG, 2-h glucose, HbA_{1c}, physical activity, diet, and metformin adherence. Covariates included age, sex, BMI, prediabetes category, HbA_{1c}, and self-reported family history of diabetes (having a first-degree relative with diabetes). Mean minutes of weekly, self-reported physical activity were estimated based on the following questions: *1*) "how many days per week do you exercise;" and *2*) "on average how long does each exercise session last" (possible values: 0–15, 16–30, 31–45, 46–60, or >60 min). Weekly physical activity was categorized as reaching study goals (≥150 min/week) or not. Dietary intake was measured using a Food Frequency Questionnaire developed for South Indian populations (19). Adherence to metformin was assessed by pill counts at each study visit.

Study physicians reviewed study records and an adverse event questionnaire to determine whether adverse events occurred and whether they were study related. If needed, the participant met with the study physician to review the event and make changes. Participants were also in frequent contact with study staff, who referred participants to the study physician if an adverse event was suspected.

Statistical Analysis

A data safety officer monitored the study. The analysis was conducted in SAS 9.4 software and followed an intention-to-treat principle. The study was designed to provide 80% power to detect a 35% difference in diabetes incidence between groups assuming a 10% loss to follow-up, an α of 0.05, and an annual conversion rate to diabetes of 9%.

Intervention adherence was assessed by evaluating *1*) class attendance; *2*) changes in dietary intake (using repeated-measures models); the percentage of participants reaching *3*) physical activity and *4*) weight loss goals at 6 and 12 months; and *5*) metformin adherence. Changes over time in intermediate outcomes of weight, waist circumference, HbA_{1c}, FPG, and 120-min glucose were modeled using repeated-measures analysis.

Time to diabetes, survival probabilities, and associated SEs were quantified through life-table methods. Cumulative incidences of diabetes in intervention and control participants were compared through product-limit curves and the log-rank test. Risk reduction and tests for heterogeneity across baseline covariates were assessed by proportional hazards regression at a significance level of $P < 0.1$. Baseline age, BMI, waist circumference, and HbA_{1c} values were examined categorically and continuously.

The number needed to treat to prevent one case of diabetes and the 95% CI were calculated using survival probabilities at 3 years and the Greenwood estimate of the SE.

RESULTS

Study Enrollment and Follow-up

Recruitment (September 2009-February 2012) included community-based screening of 19,377 individuals, of which 18,613 were ineligible for or declined additional screening (Fig. 1). The remaining 764 individuals plus 521 referrals from clinic databases attended clinic-based screening (n = 1,285). From these, 707 people were excluded (575 ineligible, 35 unwilling, and 97 other reasons), and 578 individuals were randomized to intervention (n = 283) or control (n = 295). Most of excluded individuals at each stage of screening were ineligible for the trial. Participants (63.2% male; mean age, 44.4 [SD 9.3] years) had a mean BMI of 27.9 (SD 3.7) kg/m^2, and 30.2% had iIFG, 29.7% had iIGT, and 40.1% had IFG+IGT (Table 1). Mean follow-up time was 2.54 years (range 4–48 months). Including individuals with borderline baseline glucose levels in the analysis resulted in a small, insignificant strengthening of the intervention effect, so these individuals were excluded from the reported results. Loss to follow-up (individuals lacking all follow-up data) was 4.7% (intervention, 4.7%; control, 4.6%), leaving 281 control subjects and 269 intervention participants for the primary outcome assessment.

Table 1—Baseline characteristics by groups

Characteristics*	Overall (N = 576)	Control (n = 293)	Intervention (n = 283)
Sex, n (%)			
Male	364 (63.2)	183 (62.5)	181 (64.0)
Female	212 (36.8)	110 (37.5)	102 (36.0)
Education, n (%)			
High school or less	222 (38.7)	110 (37.8)	112 (39.6)
Undergraduate/technical degree or greater	352 (61.3)	181 (62.2)	171 (60.4)
Monthly income, n (%)			
<10,000 rupees	149 (28.4)	71 (26.4)	78 (30.6)
10,000–25,000 rupees	210 (40.1)	111 (41.3)	99 (38.8)
>25,000 rupees	165 (31.5)	87 (32.3)	78 (30.6)
Family history of diabetes, n (%)	330 (57.1)	169 (57.3)	161 (56.9)
Age, years, mean (SD)	44.4 (9.3)	44.0 (9.5)	44.8 (9.0)
Weight, kg, mean (SD)	74.6 (11.4)	74.7 (11.4)	74.6 (11.3)
BMI, kg/m^2, mean (SD)	27.9 (3.7)	27.8 (3.7)	27.9 (3.7)
BMI categories, n (%)			
Normal	33 (5.7)	18 (6.1)	15 (5.3)
Overweight	262 (45.3)	134 (45.4)	128 (45.2)
Obese	283 (49.0)	143 (48.5)	140 (49.5)
Waist circumference, cm, mean (SD)	94.8 (9.1)	94.8 (8.8)	94.7 (9.4)
Plasma glucose, mmol/L, mean (SD)			
Fasting	5.7 (0.5)	5.7 (0.5)	5.7 (0.5)
30-min postload	9.7 (1.4)	9.6 (1.5)	9.8 (1.4)
120-min postload	8.3 (1.5)	8.4 (1.4)	8.2 (1.5)
HbA_{1c}, %, mean (SD)	6.0 (0.5)	6.0 (0.5)	6.0 (0.5)
HbA_{1c}, mmol/mol, mean (SD)	42 (5.5)	42 (5.5)	42 (5.5)
Glucose intolerance level, n (%)			
iIFG	174 (30.1)	84 (28.5)	90 (31.8)
iIGT	172 (29.8)	89 (30.2)	83 (29.3)
IGT+IFG	232 (40.1)	122 (41.4)	110 (38.9)
Reported any exercise, n (%)	331 (57.6)	167 (57.2)	164 (58.0)
Average minutes of exercise, n (%)			
<150 min	431 (75.2)	221 (75.7)	210 (74.7)
≥150 min	142 (24.8)	71 (24.3)	71 (25.3)
Daily dietary intake, kcal, mean (SD)			
Total calories	2,970.6 (865.0)	2,999.7 (839.6)	2,942.0 (889.9)
Calories from fat	825.8 (287.0)	839.5 (276.7)	812.2 (296.7)
Calories from carbohydrates	1,803.2 (523.9)	1,815.8 (513.0)	1,791.0 (535.1)

*Family history of diabetes defined as one or more first-degree relatives (parent, sibling, or child) with diabetes.

