Association of obesity with hypertension and type 2 diabetes mellitus in India: A meta-analysis of observational studies

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Author contributions: Babu GR conceived the study aims and design, contributed to the data extraction, planned the analysis, interpreted the results and drafted the final version of the paper; Murthy GVS has contributed to manuscript development and critical review; Ana Y and Deepa R evaluated the study articles and made decisions on inclusion and exclusion of the articles; Patel P was involved in manuscript development, provided inputs for estimations and critical review; Neelon SEB has reviewed the manuscript critically; Kinra S has contributed to the article critically for important intellectual content; Reddy KS has contributed to the article critically for important intellectual content and final approval of the version to be published.

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Abstract

AIM

To perform a meta-analysis of the association of obesity with hypertension and type 2 diabetes mellitus (T2DM) in India among adults.

METHODS

To conduct meta-analysis, we performed comprehensive, electronic literature search in the PubMed, CINAHL Plus, and Google Scholar. We restricted the analysis to studies with documentation of some measure of obesity namely; body mass index, waist-hip ratio, waist circumference and diagnosis of hypertension or diagnosis of T2DM. By obtaining summary estimates of all included studies, the meta-analysis was performed using both RevMan version 5 and "metan" command STATA version 11. Heterogeneity was measured by I^2 statistic. Funnel plot analysis has been done to assess the study publication bias.

RESULTS

Of the 956 studies screened, 18 met the eligibility criteria. The pooled odds ratio between obesity and hypertension was 3.82 (95%CI: 3.39 to 4.25). The heterogeneity around this estimate (I^2 statistic) was 0%, indicating low variability. The pooled odds ratio from the included studies showed a statistically significant association between obesity and T2DM (OR = 1.14, 95%CI: 1.04 to 1.24) with a high degree of variability.

CONCLUSION

Despite methodological differences, obesity showed significant, potentially plausible association with hypertension and T2DM in studies conducted in India. Being a modifiable risk factor, our study informs setting policy priority and intervention efforts to prevent debilitating complications.

Key words: Obesity; Meta-analysis; Hypertension; Type 2 diabetes mellitus

Core tip: India with population explosion and high burden of non-communicable diseases (NCDs) poses a great challenge for the public health specialists to find the route cause for it. Meta-analysis to find the association of obesity with hypertension and type 2 diabetes mellitus in India proved the statistical significance association of obesity with major NCD's with high degree of variability. Results provided with the possible risk factors for the NCD's and what need to be done for the preventive aspect of such diseases. As obesity being a risk factor, setting up a priority policy decisions related to interventions for the prevention of obesity can result in a huge dynamic change in the trend of NCD's in the country like India.

INTRODUCTION

Indians have a higher burden of obesity and have relatively lower muscle mass compared to the whites[1]. Indians develop metabolic syndrome, hypertension, and type 2 diabetes mellitus (T2DM) earlier compared to whites, which is independent of BMI[2,3]. The available evidence suggests the age-adjusted prevalence of obesity has doubled in men and has increased three folds in women over two decades (1970s-1990s) in India[4]. Subsequent economic reforms in India (1991) have initiated overpowering changes in the quality and quantity in a number of lifestyle factors in Indians[5]. For example, increased consumption of unhealthy food and lower levels of physical activity might likely have contributed to an increase in the prevalence of obesity and its comorbidities[6].

In India, hypertension and T2DM are the major non-communicable diseases (NCDs) leading to catastrophic complications including death. It is important to investigate the role of modifiable risk factors resulting in NCDs such as obesity, physical inactivity, tobacco use, and alcohol consumption[7]. Among these shared risk factors of NCDs, limiting the use of tobacco has fittingly received the greater attention of policy makers compared to other risk factors. However, the risk factors seldom act in isolation and it is important to alleviate the impact of their confluence. It is, therefore, important to determine the quantum of the risk contribution by individual risk factor like obesity. Available evidence suggests strong associations between obesity and NCDs[8,9]. However, none of the earlier reviews have specifically evaluated the role of obesity in the etiology of hypertension and T2DM in India.

