Diabetologia
DOI 10.1007/s00125-007-0847-1

ARTICLE

Adiposity, inflammation and hyperglycaemia in rural and urban Indian men: Coronary Risk of Insulin Sensitivity in Indian Subjects (CRISIS) Study

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Received: 6 October 2006 / Accepted: 14 September 2007

Abstract
Aims/hypothesis The aim of this study was to investigate whether the higher prevalence of insulin resistance and glucose intolerance in urban compared with rural Indian men is related to their higher adiposity (percentage body fat) and the associated inflammatory state.
Methods We studied 149 rural, 142 urban slum and 150 urban middle-class male residents (age 30–50 years), who were selected by stratified random sampling. We measured body fat (bioimpedance), waist circumference, glucose tolerance (75 g OGTT), insulin resistance [homeostasis model assessment (HOMA-IR)], beta cell function (insulinogenic index) and inflammatory markers (total leucocyte count, IL-6, TNF-α and C-reactive protein).
Results Adiposity, waist circumference, HOMA-IR, insulinogenic index and both fasting and 120 min plasma glucose concentrations increased progressively from rural through to urban slum and urban middle-class men. Inflammatory markers were higher in urban than in rural men. Adiposity was strongly related to HOMA-IR (r=0.57, p<0.001) and to insulinogenic index and glycaemic parameters (r=0.25, p<0.001 for both). Adiposity explained approximately two thirds of the difference in HOMA-IR between the urban middle-class men and the rural and slum residents, but its contribution to the difference in insulinogenic index and 120 min plasma glucose concentration was not significant. Inclusion of C-reactive protein, IL-6 and total leucocyte count in the models did not further explain these results, nor did the inclusion of waist circumference. There was a significant residual difference after these adjustments.
Conclusions/interpretation Adiposity is a major contributor to the difference in insulin resistance between rural and urban Indian men; there was no additional contribution from inflammation or central obesity. Other unmeasured factors also seem to contribute to the metabolic differences between rural and urban men.

Keywords Adiposity · Beta cell function · Inflammation · Insulin resistance · Hyperglycaemia · Rural Indians · Urban Indians

Abbreviations

ADA	American Diabetes Association
CRISIS	Coronary Risk of Insulin Sensitivity in Indian Subjects
CRP	C-reactive protein
HOMA-IR	homeostasis model assessment of insulin resistance
IFG	impaired fasting glucose

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IGT	impaired glucose tolerance
SDS	standard deviation score
TLC	total leucocyte count

Introduction

India has the largest number of diabetic patients in a single country, and is often referred to as the diabetes capital of the world [1]. The diabetes epidemic is thought to result from transition, which affects demographic, epidemiological and nutritional characteristics of the population [2, 3]. Urbanisation is an example of rapid transition. At independence (1947) less than 15% of Indians lived in cities, now some 30% live in cities [4]. Urban Indians have a four times higher prevalence of type 2 diabetes than rural residents [5, 6]. This is ascribed to higher obesity (BMI) and higher central obesity (waist circumference and WHR) in the urban residents [7]. The metabolic risks of obesity operate through higher body fat [8]. For a given level of obesity, Asian Indians have a higher percentage body fat (adiposity) than other ethnic groups [9–11] and it is also more centrally distributed [12–14]. These factors are thought to contribute to the higher insulin resistance and susceptibility to diabetes in South Asian Indians. The contribution of adiposity to the rural–urban difference in insulin resistance and diabetes prevalence is not known.

Adipose tissue is the biggest endocrine organ in the body, secreting, in addition to fatty acids, a number of proteins (adipokines), which have metabolic, endocrine, proinflammatory, thrombotic and vascular effects [15]. In a preliminary study, we found higher circulating levels of proinflammatory adipokines in urban Indians than in their rural counterparts [16], a finding which might explain the higher metabolic risk in the former. Based on these findings, we designed the CRISIS Study (Coronary Risk of Insulin Sensitivity in Indian Subjects), which is the first Indian study to look at accurate measures of body fat and its potential relationship with measures of both insulin resistance and secretion, inflammatory markers and glycaemia in rural, urban slum and urban middle-class participants. In this paper, we tested the hypothesis that: the higher prevalence of insulin resistance and glucose intolerance in urban Indian men is related to their higher adiposity and associated inflammation.