Changes in Diabetes Incidence

During the 3 years of follow-up, there was a 32% (95% CI 7–50) relative reduction in diabetes incidence in intervention participants compared with control subjects (Table 2). The incidence remained lower in the lifestyle participants throughout the follow-up (Fig. 2). At 3 years, 34.9% of control subjects (n = 98) and 25.7% of intervention participants (n = 69) had developed diabetes for an average annual incidence of diabetes of 11.1% and 7.8%, respectively (P = 0.014), and the number needed to treat to prevent one case of diabetes with the D-CLIP intervention was 9.8 (95% CI 5.4–53.9).

The RRRs were stronger in some subgroups (Table 2). When comparing across prediabetes type, the intervention effects were only significant among participants with IFG+IGT (36% [95% CI 3–57]), although the relative reduction in incidence was similar in magnitude among iIGT participants (31%). For individuals with iIFG, the RRR was 12% (95% CI −80 to 57). The reduction in incidence was strongest among older participants and men. Reduction in diabetes incidence was more than two-times higher in obese participants than in overweight participants. The differences in RRR across glycemic status group, BMI category, age, and sex did not reach statistical significance.

Changes in Intermediate Outcomes

Change in weight and waist circumference differed significantly between intervention and control participants during the 3 years of follow-up (P < 0.001 for each) (Supplementary Fig. 1). The intervention group lost weight throughout the 6-month intervention period, with a maximum weight loss at 6 months (weight loss: −2.4 [SD 2.7] kg/−3.2% [SD 3.4] at 4 months and −2.9 [SD 2.9] kg/−4.0% [SD 3.8] at 6 months). The control arm only lost weight in months 0–4 (−0.8 [SD 2.2] kg/−1.0% [SD 2.9]). Similarly, waist circumference decreased in the intervention arm by month 4 (−3.6 [SD 4.6] cm) and month 6 (−3.9 [SD 4.3] cm), but only in months 0–4 in the control group (−1.5 [SD 3.6] cm). Glucose measures

Table 2—Incidence of diabetes incidence and risk reduction and numbers needed to treat in D-CLIP intervention and control participants by population subgroup

		Incidence density (cases/100 person-years)		Reduction in incidence*		Number needed to treat	
	N	Control	Intervention	%	95% CI	*n*	95% CI
Overall	550	14.2	9.8	32	7, 50	9.8	5.4, 53.9
Age, years†							
≤35	96	14.5	10.4	34	−46, 70	4.0	2.1, 46.0
36–50	292	13.7	10.0	21	−21, 49	13.9	5.4, −25.0
≥51	162	15.1	9.0	47	6, 70	10.1	4.0, −20.6
Sex†							
Male	344	14.5	9.6	37	7, 58	9.2	4.7, 245.6
Female	206	13.9	10.1	24	−27, 54	12.0	4.6, −19.0
BMI, kg/m^2†							
23 to <27.5	246	10.5	8.7	14	−43, 48	46.3	10.9, −20.5
≥27.5	273	19.1	10.5	49	23, 66	6.8	4.3, 16.6
Prediabetes type†							
iIFG	166	7.2	6.5	12	−80, 57	15.5	7.8, 854.4
iIGT	162	10.7	7.4	31	−31, 64	11.0	5.4, −188.3
IFG+IGT	222	22.2	14.5	36	3, 57	12.3	5.4, −43.6
HbA_{1c}, % (mmol/mol)†							
<5.7 (<39)	117	7.7	6.1	13	−106, 64	19.3	7.9, −43.1
5.7–6.4 (39–46)	340	15.3	8.1	50	25, 67	8.2	5.2, 19.6
≥6.5 (≥48)	93	19.4	20.3	−18	−114, 35	256.4	5.9, −6.2
Family history†							
No	200	12.8	7.3	46	5, 70	8.3	3.8, −55.5
Yes	349	15.1	11.3	23	−12, 47	10.8	5.1, −80.1

*Based on the hazard ratio. †Tests for heterogeneity across strata were not statistically significant except for HbA_{1c} (P = 0.05).

(Supplementary Fig. 2) were significantly lower in the intervention arm at most (HbA_{1c}, FPG) or all (2-h glucose) follow-up visits. FPG and HbA_{1c} both decreased more steeply in the intervention group until month 6, when lifestyle education classes ended. The 2-h glucose decreased slightly in the intervention group between baseline and 1 year and increased thereafter.

Intervention Adherence

Participants attended an average of 12 (SD 3.9) core intervention classes: 22% of participants attended all 16 (n = 63), 70% attended 12 or more (n = 196), and 90% attended at least half (n = 253). Class attendance did not vary by sex; however, significantly fewer participants in the youngest age group (≤35 years) attended 75% or more of the study classes (46.9% [n = 23 of 49] compared with 73.0% of those aged 36–50 [n = 116 of 159] and 76.0% [n = 57 of 75] of those aged 51 or older, P = 0.0009).