The prevalence of obesity has increased significantly in India over the last few decades. About a third of the adult population in urban India is currently estimated to be overweight or obese. As a result, the number of persons with hypertension and T2DM could increase exponentially[10]. Apart from contributing to T2DM and hypertension, obesity is a major risk factor for pulmonary diseases, metabolic diseases, osteoarthritis, several cancers and serious psychiatric illness[9,11]. We limit our investigation to T2DM and hypertension. Specifically, we plan to systematically review studies exploring the plausible role of obesity in the etiology of hypertension and T2DM, synthesize the evidence, and perform a meta-analysis if appropriate. Understanding the putative role of obesity and its impact on NCDs will inform future interventions to reduce the burden of

these diseases.

MATERIALS AND METHODS

The objective of our study is to estimate the association of obesity with hypertension and T2DM in Indian settings in adults. We developed a protocol for conducting the meta-analysis; with the searching strategy encompassing key MeSH terms, selection of article based on inclusion and exclusion criteria, data extraction, quality assessment of the study, the summary of evidence and analysis.

Literature search and article selection

We included only studies published in English and are conducted in India. We included both the original and review articles restricting the analysis to studies having: (1) documentation of some measure of obesity; AND (2) diagnosis of hypertension was reported; OR (3) T2DM was reported and diagnosed using World Health Organization (WHO) and American Diabetes Association (ADA) criteria. In addition, case-control studies must have compared participants with the disease (T2DM or hypertension) with controls without the disease. We excluded intervention studies, as this was beyond the scope of our review. We defined the exposure variable (obesity as adults with BMI $\geq$ 30 (studies have considered obesity as BMI with $\geq$ 25 and $\geq$ 30), waist circumference (WC) ($\geq$ 80 cm for females and $\geq$ 90 cm for males), and waist to hip ratio ($\geq$ 0.80 for females and $\geq$ 0.90 for males). We followed the Joint National Committee VII (JNC VII) criteria for the diagnosis of hypertension; with readings of Systolic Blood Pressure (SBP) $\geq$ 140 mmHg or Diastolic Blood Pressure (DBP) $\geq$ 90 mmHg. T2DM was diagnosed as per WHO and ADA classification, when Fasting Blood Sugar (FBS) is 126 mg/dL ($\geq$ 7.0 mmol/L) or 2-h Post Prandial Blood Sugar (2 h-PPBS) is 200 mg/dL ($\geq$ 11.1 mmol/L)[12] (Table 1).

We conducted a comprehensive search of all papers published between January 1980 and January 2016 using MeSH terms for articles in PubMed (Table 2). We also screened other databases, including CINAHL Plus and Google Scholar for additional papers from January to October 2016. We contacted individual authors as necessary to clarify information and assess other relevant papers. We also reviewed cross-referenced papers cited in the assessed articles.

Data extraction and analysis

Stage 1: Identification of studies for inclusion: As a preliminary step two authors (Yamuna Ana and R Deepa) independently assessed the study abstracts retrieved from electronic databases.

Stage 2: Choice of valid studies: Studies selected in stage 1 with necessary information were independently assessed against the inclusion criteria. We included only those studies which aided in the calculation of the relative risk or odds ratio of exposure (obesity) and outcome (T2DM or hypertension).

Stage 3: Quality assessment: The primary author (Giridhara R Babu) developed the protocol for the review and monitored the overall quality of the review at each step. Criteria for defining obesity, T2DM, and hypertension were noted and crosschecked by primary and secondary authors (Giridhara R Babu, GVS Murthy). Two authors (Yamuna Ana and R Deepa) independently reviewed each article in its entirety for inclusion. The primary author (Giridhara R Babu) conducted random checks before data were extracted and tabulated.

We employed the following set of criteria to evaluate the papers: (1) suitability of the study design; (2) appropriate sample size; (3) evidence regarding obesity and attributes of participants; and (4) accuracy of the tools used for quantifying obesity, diabetes and blood pressure. We also reviewed controlling for confounding, selection bias, reduction of reporting errors and strategies employed to minimize measurement bias.