Methods

Participants We aimed to study approximately 450 apparently healthy men between 30 and 50 years of age from villages, urban slums and urban middle-class locations in and around the city of Pune (Table 1). The study was approved by the Ethics Committee of the King Edward Memorial Hospital Research Centre and by the local community leaders. Individual consent was signed by all participants. The study took place between April 2000 and June 2001.

We did house-to-house surveys in ten hamlets of two villages (~50 km from Pune) and in two of 55 slum wards and two of 69 middle-class wards in Pune city with a view to listing all men aged 30 to 50 years. Three of 354 (0.8%) rural men, 15 of 425 (3.5%) slum residents and 21 of 443 (4.7%) urban middle-class men were receiving treatment for diabetes, hypertension or CHD and were excluded. Of the remaining men, 86% of the rural men, 79% of the slum residents and 71% of the urban middle-class group agreed to participate in the study. We randomly selected and studied 149 rural, 146 urban slum residents and 151 urban middle-class men.

Those with temporary concurrent illness were rescheduled to attend 4 weeks later. Participants stayed overnight at the Research Centre, ate a standard dinner and were medically examined. After overnight fast, an ante-cubital vein was cannulated and three fasting blood samples were drawn 5 min apart. Mean of the three samples was used as a fasting value for glucose and insulin. A 75 g OGTT was performed, with blood samples collected at 30 and 120 min.

An investigator used a questionnaire to record the following information: (1) demographic and social characteristics, and (2) the number of 'infective' episodes in the past year [fever, respiratory symptoms (cold, sore throat and cough) and diarrhoea] (Table 1). Standardised anthropometric measurements (height, weight, waist and hip circumferences) were made by one of two trained observers. Body fat was measured using a bioimpedance device (Multiscan 5000; Bodystat, Douglas, UK) following NIH guidelines [17]. Thus, participants were tested on an empty stomach and having emptied their bladders, after resting in a horizontal position for 5 min. The four electrode sites were meticulously cleaned with ether. We recorded the impedance value and used our own population-specific equation for body fat, calibrated against the deuterated water method in 141 men [17].

Laboratory methods Haematological measurements were performed on an analyser (Coulter A^C.T diff; Coulter, Miami, FL, USA). Plasma glucose concentration was measured on a Hitachi 911 analyser (Hitachi, Tokyo, Japan) using the glucose oxidase method (intra and inter-batch CV <4%). Insulin concentration was measured using in-house DELFIA method [18]. The UK National External Quality Assessment Service (UKNEQAS) (Guildford Peptides, Guildford, UK) results showed that the CV was 12.5% at <45 pmol/l, 9.6% at 45–90 pmol/l and 4.3% at >90 pmol/l. C-reactive protein (CRP) was measured by high-sensitivity ELISA kit (United Biotech, Mountain View, CA, USA), and IL-6 and TNF-α concentrations were measured by ELISA

Table 1 Characteristics of rural, slum and urban middle-class men in CRISIS Study