Calories, carbohydrates, and fat intake all improved ($P < 0.001$ for all) during the 6-month intervention period (6-month intakes were 2,586.4 [SD 820.0] kcal, 1,558.7 [SD 506.0] kcal, and 719.0 [SD 273.4] kcal, respectively). In the control arm, there were slight, nonsignificant decreases in calorie, carbohydrate, and fat intake.

About half of intervention participants reported reaching the physical activity goal (≥150 min/week) at 6 months (51.1% [n = 121 of 237]) or 1 year (52.1% [n = 124 of 238]). Men were more likely than women to reach physical activity goals at 6 months (43.8% [n = 130 of 297] vs. 23.8% [n = 43 of 181], respectively, $P < 0.0001$) and at 1 year (50.5% [n = 149 of 295] vs. 35.0% [n = 62 of 177], respectively, P = 0.0011). At 1 year, 54.1% (n = 79 of 146) of participants in the oldest age category (≥51 years) reached the exercise goal compared with 42.4% (n = 111 of 262) of those aged 36–50 years, and 32.8% (n = 21 of 64) of those aged ≤35 years (P = 0.0088). The percentage of control individuals reaching this level of physical activity was lower (25.9% [n = 52 of 201] at 6 months and 37.7% [n = 87 of 231] at 1 year). Conversely, very few intervention participants reached the 7% weight loss goal (0 at 6 months, 2 at 1 year).

During the trial, 188 of the intervention participants (72%) presented with both IFG and either IGT or elevated HbA_{1c} and were eligible for metformin. Of those, only 20 individuals (11%) refused the metformin prescription, citing a desire to continue with lifestyle intervention alone, and 13 (7%) accepted the prescription but never took any of the metformin tablets. Of the metformin users, 97 (52%) initiated metformin after the core intervention classes (month 4). Most individuals with baseline iIFG or IFG+IGT required metformin during the

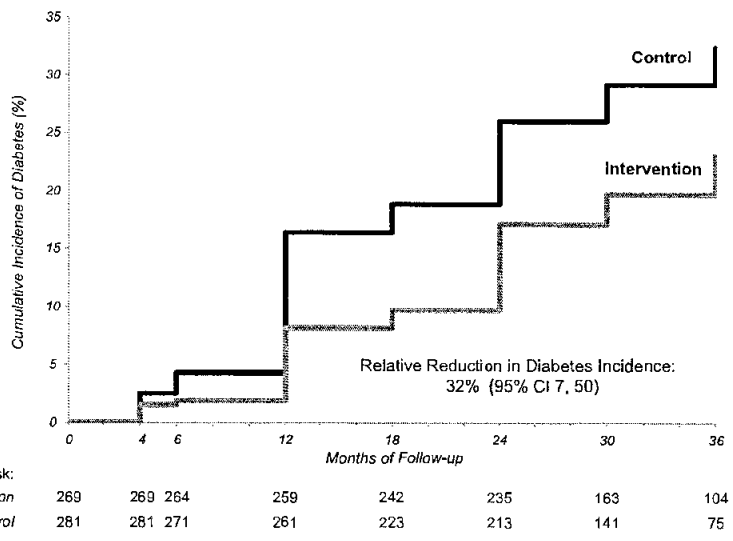

Figure 2—Cumulative incidence of diabetes by study arm in the D-CLIP trial from baseline to year 3.

trial (76.5% [n = 65 of 85] and 83.0% [n = 83 of 100], respectively), whereas 51.3% (n = 40 of 78) of individuals with iIGT at baseline were prescribed metformin. Mean adherence to metformin was 69.6% (SD 37.9).

Adverse Effects

There were no severe adverse events (e.g., hospitalization, severe injury or illness) related to participation in the study, no injuries related to the exercise program, and no adverse events from diet changes made. All participants survived to the end of follow-up. Some participants reported mild or moderate gastritis related to taking metformin, but none of these cases were severe enough to stop taking the medication. One participant developed a rash after taking metformin, which resolved after metformin was discontinued.

CONCLUSIONS

A stepwise diabetes prevention program reduced the 3-year diabetes risk by 32% (95% CI 7–50) in overweight or obese Asian Indian adults with any form of prediabetes. There was evidence, however, indicating heterogeneity of effect across prediabetes type, with the strongest benefit in people with combined IFG+IGT (36%), followed by iIGT (31%) and then iIFG (12%).

The overall RRR shown here is similar to that reported at 3 years among the lifestyle (28.5%) and lifestyle plus metformin (28.2%) arms in the Indian Diabetes Prevention Program (IDPP) (3), but less than that shown at 2.8 years in the DPP (58%) (1), 4 years in the Finnish Diabetes Prevention Study (DPS) (58%) (20), 6 years in the diet and physical activity education group in the Da Qing IGT and Diabetes Study (42%) (2), and 4 years in the Japanese lifestyle intervention trial (67.4%) (5). This lower reported effect is likely, at least in part, because D-CLIP recruited people across the prediabetes spectrum, including those with iIFG, whereas the other studies only included individuals with IGT (2,3,5,20) or IGT+elevated FPG (1). In a multicenter diabetes prevention study of lifestyle modification among adults with iIFG or IFG+IGT, lifestyle intervention, although highly effective among individuals with IFG+IGT (hazard ratio 0.41, 95% CI 0.24–0.69), did not reduce diabetes risk among individuals with iIFG (hazard ratio 1.17, 95% CI 0.50–2.74) (21).