For assessing eligibility, 2 authors (Yamuna Ana and R Deepa) individually reviewed the full-text papers. Discrepancies were resolved by agreement among both authors which arose during the selection of articles based on study inclusion criteria. Disagreements regarding the inclusion of article were resolved by consulting Giridhara R Babu. If there were multiple reports related to a single study, we included the report with the details relevant to obesity and the outcome of interest.

Stage 4: Extraction of the data and synthesis of results: We did a preliminary search of the electronic databases, after which we selected papers with a title and abstract that matched our criteria. We obtained additional articles from the references provided in the reviewed articles, downloaded the full texts of the article for review. We noted the following details; first author of the paper, year of publication, study design deployed, cut-off values for defining obesity, the prevalence of exposure (obesity), relative risk and odds ratio for T2DM and hypertension. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were used as the reference for assessing the quality of each study[13].

We derived the summary estimate by combining estimates from all the selected studies[14-24]. We did statistical analysis using RevMan version 5 and STATA version 11[25]. We used double data entry procedure and analysed in the Cochrane Collaboration's Review Manager Software version 5 for Windows (Cochrane Collaboration, Oxford, England). Further, the data in the spreadsheet was analysed using the "metan" command of STATA 11 version for Mac (STATA Corporation, College Station, Texas, United States)[25]. Crosschecking of outputs for internal consistency has been done and we obtained the pooled odds ratios reported in selected studies using Generic Inverse variance for overall estimates. We strictly conformed to the guidelines for meta-analysis of observational studies used in epidemiology[26]. We used RevMan for developing flowcharts and for examining

Table 1 Criteria for obesity, hypertension, and type 2 diabetes mellitus

Criteria for obesity, hypertension and T2DM

Obesity	Hypertension (JNC VII criteria)	T2DM
BMI ($\geq$ 30)	SBP greater than or equal to 140 mmHg or	WHO and ADA classification: Fasting plasma glucose $\geq$ 7.0 mmol/L (126 mg/dL) or 2 h plasma glucose $\geq$ 11.1 mmol/L (200 mg/dL)
Waist-hip ratio (> 0.80 for females and > 0.90 for males)	DBP greater than or equal to 90 mmHg respectively	
Waist circumference ($\geq$ 90 cm, > 88 cm for female and > 102 cm for male)		

DBP: Diastolic blood pressure; SBP: Systolic blood pressure; ADA: American Diabetes Association; JNC: Joint National Committee; WHO: World Health Organization; T2DM: Type 2 diabetes mellitus; BMI: Body mass index.

Table 2 Search terms used for literature review

Search terms for obesity and hypertension	Search Terms for Obesity and type 2 diabetes
(((obesity[MeSH Terms]) AND hypertension[MeSH Terms]) AND prevalence[MeSH Terms]) AND India [MeSH Terms]	(((obesity[MeSH Terms]) AND type 2 diabetes[MeSH Terms]) AND incidence[MeSH Terms]) AND India[MeSH Terms]
(((obesity[MeSH Terms]) AND hypertension[MeSH Terms]) AND incidence[MeSH Terms]) AND India[MeSH Terms]	(((obesity[MeSH Terms]) AND type 2 diabetes[MeSH Terms]) AND prevalence[MeSH Terms]) AND India[MeSH Terms]
(((obesity[MeSH Terms]) AND hypertension[MeSH Terms]) AND relative risk[MeSH Terms]) AND India[MeSH Terms]	(((obesity[MeSH Terms]) AND type 2 diabetes [MeSH Terms]) AND risk ratio[MeSH Terms]) AND India[MeSH Terms]
(((obesity[MeSH Terms]) AND hypertension[MeSH Terms]) AND risk ratio[MeSH Terms]) AND India[MeSH Terms]	(((obesity[MeSH Terms]) AND type 2 diabetes[MeSH Terms]) AND relative risk[MeSH Terms]) AND India [MeSH Terms]
(((obesity[MeSH Terms]) AND hypertension[MeSH Terms]) AND attributable risk[MeSH Terms]) AND India[MeSH Terms]	(((obesity[MeSH Terms]) AND type 2 diabetes [MeSH Terms]) AND attributable risk[MeSH Terms]) AND India[MeSH Terms]
((((obesity[MeSH Terms]) AND hypertension[MeSH Terms]) AND prevalence[MeSH Terms]) OR incidence[MeSH Terms]) AND India [MeSH Terms]	((((obesity[MeSH Terms]) AND type 2 diabetes [MeSH Terms]) AND prevalence[MeSH Terms]) OR incidence[MeSH Terms]) AND India [MeSH Terms]