	Rural	Urban slum	Urban middle-class
Listed men (30–50 years)	354	425	443
Known diabetes + hypertension + CHD	3	15	21
Agreed to participate	301	323	301
Studied	149	146	151
Excluded	0	4	1
Analysed	149	142	150
Age (years)	38 (29–50)	38 (29–50)	40 (31–50)
Place of birth			
Rural (%)	95.3	53.2	14.0
Slum (%)	4.0	40.4	10.0
Urban middle-class area (%)	0.7	6.4	76.0
Education ≥10th std (%)	17.7	23.7	83.3[c,f]
Smoking			
Never (%)	63	47[b]	48[a]
Past (%)	13	14[b]	26[a]
Current (%)	24	39[b]	26[a]
Alcohol			
Never (%)	71	35[b]	42[c,f]
Past (%)	9	14[b]	15[c,f]
Current (%)	20	51[b]	43[c,f]
Monthly income (%)			
<1000 Indian rupees	53	3	2
1,000–5,000 Indian rupees	45	88	12
5,000–10,000 Indian rupees	2	7	39
≥10,000 Indian rupees	0	2	47
Infective episodes per year (*n*)	1 (0–2)	2 (0–3)[a]	2 (0–3)[a]
Height (cm)	164.8 (161.4–168.7)	163.5 (159.6–167.6)[a]	166.0 (162.5–170.6)[a,f]
Weight (kg)	55.6 (50.2–61.0)	57.2 (49.7–66.8)[a]	64.8 (57.3–72.1)[c,f]
BMI (kg/m^2)	20.1 (18.6–22.2)	21.1 (18.7–24.7)[b]	23.6 (21.0–25.9)[c,e]
Overweight (25–30.0 kg/m^2) (%)	6.0	19.0[b]	26.7[c]
Obese (>30 kg/m^2) (%)	0.7	4.2	6.0
Waist circumference (cm)	77.8 (73.2–84.9)	82.7 (73.1–91.5)[b]	90.3 (84.0–96.9)[c,f]
>90 cm (%)	12.1	31.0[c]	52.7[c,f]
WHR	0.89 (0.85–0.93)	0.91 (0.86–0.97)[a]	0.94 (0.90–0.98)[c,f]
>0.90 (%)	45.0	53.5	76.7[c,f]
Fat mass according to bioimpedance (kg)	12.1 (9.3–16.2)	13.8 (9.8–19.1)[b]	18.6 (14.6–22.3)[c,f]
Total body fat %	21.2 (17.9–25.5)	23.8 (18.6–28.9)	28.4 (25.4–30.9)[c,f]
Adipose >25% (%)	31.3	43.5[a]	77.2[c,f]

Values are median (25th–75th centiles), number or %; full range is shown for age.
[a] $p<0.05$, [b] $p<0.01$ and [c] $p<0.001$ vs rural, adjusted for age
[d] $p<0.05$, [e] $p<0.01$ and [f] $p<0.001$ vs urban slums, adjusted for age
10th std refers to the Secondary School Certificate examination

kit (R&D Systems, Minneapolis, MN, USA), the respective CVs being <11, <13 and <18%. All assays were performed according to the manufacturer's instructions.

Terms, calculations and classification Body mass index (kg/m^2) is used to measure overweight and obesity [19] and waist circumference to measure central obesity (>90 cm) [20]. 'Adiposity' refers to specific body fat measurement and the cut-off point is total body fat ≥25% [21]. Glycaemic classification is shown by both WHO (75 g OGTT) [22] and American Diabetes Association (ADA) (fasting plasma glucose concentration only) [23] criteria. Total hyperglycaemic burden includes both fasting (plasma glucose >5.5 mmol/l) or post-glucose hyperglycaemia (120 min plasma glucose >7.8 mmol/l). Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) [24] and beta cell function by the insulinogenic index [25].

Statistical methods Data are presented as medians (25th–75th centile) and percentages. For statistical analysis variables with skewed distribution (glucose, insulin, CRP,