In addition, baseline risk among all D-CLIP participants was 14.2% per annum, considerably higher than the 11.0% annual risk shown for individuals with IGT+elevated FPG in DPP (1); among comparable people in D-CLIP, namely those with IFG+IGT, the risk was 22.2% per annum, supporting data showing that Asian Indians have a higher rate of prediabetes-to-diabetes conversion (22). The high percentage of intervention participants requiring metformin, 72%, and the fact that half required metformin within 4 months of trial enrollment further supports this and raises questions about whether factors other than insulin resistance are involved in the pathogenesis of type 2 diabetes in Asian Indians.

The program appeared to be less effective in people with iIFG; there was only a 12% (not significant) RRR, and a higher proportion of individuals with baseline iIFG required metformin (IFG+IGT or IFG+ HbA_{1c} ≥5.7% [39 mmol/mol] at 4 months or later), indicating a failure of lifestyle to curtail disease progression. iIFG may be a phenotype more related to poor insulin secretion and gluconeogenesis than to insulin resistance, and if so, lifestyle interventions may be insufficient because they target the wrong pathophysiological mechanism. D-CLIP was also more effective in participants with no family history of diabetes (46%), a group likely affected by weight or lifestyle-related insulin resistance, than in those with a family history of diabetes (23%) and genetic susceptibility to insulin resistance, β-cell dysfunction, or both. Furthermore, the D-CLIP intervention might not have been ideal for those with iIFG. The Mediterranean diet, which has been inversely associated with IFG (23), might be more appropriate than the low-fat diet used in D-CLIP. On-going lifestyle intervention trials for individuals with IFG (24,25) will be important for determining the best course of action for this group. In addition, other drug classes that act more directly on β-cell function (e.g., gliptins) might be better candidate drugs for this group than metformin, which increases insulin sensitivity and inhibits gluconeogenesis (26).

There were differences in RRR by age, BMI group, and sex that were not statistically significant but might indicate a trend. Like the DPP (1), the strongest intervention effect was among the oldest participants, perhaps a result of the beneficial effects of weight loss and increased physical activity on age-related peripheral insulin resistance (27). Older D-CLIP participants also met exercise goals more frequently at 1 year and were more likely to attend 75% of the study classes than the younger participants. However, pooled data from the IDPP studies found no difference in RRR when comparing individuals younger than age 45 or 45 years of age or older (28). The difference between D-CLIP and these studies might be due to differences in age cutoffs or intervention methods. Regardless, the data reported from the D-CLIP trial add further support for targeting diabetes prevention efforts in all age groups, including older adults.

This study differed from the DPP (1) and a meta-analysis of the IDPP trials (28) in that individuals with obese-level BMIs showed markedly higher diabetes risk reduction than individuals with lower, but still overweight, BMIs (a 49% reduction vs. a nonsignificant 14% reduction). Participation in the intervention reduced diabetes incidence among obese participants to the incidence rate found among overweight control subjects (10.5 cases/100 person-years). Further analyses are needed to clarify the factors associated with this increased intervention success, but it is possible that obese individuals were more motivated to make the necessary lifestyle changes or that improved lifestyle, particularly increased physical activity, resulted in greater improvements in peripheral insulin sensitivity in the obese group. Alternatively, people with lower BMIs and high diabetes risk may be more β-cell deficient and thus less amenable to interventions targeting insulin resistance.

Also, unlike the DPP (1) and a recent meta-analysis of diabetes prevention studies (29), we found that the intervention effect was stronger in men than in women. Women reported more barriers to joining the study initially (30), which influenced recruitment outcomes and might have influenced lifestyle changes. Although class attendance did not differ by sex, men were significantly more likely to reach exercise goals at 6 months and 1 year.

D-CLIP intervention arm participants reached maximum weight loss (2.9 kg/4.0%) at 6 months, although only two participants reached the 7% weight loss goal. This weight loss was less than that seen in the DPP (7 kg/7%) or the DPS (4.2 kg/4.7%) (1,20); however, mean baseline weight and BMI were lower in D-CLIP, so a smaller weight loss may be more attainable. A meta-analysis of U.S.-based DPP translation studies also showed a mean weight loss of 4.0%, indicating that the weight loss seen in D-CLIP aligns with other DPP translation research (31). In diabetes prevention studies in Asian populations in India, China, and Japan (2,3,5), weight loss was similar to or less than that seen in D-CLIP. Even with no weight loss, studies in Asia report significant reductions in diabetes incidence (2,3), which might indicate that in populations with a lower average BMI, physiological changes other than weight loss may be more influential in reducing diabetes risk. Waist circumference loss at 6 months in D-CLIP (3.9 cm) exceeded the 1-year loss in the DPP (2.7 cm) (32). Abdominal adiposity is common in Asian Indians and can present at lower BMIs than in other ethnicities (33), so a waist circumference decrease may better represent adiposity loss than weight change.

Although lifestyle intervention participants showed short-term improvements in adiposity and glucose markers, all measures increased over longer follow-up. The inability of interventions to sustain improvements in anthropometry or glycemic control has previously been shown (1,34,35). The consistency of these patterns in multiple studies indicates a need for further research on maintenance of weight loss and other lifestyle changes associated with glucose control.

D-CLIP is a large, well-randomized trial with good follow-up, attendance, and adherence. This is the first large diabetes prevention translation trial to include individuals with all three types of prediabetes and the first study to test expert group recommendations for stepwise diabetes prevention. This study was conducted in a region at high-risk for diabetes and can provide important data for understanding diabetes prevention in LMIC settings. This study also has a large population of men, an underrepresented group in diabetes prevention trials (31).

The major weakness of this study is the lack of power for subgroup comparisons; however, several results do indicate interesting patterns that warrant further investigation. Also, the simplistic assessment of physical activity may not accurately reflect true activity. Finally, the D-CLIP study population was ethnically homogenous, which might affect generalizability; however, the inclusion of individuals across the prediabetes spectrum makes these results more broadly applicable to community-level diabetes prevention.