the quality of study methodology. We calculated the unadjusted odds ratios with 95%CI using random-effects model for all analyses[27]. We used funnel-plot analysis to assess small-study and publication bias. We calculated odds ratio for individual study from the data cell values. We calculated the pooled odds ratio using the individual unadjusted odds ratios of each study within each subgroup of case-control and cohort studies. Hence the pooled odds ratio was also unadjusted. We measured heterogeneity using I^2 statistic. This describes the percentage of total variation across studies that is due to heterogeneity rather than mere chance alone producing this[28]. I^2 can be readily calculated from basic results obtained from a typical meta-analysis as $I^2 = 100\% \times (Q - df)/Q$, where Q is Cochrane's heterogeneity statistic and df being the degrees of freedom. An advantage of I^2 is that it does not depend on the number of studies included in the meta-analysis[29].

Risk of bias
To assess the risk of publication bias we constructed funnel plots for all the association between exposure and outcome variables.

RESULTS
Study selection
The initial search identified 6907 studies. After checking for duplicates, we screened 956 studies and excluded 774 that were not relevant. Hence we included 182 studies for full article review and among those we excluded 164 studies from the meta-analysis. Of these, 131 articles were not eligible due to non-availability of exposure or outcome criteria (Figure 1). The ineligible studies were rejected for the following reasons: Exposure criteria were not defined (46), obesity or overweight was not used as an exposure (26), studies were conducted outside India (21), T2DM or hypertension was not included in study (23) and data provided was insufficient to calculate odds ratio or relative risk (15). Finally, 6 studies satisfying the review criteria for hypertension and 12 for T2DM were involved in the meta-analysis.

A descriptive overview of studies included in meta-analysis
One cohort study was included and rest were cross-sectional studies. The age groups of the participants ranged from 20 to 55.5 years. In studies with T2DM as the outcome, the exposure was assessed using BMI in 5 studies, WC in 3 studies and WHR in 4 studies. For the studies involving hypertension as an outcome of interest, five studies used BMI and one used WHR (Tables 3 and 4).