IL-6 and TNF-α,) were logarithmically ($\log_e$) transformed to satisfy the assumption of normality. ANOVA and χ^2 test were used for comparison between three places of residence. Relative differences in metabolic parameters (HOMA-IR and insulinogenic index) between rural and the two urban groups of men were calculated using standard deviation scores (SDSs), with rural mean and standard deviation as reference. Associations between continuous variables were tested by linear regression, adjusted for age and place of residence. The contribution of adiposity and inflammation to the differences in glycaemia, HOMA-IR and insulinogenic index (continuous variables) between the three groups was by multiple linear regression using indicator variables for the three places of residence. The dependent variables were natural log-transformed, while independent variables were kept in original form. This enabled us to express the change in dependent variable as a percentage change for a unit change in independent variable. Thus, the results of this analysis are presented as percentage difference (95% CI) between two places of residence at each step of adjustment for a given independent variable. The contribution of the last added independent variable is the difference in the value from the previous step; this is significant if the confidence intervals before and after are exclusive. We sequentially added age, adiposity, waist circumference, CRP, IL-6 and total leucocyte count (TLC) as independent variables. The significance value (*) represents the significance of the residual difference at that stage. SPSS version 11.0 for Windows (SPSS, Chicago, IL, USA) was used for the statistical analyses.

Based on our earlier work [16], the numbers provide 94% power to detect a 50% difference in levels of HOMA-IR between rural and urban residents and 90% power to detect both a 57% difference in levels of IL-6 and a 31% difference in those of TNF-α, all at the 5% level. The sample size provides adequate numbers to detect significant relationships between continuous variables, with a univariate correlation coefficient of r=0.16 within groups and r=0.10 in the total population.

Results

Living conditions of the participants We diagnosed and excluded from analysis three men with tuberculosis, one with leprosy and one with rheumatoid arthritis. The analysis is based on 149 rural, 142 slum and 150 urban middle-class participants (Table 1).

The majority of rural and urban middle-class men were born in their place of residence. On the other hand, the majority (53%) of urban slum residents were born in the villages and migrated to the city, with an average duration of residence in the city of 25 years (range 10–37 years). Rural men lived in farmhouses without substantial crowding, drank water from bore wells and used temporary or open toilets. The urban slum residents lived in crowded temporary constructions in unhygienic surroundings and shared a community water tap and community toilet. The urban middle-class lived in built houses in affluent areas of the city and had individual taps and toilets. Smoking and alcohol drinking was most prevalent in the urban slums. Urban middle-class men were the best educated and had the highest incomes. The frequency of 'infective' episodes was higher in both groups of urban men than in their rural counterparts, with no significant difference between the two urban groups.

Adiposity, metabolic variables and inflammatory markers in the three places of residence Tables 1 and 2 show that body weight, BMI, waist circumference, WHR and fat mass increased progressively from rural through to urban slum and urban middle-class residents. Percentage body fat was similar in rural and urban slum men and highest in urban middle-class men. Very few rural men and a third of urban middle-class men were overweight and obese by BMI criteria. On the other hand, a third of rural and three-quarters of urban middle-class men were 'adipose' by percentage body fat criteria. Half of urban middle-class men were centrally obese.

Fasting and post load plasma glucose concentrations were progressively higher from rural through to urban slum and urban middle-class residents. This is reflected in a progressively higher prevalence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus. The 'burden' of hyperglycaemia was 26% in rural, 33% in slum residents and 48% in the urban middle-class residents.

Plasma insulin concentrations (fasting and post glucose) increased progressively from rural through to urban slum and urban middle-class residents, as did HOMA-IR and insulinogenic index. The relative differences from the rural group for HOMA-IR [slum residents SDS 0.45 (95% CI 0.23–0.66), urban middle-class SDS 1.23 (95% CI 1.06–1.40)] were higher than those for the insulinogenic index [slum residents SDS 0.10 (95% CI −0.09 to 0.28), urban middle-class SDS 0.45 (95% CI 0.27–0.63)]. Plasma 120 min glucose concentration was directly associated with HOMA-IR (r=0.39, p<0.001) and inversely with insulinogenic index (r=−0.27, p<0.001).