In conclusion, the D-CLIP trial shows that expert recommendations of adding metformin in a stepwise manner to lifestyle education is an effective method for preventing or delaying diabetes in adults with prediabetes, even in a resource-challenged setting like an LMIC. However, further research is needed to better understand diabetes prevention among people with iIFG. This is especially important because iIFG is the more common form of prediabetes in many racial/ethnic groups like Asian Indians (36–38). The possible need for specialized interventions for diabetes prevention among different categories of prediabetes has important public health and clinical significance.

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

Author Contributions. M.B.W. was primary author of the manuscript and conducted some analysis. H.R. oversaw data collection and participant management at the study site. L.R.S. conducted the primary analysis. M.B.W., H.R., K.M.V.N., and V.M. designed the trial. M.B.W., H.R., and R.M.A. developed the lifestyle intervention curriculum. All authors contributed to the manuscript discussion, provided edits to the text, and reviewed and approved the manuscript. K.M.V.N. and V.M. are co-primary investigators of the study and provided senior leadership and direction to the team. M.B.W. 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.

Prior Presentation. Parts of this study were presented at the 75th Scientific Sessions of the American Diabetes Association, Boston, MA, 5–9 June 2015 (39).

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Effect of Conventional Lifestyle Interventions on Type 2 Diabetes Incidence by Glucose-Defined Prediabetes Phenotype: An Individual Participant Data Meta-analysis of Randomized Controlled Trials

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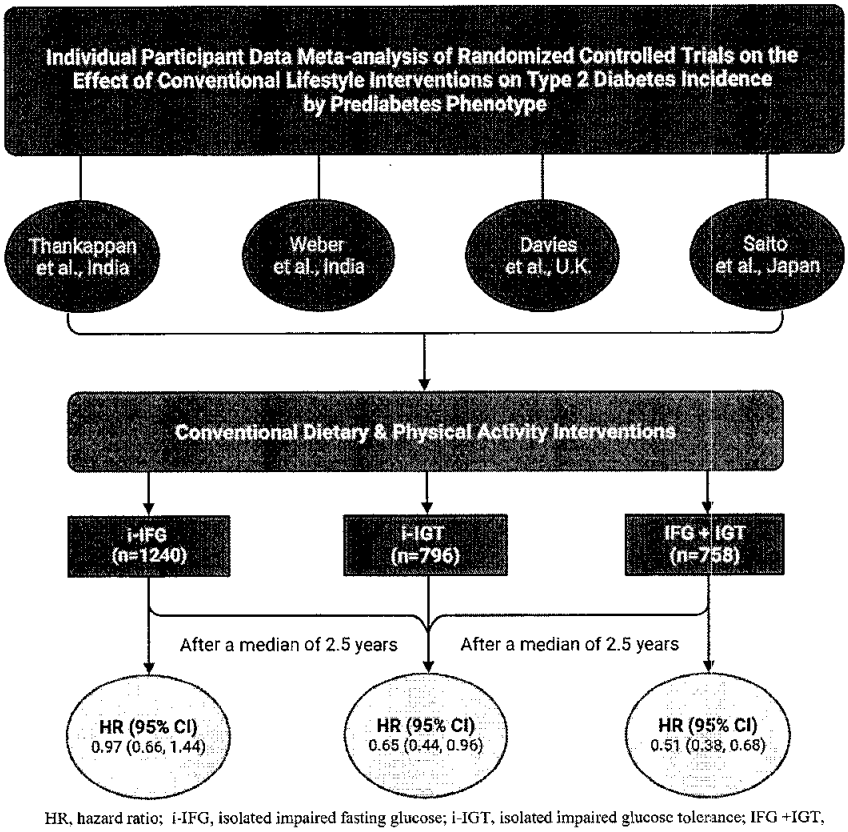

HR, hazard ratio; i-IFG, isolated impaired fasting glucose; i-IGT, isolated impaired glucose tolerance; IFG +IGT, impaired fasting glucose plus impaired glucose tolerance.

ARTICLE HIGHLIGHTS

- We undertook this study because it is unclear whether conventional lifestyle interventions could reduce diabetes incidence in all three glucose-defined prediabetes phenotypes.
- We specifically sought to answer the question of whether the effect of conventional lifestyle interventions on diabetes incidence differs by prediabetes phenotype.
- We found that diabetes incidence was reduced significantly in individuals with impaired glucose tolerance (with or without impaired fasting glucose) but not in those with isolated impaired fasting glucose.
- The implications of our findings are that there is a need for precision prevention of type 2 diabetes.

Effect of Conventional Lifestyle Interventions on Type 2 Diabetes Incidence by Glucose-Defined Prediabetes Phenotype: An Individual Participant Data Meta-analysis of Randomized Controlled Trials

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OBJECTIVE

To examine whether the effect of conventional lifestyle interventions on type 2 diabetes incidence differs by glucose-defined prediabetes phenotype.

RESEARCH DESIGN AND METHODS

We searched multiple databases until 1 April 2023 for randomized controlled trials that recruited people with isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT), and impaired fasting glucose plus impaired glucose tolerance (IFG+IGT). Individual participant data were pooled from relevant trials and analyzed through random-effects models with use of the within-trial interactions approach.

RESULTS

Four trials with 2,794 participants (mean age 53.0 years, 60.7% men) were included: 1,240 (44.4%), 796 (28.5%), and 758 (27.1%) had i-IFG, i-IGT, and IFG+IGT, respectively. After a median of 2.5 years, the pooled hazard ratio for diabetes incidence in i-IFG was 0.97 (95% CI 0.66, 1.44), i-IGT 0.65 (0.44, 0.96), and IFG+IGT 0.51 (0.38, 0.68; $P_{interaction}$ = 0.01).