Methodological quality
Information regarding confounding factors is reported in all the studies and in 2 studies, the selection bias is
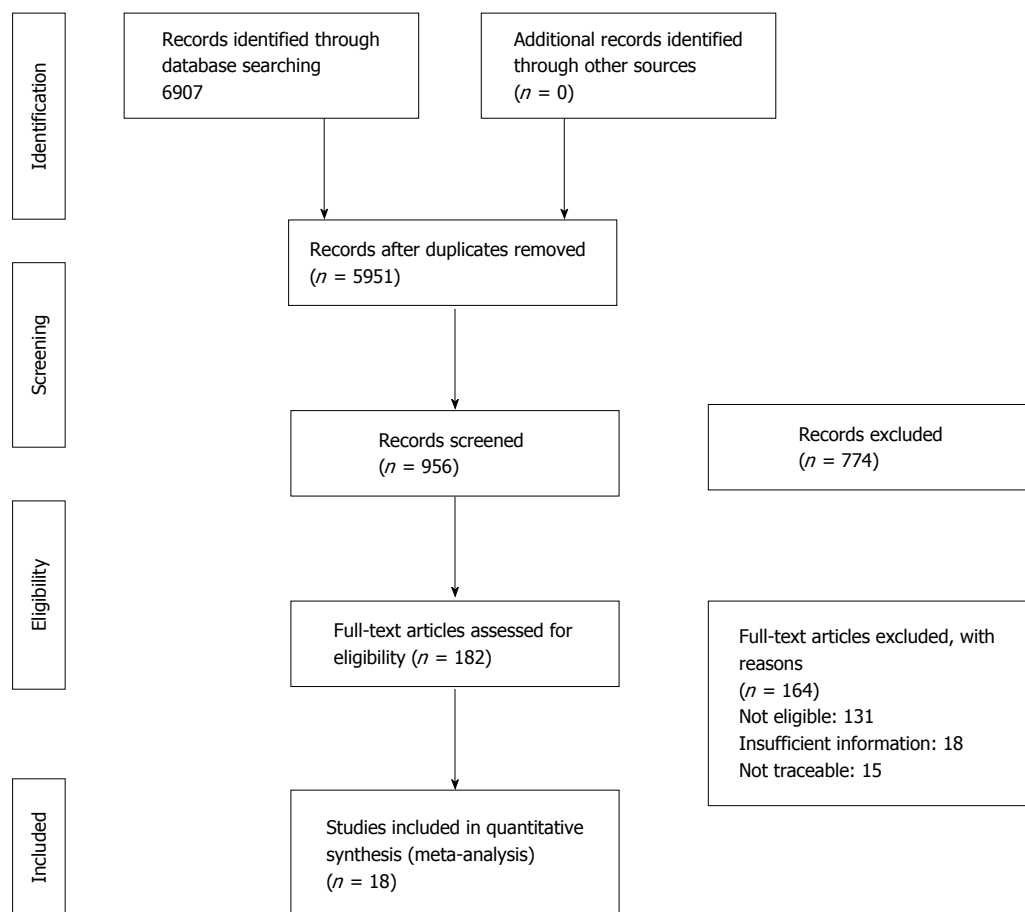
Figure 1 Preferred reporting Items for systematic reviews and meta-analysis study flow diagram.

discussed. In studies with hypertension as an outcome, all studies discussed measurement error *vs* 6 studies with T2DM as the outcome (Tables 3 and 4).

Publication bias
The funnel plot that depicts the publication bias showed an inverted funnel shape with studies of higher precision relatively closer to the pooled odds ratio. This corroborates minimal publication bias (Figures 2 and 3).

Combined effect of obesity and type 2 diabetes mellitus
Odds ratio pooled from all the included studies in meta-analysis exhibited statistically significant association between obesity and T2DM (OR = 1.14, 95%CI: 1.043 to 1.237). We noticed substantial heterogeneity among these study estimates, with the I^2 statistic being 83.9% and P = 0.0001. Similarly, the pooled odds ratio of obesity and hypertension was 3.820 (95%CI: 3.392 to 4.248). The heterogeneity around this estimate (I^2 statistic) was 0%, and P = 0.435 indicating low variability among the included studies.

DISCUSSION
Our results show that the association between obesity and hypertension is strongly positive and T2DM is moderately positive compared with healthy non-obese adults in India. Through the synthesis of available evidence using random effects meta-analysis, we show that obesity in India is a formidable independent risk factor to mitigate; albeit the risk appears to be relatively less for T2DM. With industrialization and urbanization, the prevalence of obesity has increased gradually in India, heightening the need to focus on the prevention of these NCDs.

Our analysis suggests that after adjustment for covariates, obesity is significantly associated with hypertension. These estimates were stable, suggested by low variability in the heterogeneity (I^2 statistic, 0%)[30]. The findings concur with other studies linking body mass as an important risk factor to hypertension[31-33]. This also coincides with the observed trend of increasing prevalence of hypertension in India across different risk groups for obesity[34-37]. More specifically, the estimates of meta-analysis are analogous to the estimates from (odds ratio, 3.7; 95%CI: 2.1-6.8) synthesis of evidence covering 6 middle-income countries by Sanjay Basu *et al*[34], indicating increased correlation of obesity prevalence with hypertension across dissimilar cultures. The pathophysiology of developing hypertension in obese individuals is explained by elevated cardiac output, perhaps due to excess intravascular volume and reduced