Levels of all inflammatory markers except TNF-α were higher in the urban than in rural men. TLC and plasma IL-6 concentrations were highest in slum residents, while plasma CRP concentration was highest in the urban middle-class residents. Plasma TNF-α concentration was similar in all three groups. TLC and CRP were related to adiposity (p< 0.01 for both) in addition to age and place of residence, but TNF-α and IL-6 were not. Thus both adiposity and place of

Table 2 Glucose, insulin and inflammatory markers in men in CRISIS Study

	Rural	Urban slum	Urban middle-class
N	149	142	150
Plasma glucose (mmol/l)			
Fasting	5.0 (4.7–5.4)	5.2 (4.7–5.5)[a]	5.3 (4.7–5.8)[b]
30 min	8.3 (7.3–9.7)	8.4 (7.4–9.5)	8.8 (7.5–10.6)[b]
120 min	5.6 (4.7–6.5)	6.0 (5.2–7.0)[c]	6.8 (5.7–8.2)[c,e]
WHO 1999 (%)			
IFG	3.4	4.9	11.3[a,d]
IGT	8.8	10.6	19.5[b,d]
Diabetes mellitus	0	5.6[b]	10.1[c]
ADA 2003 (%)			
IFG	19.6	23.2	38.0[b,e]
Diabetes mellitus	0	3.5 [a]	4.7[b]
Total hyperglycaemic burden (%)[g]	25.7	33.1	47.7[c,e]
Plasma insulin (pmol/l)			
Fasting	26.9 (19.4–37.9)	34.7 (20.9–50.6)[b]	49.5 (35.0–68.7)[c,f]
30 min	243.4 (137.9–422.4)	295.8 (154.2—486.0)	404.6 (238.4–657.6)[c,f]
120 min	145.6 (86.2–248.6)	206.3 (101.6–360.1)[b]	430.3 (221.9–718.9)[c,f]
HOMA-IR	0.58 (0.42–0.81)	0.76 (0.46–1.1)[c]	1.07 (0.79–1.46)[c,f]
Insulinogenic index	4.23 (2.51–7.55)	5.33 (2.68–8.69)	6.38 (3.65–12.2)[b,e]
TLC $\times 10^9$/l	5.9 (4.8–6.8)	6.6 (5.4–7.7)[c]	6.0 (5.3–7.0)[d]
Erythrocyte sedimentation rate (mm at 1 h)	5 (3–8)	6 (4–9)[a]	5 (4–10)
CRP (mg/l)	0.31 (0.17–0.80)	0.45 (0.26–1.29)[c]	0.74 (0.38–1.50)[f]
>3 mg/l (%)	6.1	12.0	8.2
IL-6 (pg/ml)	1.65 (1.00–2.90)	2.30 (1.40–3.90)[c]	2.20 (1.40–3.10)[b,d]
TNF-α (pg/ml)	1.61 (1.09–3.01)	1.87 (1.30–3.20)	1.46 (1.09–2.28)[d]

Values are median (25–75th centile) or %
[a] $p<0.05$, [b] $p<0.01$ and [c] $p<0.001$ vs rural, adjusted for age
[d] $p<0.05$, [e] $p<0.01$ and [f] $p<0.001$ vs urban slums, adjusted for age
[g] Total hyperglycaemic burden refers to men with a fasting plasma glucose level of >5.5 mmol/l or a 120 min glucose level of >7.8 mmol/l

residence contributed to the fact that the highest plasma CRP concentration was found in urban middle-class men, whereas it was mainly place of residence that contributed to the highest concentrations of TLC and IL-6 being found in slum residents.

Contribution of adiposity and inflammation to differences in glycaemia, HOMA-IR and insulinogenic index in rural and urban men As seen in Table 3, the difference between metabolic parameters was highest between rural and urban middle-class men and higher for HOMA-IR and insulinogenic index than for glucose concentrations. Percentage body fat explained approximately a third of the difference in 120 min plasma glucose concentrations and two thirds of the difference in HOMA-IR and the insulinogenic index between rural and urban middle-class men. The contribution of adiposity was statistically significant for the difference in HOMA-IR but not for insulinogenic index and glycaemia. The addition of waist circumference, TLC and both plasma CRP and IL-6 concentrations to the model did not make any further significant contribution for any of the metabolic parameters. Adiposity also made a significant contribution to the difference in HOMA-IR between urban slum and urban middle-class men, but not to any other factors. There were no significant contributions to the differences between rural and urban slum men.