CONCLUSIONS

Conventional lifestyle interventions reduced diabetes incidence in people with IGT (with or without IFG) but not in those with i-IFG.

Conventional lifestyle interventions incorporating behavioral counseling to change diet and physical activity reduce type 2 diabetes incidence in people with prediabetes (1). It remains unclear, however, whether they are effective in all three glucose-defined prediabetes phenotypes, including isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT), and impaired fasting glucose plus impaired glucose tolerance (IFG+IGT) (2). In this systematic review and individual participant data (IPD)

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See accompanying article, p. 1894.

BRIEF REPORT

meta-analysis, we examined whether the effect of conventional lifestyle interventions on diabetes incidence differs by glucose-defined prediabetes phenotype.

RESEARCH DESIGN AND METHODS

We followed standard guidelines for the conduct and reporting of this study (Supplementary Table 1) (3,4), which is registered with International prospective register of systematic reviews (PROSPERO) (no. CRD42020197356).

Search Strategies and Eligibility Criteria

We searched MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Scopus, and ClinicalTrials.gov from inception to 1 April 2023 using the search strategies given in Supplementary Table 2. No language restrictions were applied. We considered randomized controlled trials (RCTs) satisfying the eligibility criteria: *1*) recruiting of adults (≥18 years) with i-IFG, with i-IGT, and with IFG+IGT, defined based on the American Diabetes Association (ADA) (5) or World Health Organization (WHO) (6) criteria, and *2*) evaluation of the effect of conventional dietary or physical activity interventions on diabetes incidence (fasting plasma glucose ≥126 mg/dL, 2-h plasma glucose ≥200 mg/dL, or taking antidiabetes medications) (5) in comparison with a control group (usual care or minimal intervention). Conventional lifestyle interventions are similar to or based on the interventions tested in landmark lifestyle RCTs for diabetes prevention (1,7). We excluded studies reporting exclusively pharmaceutical or surgical interventions.

Data Sharing

We contacted principal investigators (PIs) of eligible studies to obtain IPD that are relevant for this study. The PIs had ethics approval to share their study data. After signing data-sharing agreements, de-identified IPD were obtained and checked for accuracy, consistency, and completeness.

Risk of Bias and Certainty of the Evidence Assessment

The Cochrane risk-of-bias tool, version 2 (RoB 2), was used to assess the bias in each study (8), and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used

Table 1—Characteristics of studies and participants included in the meta-analysis

First author and year (study), country (ref. no.)	Study design	Study setting	Type of data	Criteria for prediabetes	*N*	Age in years	% Male	Components of lifestyle intervention programs		Control group
								Diet	Physical activity	
Thankappan 2018 (K-DPP), India (14)	Cluster RCT	Community (clusters are polling areas*)	IPD	ADA	695	46.4 (7.3)	55.0	Increase fruit and vegetable intake and reduce portion size of rice and intake of fried foods and refined sugars	Walking groups and yoga sessions	Received a booklet on healthy lifestyle advice
Weber 2016 (D-CLIP), India (12)	RCT	Community	IPD	ADA	578	44.4 (9.3)	63.2	Reduce daily calorie intake and portion sizes and increase fiber intake	≥150 min of moderate-intensity exercise weekly	One-on-one visits with a clinician, dietitian, and fitness trainer on a single day and one group class on diabetes prevention
Davies 2016 (LPD), UK (15)	Cluster RCT	General practices (clusters)	IPD	WHO	880	63.9 (7.8)	63.6	Restrict total fat and saturated fat intake to 30% and 10% of daily total energy intake, respectively, and increase fiber intake	Participants were provided with a pedometer to help increase daily physical activity	Received an information booklet on lifestyle change
Saito 2011 (ZSPLD), Japan (16)	RCT	Clinics and hospitals	Aggregate data	ADA	641	N/A	N/A	Limit fat and carbohydrate intake to 20–25% and 55–60% of total energy intake, respectively	Advised to walk to achieve an energy expenditure of 200 kcal/day. Sedentary individuals were encouraged to increase daily physical activity	Received individual instructions on lifestyle modification from the medical staff four times at 12-month intervals for 3 years

Data for age are means (SD). K-DPP, Kerala Diabetes Prevention Program; D-CLIP, Diabetes Community Lifestyle Improvement Program; LPD, Let's Prevent Diabetes; ZSPLD, Zensharen Study for Prevention of Lifestyle Diseases; N/A, not available; RCT, randomized controlled trial; ADA, American Diabetes Association; WHO, World Health Organization. *polling areas are well-defined and identifiable locations demarcated with landmarks such as hills, rivers, roads, etc. by the Election Commission of India.

to determine the certainty of the evidence (9).

Two reviewers (T.S. and R.B) independently screened study titles, abstracts, and full texts; extracted study-level data from published articles; and performed the risk of bias and GRADE assessments, with disagreements resolved by discussion or by a third author (R.J.T).

Statistical Analyses

Analyses were done per the intention-to-treat principle (3). We pooled the incidence rates of diabetes (per 1,000 person-years) across studies using the random-effects DerSimonian-Laird models (3). Cox regression was used to estimate hazard ratios (HRs) (and 95% CIs) for diabetes incidence in individually randomized trials, and shared frailty models (10) were used in cluster-randomized trials to account for the correlation of observations within clusters. We conducted a two-stage IPD meta-analysis (3). Firstly, we analyzed the IPD of each study separately to obtain relevant aggregate data (HRs and 95% CIs). If no IPD were available for a study, we used the effect estimates from the published article. Secondly, we pooled these aggregate estimates using random-effects models (3). Effect modification by prediabetes phenotype was assessed with addition of an interaction term between the phenotype and the treatment group in each study separately. If only aggregate data were available for a study, we used the HRs (and 95% CIs) from the published article to estimate the interaction HR (and 95% CI) using the equation developed by Riley and Fisher (11) (Supplementary Table 3). The interaction estimates were then pooled with use of random-effects models (3). The proportion of variability in effect estimates due to between-study heterogeneity was quantified with I^2 (3). We did not assess publication bias, as the number of included studies was <10 (3). We conducted sensitivity analyses to assess the robustness of our results. In the Diabetes Community Lifestyle Improvement Program (D-CLIP), 72.2%, 48.2%, and 75.5% of intervention participants with i-IFG, with i-IGT, and with IFG+IGT, respectively, required metformin (500 mg twice daily), in addition to undergoing lifestyle interventions, at 4 months or later (12). So, in D-CLIP, we adjusted for metformin use (yes or no) in Cox models. In addition, we imputed missing outcome data (varied from 0 to 9.1% across studies) using multiple imputation (13) (Supplementary Table 4). Analyses were performed in Stata software.

Data and Resource Availability

Data-sharing agreements with PIs of the individual studies restrict further dissemination of data to third parties.

RESULTS

A total of 3,678 articles were identified through our systematic search, among which four studies met our eligibility criteria and were included in this meta-analysis (Supplementary Fig. 1).

Table 1 shows the characteristics of included studies. We obtained the IPD of three studies: Kerala Diabetes Prevention Program (K-DPP) (14) and D-CLIP (12) from India and Let's Prevent Diabetes from the U.K. (15). IPD of the Zensharen Study for Prevention of Lifestyle Diseases (ZSPLD) from Japan (16) were unavailable because the organization that conducted this study no longer exists. K-DPP and D-CLIP were conducted in the community (12,14), whereas Let's Prevent Diabetes and ZSPLD were done in clinical settings (15,16). In all four studies behavior change counseling was implemented for achievement of diet and physical activity modification, lasting 0.5–3.0 years.

A total of 2,794 participants (mean age 53.0 years, 60.7% men) were included in the meta-analysis: 1,240 (44.4%), 796 (28.5%), and 758 (27.1%) had i-IFG, i-IGT, and IFG+IGT, respectively. The overall pooled incidence rate of diabetes was highest in the IFG+IGT group, followed by the i-IGT and i-IFG groups (Table 2). After a median of 2.5 years (interquartile range 2.3, 2.8), the pooled HR for diabetes incidence in i-IFG was 0.97 (95% CI 0.66, 1.44; I^2 = 0), i-IGT 0.65 (0.44, 0.96; I^2 = 0), and IFG+IGT 0.51 (0.38, 0.68; I^2 = 0) ($P_{interaction}$ = 0.01) (Fig. 1 and Supplementary Fig. 2). The main results were not materially altered in sensitivity analyses (Supplementary Tables 4 and 5). The risk of bias was low in all four studies (Supplementary Fig. 3), and the certainty of the evidence was moderate (Supplementary Table 6). There are minor discrepancies in effect estimates between the original articles (12,14–16) and the current study, the reasons for which are explained in Supplementary Table 7.

CONCLUSIONS

The findings of this systematic review and meta-analysis show that the effect of conventional lifestyle interventions on type 2 diabetes incidence varies among prediabetes phenotypes, with a significant risk

Table 2—Pooled incidence rate of diabetes across studies by prediabetes phenotype

Prediabetes phenotype	Study arm	No. of participants	No. of events	IR (95% CI) per 1,000 person-years
i-IFG	Total	1,240	161	54.77 (20.34, 89.20)
	Control arm	634	83	55.47 (16.40, 94.53)
	Intervention arm	606	78	53.13 (21.98, 84.28)
i-IGT	Total	796	105	65.21 (19.96, 110.45)
	Control arm	405	58	72.16 (14.71, 129.60)
	Intervention arm	391	47	49.17 (20.28, 78.05)
IFG+IGT	Total	758	250	147.01 (93.07, 200.95)
	Control arm	373	149	180.46 (113.84, 247.09)
	Intervention arm	385	101	107.02 (63.22, 150.82)

IR, incidence rate; CI, confidence interval; i-IFG, isolated impaired fasting glucose; i-IGT, isolated impaired glucose tolerance; IFG+IGT, impaired fasting glucose plus impaired glucose tolerance.