When we added CRP to the multivariate analysis without adiposity, it did not make a significant contribution to the difference in metabolic parameters (HOMA-IR etc) between places of residence.

Discussion

Within one generation of migration to the city, Indian slum residents were more insulin-resistant and hyperglycaemic than their rural counterparts, while the urban middle-class residents, whose families had settled in the city generations previously, were the most insulin-resistant and hyperglycaemic. At a comparatively young age (average 40 years), a third of urban slum residents and half of the urban middle-class men were hyperglycaemic by the criteria of one or other of the two major diabetes committees (ADA and WHO).

Table 3 Differences in glycaemia, HOMA-IR (insulin resistance) and insulinogenic index (beta cell function) in the three places of residence in the CRISIS Study

	Slum–rural	Urban middle-class–slum	Urban middle-class–rural
Fasting glucose (mmol/l)			
Adjusted for age	3.9 (0.30 to 7.68)*	2.5 (−1.19 to 6.29)	6.5 (2.7 to 10.4)**
Adjusted for age, body fat%	3.2 (−0.5 to 7.0)	1.1 (−2.3 to 5.1)	4.1 (0.3 to 8.6)*
Adjusted for age, body fat%, waist circumference	3.0 (−0.8 to 6.8)	1.4 (−2.6 to 5.4)	4.4 (0.3 to 8.5)
Adjusted for all of above and CRP	2.8 (−1.0 to 6.7)	1.4 (−2.6 to 5.5)	4.3 (0.2 to 8.5)
Adjusted for all of above and IL-6	2.7 (−1.1 to 6.6)	1.5 (−2.5 to 5.8)	4.2 (0.2 to 8.5)
Adjusted for all of above and TLC	2.6 (−1.3 to 6.6)	1.6 (−2.5 to 5.8)	4.2 (0.1 to 8.4)
120 min glucose (mmol/l)			
Adjusted for age	13.1 (5.9 to 20.8)***	12.1 (4.8 to 19.9)***	26.7 (18.7 to 35.5)***
Adjusted for age, body fat%	11.2 (4.0 to 19.0)**	5.8 (−1.5 to 13.7)	17.7 (9.4 to 26.5)***
Adjusted for age, body fat%, waist circumference	9.3 (2.2 to 17.0)**	7.8 (0.3 to 15.8)*	17.9 (9.6 to 26.9)***
Adjusted for all of above and CRP	9.4 (2.22 to 17.1)**	8.1 (0.5 to 16.2)*	18.2 (9.9 to 27.0)***
Adjusted for all of above and IL-6	9.0 (1.8 to 16.6)**	8.4 (0.8 to 16.5)*	18.2 (9.9 to 27.0)***
Adjusted for all of above and TLC	7.7 (0.6 to 15.5)*	9.3 (1.6 to 17.6)*	17.8 (9.6 to 26.6)***
HOMA-IR			
Adjusted for age	26.1 (10.7 to 43.8)**	45.5 (27.4 to 66.2)***	83.7 (61.1 to 109.2)***
Adjusted for age, body fat%	19.1 (6.2 to 33.6)**	11.1 (−1.6 to 25.5)	32.3 (17.0 to 49.8)***
Adjusted for age, body fat%, waist circumference	14.2 (2.0 to 28.0)*	16.4 (3.1 to 31.4)*	32.9 (17.8 to 50.1)***
Adjusted for all of above and CRP	14.0 (1.6 to 27.8)*	16.6 (3.2 to31.6)*	32.8 (17.7 to 50.1)***
Adjusted for all of above and IL-6	12.4 (0.2 to 25.9)*	18.3 (4.7 to 33.5)**	32.8 (17.7 to 50.1)**
Adjusted for all of above and TLC	10.3 (−1.7 to 23.9)	19.9 (6.2 to 35.4)**	32.3 (17.3 to 49.3)***
Insulinogenic index			
Adjusted for age	7.9 (−12.1 to 32.3)	35.9 (10.4 to 67.4)**	46.7 (19.4 to 80.2)***
Adjusted for age, body fat%	3.1 (−16.1 to 26.7)	9.6 (−11.8 to 36.3)	13.1 (−9.6 to 41.3)
Adjusted for age, body fat%, waist circumference	0.4 (−18.5 to 23.7)	12.9 (−9.4 to 40.9)	13.4 (−9.2 to 41.8)
Adjusted for all of above and CRP	−0.5 (−19.3 to 22.6)	12.4 (−9.9 to 40.3)	11.8 (−10.6 to 39.8)
Adjusted for all of above and IL-6	−1.2 (−20.0 to 22.0)	13.5 (−9.1 to 41.9)	12.2 (−10.4 to 40.3)
Adjusted for all of above and TLC	1.4 (−18.1 to 25.7)	11.3 (−11.1 to 39.4)	12.9 (−9.9 to 41.3)