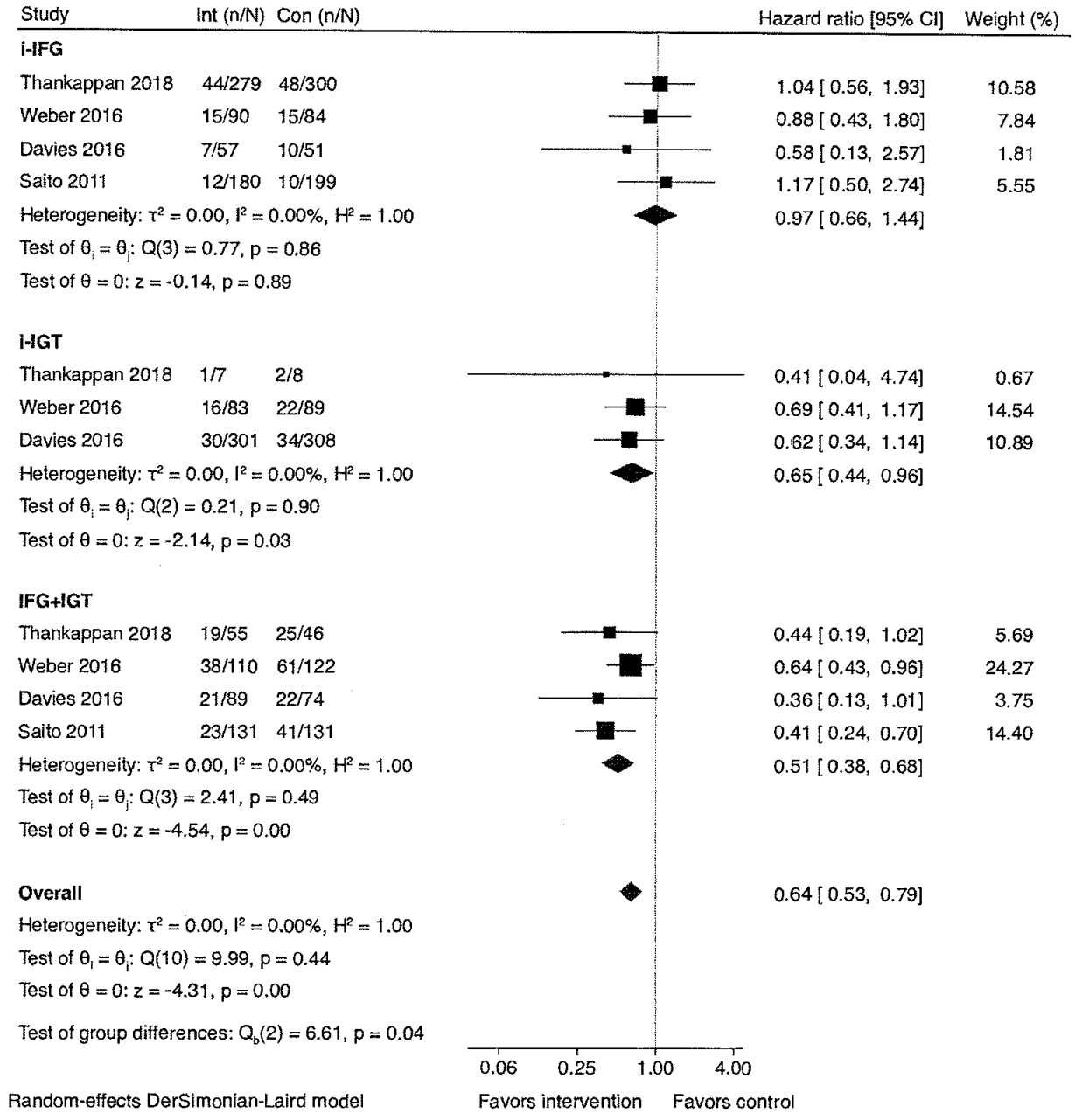

Figure 1—Forest plot for the effect of conventional lifestyle interventions on type 2 diabetes incidence by prediabetes phenotype. Con, control; Int, intervention; i-IFG, isolated impaired fasting glucose; i-IGT, isolated impaired glucose tolerance; IFG+IGT, impaired fasting glucose plus impaired glucose tolerance. *n* refers to the number of events, and *N* refers to the sample size.

reduction in people with i-IGT and with IFG+IGT but not in those with i-IFG.

These differences in risk reduction could be attributed mainly to the variations in the pathophysiological abnormalities between prediabetes phenotypes (17). People with i-IFG have decreased early-phase insulin secretion and increased hepatic insulin resistance, whereas i-IGT is characterized by reduced early- and late-phase insulin secretion and elevated skeletal muscle insulin resistance and IFG+IGT includes a combination of defects seen in i-IFG and i-IGT (17). These pathophysiological abnormalities that differentiate individuals with IGT and i-IFG might mean that different therapeutic interventions are likely required to prevent progression to diabetes (2,17).

People with i-IFG constitute a substantial proportion of the global prediabetes population. A recent meta-analysis of 14 studies with 27,112 individuals with prediabetes found that the proportional prevalence of i-IFG (ADA criteria) was 58% in Caucasians and 48% in Asians (18). The proportional prevalence of i-IFG among adults in India was much higher (84% with ADA criteria), as reported in a nationwide study (19). In addition to its high prevalence, i-IFG increases the risk of developing diabetes four- to sixfold in comparison with normoglycemia (20) and is a

high-risk state for cardiovascular disease and all-cause mortality (2). Thus, more research is required to identify effective interventions for this large group at high risk. Some promising strategies include a low-calorie diet (~1,200 kcal/day) or high-intensity interval training, as they have been shown to normalize fasting plasma glucose and reverse the pathophysiology in people with type 2 diabetes (2).

The strengths of this analysis included the ability to obtain IPD, permitting standardization of the effect measure and outcome definition across studies, and imputation of missing outcome data. We used the "within-trial interactions" approach to assess the differences in the intervention effect between prediabetes phenotypes, thereby eliminating aggregation bias (3). However, the analyses are post hoc and observational, so the results should be considered hypothesis generating. We combined studies with i-IFG defined based on the ADA (three studies) or WHO (one study) criteria for the meta-analysis. However, this did not affect our results, as the pooled HRs for i-IFG defined only according to ADA criteria and WHO criteria were similar (1.01 vs. 0.96, respectively), and they were also similar to the pooled HR in Fig. 1 (0.97). Further, the meta-analysis is constrained by a small number of studies, the majority of which were conducted among Asian Indians or Japanese, and so the effect of lifestyle interventions in i-IFG may be different for other ethnicities. Finally, there is a possibility of confirmation bias based on findings from the individual studies included in the systematic review. However, the meta-analysis mitigated any substantial risk from this bias.

In conclusion, conventional lifestyle interventions significantly reduced type 2 diabetes incidence in people with IGT (with or without IFG) but not in those with i-IFG. Further confirmation and efforts to lower diabetes incidence in people with i-IFG are needed.

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