Values were calculated by linear regression using place of residence as indicator variables
Values represent percentage difference (95% CI) in metabolic parameters between two places of residence when adjusted for a given independent variable (age, body fat% etc)
*$p<0.05$, **$p<0.01$ and ***$p<0.001$ for the difference between the two places of residence included in the analysis

Hyperglycaemia in urban men was associated with higher insulin resistance, which was not matched by a proportionate rise in beta cell function. Higher insulin resistance in the urban middle-class men was significantly attributable to their adiposity; however, central obesity and inflammation made little further independent contribution.

Despite a relatively low BMI, adiposity was very prevalent in these men and was associated with the two pathophysiological risk factors for hyperglycaemia. The relationship was stronger with insulin resistance (r^2= 32.5%, $p<0.001$) than with insulin secretion (r^2=6.2%, $p<0.001$). Adiposity was also associated with circulating concentrations of inflammatory markers, but only with TLC and CRP, and not with IL-6 and TNF-α. Though related to different risk factors, the contribution of adiposity to differences between rural and urban men was somewhat variable. It explained two thirds of the difference in insulin resistance between urban middle-class and rural as well as urban slum residents. Inclusion of waist circumference and inflammatory markers in the models made no further significant contribution. Despite an apparently large contribution to the differences in beta cell function and 120 min plasma glucose concentration, this did not reach statistical significance (Table 3). We found no significant contribution of adiposity, waist circumference and inflammatory markers to the relatively smaller difference between rural and urban slum men. After the effect of adiposity, central obesity and inflammation were taken into account, residual differences in insulin resistance and glycaemic parameters remained between rural and urban men, suggesting that factors not measured in this study could have contributed (including adiponectin and retinol binding protein 4 [26, 27]).

The increased metabolic risk of adiposity is traditionally ascribed to excess release of NEFA, which influence both insulin secretion [28] and insulin action (glucose–fatty acid cycle) [29]. The effect of NEFA on insulin secretion is ‘dual’, i.e. stimulatory at lower and suppressive at higher concentrations (lipotoxicity) [28]. This could explain the

relative beta cell dysfunction in the face of higher insulin resistance in the most adipose urban middle-class men. Fat cells secrete a number of adipokines, including the proinflammatory cytokines IL-6 and TNF-α [15]. Levels of inflammatory markers IL-6, CRP and TLC were higher in the urban than in the rural men; IL-6 and TLC were highest in slum residents, while CRP was highest in the middle-class men. This difference in the levels of inflammatory markers between places of residence could be the result both of atmospheric (air pollution, smoking etc.) and living (crowding and hygiene) conditions, and of adiposity. Slum residents were exposed to an excess of the former, while middle-class residents had an excess of the latter, while also sharing some of the former. The contribution of adiposity to high CRP concentration in the urban middle-class men might also reflect the effect of liver adiposity (hepatosteatosis) [30] as a part of their adiposity and central obesity because CRP is synthesised in the liver under the influence of IL-6 [31]. The levels of CRP were predominantly in the range described as 'chronic low-grade' inflammation, which is thought to be a result of stimulation of cellular immune pathways in adipocytes [32], unlike the very elevated levels in the acute inflammatory range (>3 mg/l). Low-grade inflammation affects various metabolic processes like insulin signalling pathways [32]. Interestingly, concentrations of inflammatory markers in our study were associated with insulin resistance but not beta cell function. This could be an additional explanation for the relatively higher levels of insulin resistance versus insulinogenic index in urban middle-class men. We have no explanation for the lack of association between adiposity and plasma TNF-α concentration in our study. Only a few studies of inflammatory markers and their metabolic associations in Indians have been published. A study from Delhi showed an association between plasma CRP concentration and adiposity in adolescents [33], while studies from Chennai showed an association with glycaemia and HOMA-IR, and suggested that the association between adiposity and diabetes was mediated by CRP [34, 35].

There are few reports on beta cell function in Indians. Our study highlights the role of beta cell dysfunction in the pathophysiology of hyperglycaemia in insulin-resistant men. We did not find any significant associations of insulin secretion with many of the risk factors associated with insulin resistance. Beta cell function is affected by genetic factors [36, 37], but these are unlikely to explain rural–urban differences in people of the same gene pool. Epigenetic regulation by nutritional and other environmental factors (programming) may be important in regulating beta cell function, as demonstrated in animals [38]. This may happen during the intrauterine period [39–41].

Our study has a number of strengths and some weaknesses. Thus it is the first study to measure both insulin resistance and secretion in rural and urban Indians, which allows a better appreciation of the factors contributing to hyperglycaemia in the latter. Inclusion of slum residents, who form an increasing proportion of urban population in India, allowed us to assess the effect of unhygienic surroundings and lifestyle on metabolic risk. Restricting the study to 30- to 50-year-old men reduced the age- and sex-related variability in measurements and also reduced chances of survivor bias (life expectancy in Indian men is 62 years). Impedance measurements of adiposity were made with careful attention to methodological details and used a population-specific equation [17]. Three fasting samples (5 min apart) minimised the effect of cyclical insulin secretion. The power calculations were based on our own pilot research. However, the levels of inflammatory markers in this study were lower and the differences between groups smaller than those in our pilot study, which might explain the lack of contribution to the metabolic differences, We were also limited by the lack of precise measurements of insulin resistance (e.g. by euglycaemic clamp) and of abdominal adiposity (e.g. computerised tomography or magnetic resonance imaging), using instead HOMA-IR and waist circumference, which are both accepted epidemiological measures. Our findings on magnetic resonance imaging on a smaller number of participants will be discussed in a separate paper. Finally, in this cross-sectional study we were not able to establish causality; in addition, our findings apply only to men.

In summary, we report a strong association between urban residence, adiposity, a subclinical inflammatory state, insulin resistance and hyperglycaemia. Adiposity in urban middle-class men contributed to their higher insulin resistance compared with rural and slum residents. Prevention and control of adiposity may help control the burgeoning diabetes epidemic in India.

Acknowledgements The study was funded by the Nestle Foundation (Lausanne, Switzerland) and by a Collaboration Grant of the Wellcome Trust (London, UK). We thank all the men who participated in the study and A. Kolhatkar, N. Joshi, S. Gandhi, A. Khadilkar, K. Shelgikar, J. Deshpande, L. Ramdas, S. Yenge, T. Deokar, S. Chaugule, A. Bhalerao, V. Solat, A. Ganpule, N. Thuse, M. Sayyad, S. Deshpande, P. Yajnik and A. Kurpad for their invaluable contribution.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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