Table 3 Characteristics of included obesity and hypertension studies

Ref.	Year	Participants characteristics	Study characteristics				Measurements		Methodological quality of study			
		Age M (sd) in yr	Setting	Study design	Sample size	Inclusion criteria	Exposure	Outcome	Adjusting confounders	Selection bias	Measurement error	Response rate
Reddy *et al*[14]	2003	20-30	Urban slums	Cross-sectional	1000 (500 male and 500 female)	Adults of 20-60 yr age	BMI > 25	Mean blood pressure levels	Important Confounders[1]	Not mentioned	Mentioned	100%
Mandal *et al*[15]	2008	40-49	Kolkata Municipal Corporation	Cross-sectional	887	Aged 20 yr or more	BMI ⩾ 25	JNC VII guideline	Important confounders[1] + religion, marital status, nature of work, family type, animal protein intake	Not mentioned	Mentioned and discussed	98.30%
Bhadoria *et al*[16]	2014	38-50	Urban wards	Cross-sectional	939	Individuals aged 20 yr and above	BMI ⩾ 27.5	JNC VII guideline	Important confounders[1]	Not mentioned	Mentioned	97.02%
Bhadoria *et al*[16]	2014	Males: 25-52 Female: 24-53	48 villages and 15 urban wards of Jabalpur District	Cross-sectional	939	Aged 20 yr and above	W/H ratio > 0.85 for females and > 0.90 for males	JNC VII guideline	Important confounders[1]	Not mentioned	Mentioned	97.02%
Bhadoria *et al*[16]	2014	Males: 25-52 Female: 24-53	Villages of Jabalpur district	Cross-sectional	939	Aged 20 yr and above	BMI ⩾ 27.5	JNC VII guideline	Important confounders[1]	Not mentioned	Mentioned	97.02%
Adhikari *et al*[17]	2015	53.9 ± 12.7	Semi-urban in Mangalore city	cross-sectional	800	⩾ 20 yr	BMI ⩾ 25	JNC VII criteria	Important confounders[1] + serum cholesterol, serum triglycerides	Mentioned and discussed	Mentioned and discussed	68.80%

[1]Important confounder: Age, sex, family history, history of previous events, DM, diet, smoking, alcohol, no regular exercise, saturated fat intake, excess salt intake, sedentary physical activity. JNC VII criteria for diagnosis: Considering JNC 7 category guideline, normal blood pressure is defined as < 120/80 mmHg, prehypertension state is detected when systolic blood pressure (SBP) and diastolic blood pressure (DBP) is 120-139 mmHg and 80-89 mmHg respectively. If the blood pressure is > 140/90 mmHg it is diagnosed as hypertension with Stage 1 hypertension (when SBP and DBP are 140-159 mmHg and 90-99 mmHg respectively) and Stage 2 hypertension (when SBP and DBP are ⩾ 160 mm Hg and ⩾ 100 mmHg respectively). BMI: Body mass index; JNC: Joint National Committee.

cardiac contractility[38]. Recent evidence suggests that among obese, alteration in nutritional status, gut microbiota, sunlight exposure and increased physical activity have an important role in the presence or absence of hypertension[39]. Future studies may provide more details on these variables, including possible mediation.

Our results indicate that obesity is only moderately associated with T2DM. Also, we observed considerable heterogeneity in studies involving T2DM. The results also indicate that this is not explained by differences in participant age, baseline characteristics, or study quality. Such heterogeneity might be seen for several reasons. First, the "Asian Indian Phenotype" refers to unique abnormalities characterized by higher chances of adverse effects of obesity despite lower BMI, higher WHR, comparatively low WC and thin stature as compared to other ethnic groups[40]. The lean T2DM

is a distinct clinical entity in India. Due to temporal ambiguity in cross-sectional studies, it is possible that loss of weight might have ensued after the diagnosis of T2DM. In a recent survey covering eleven cities of India, 45% patients with diabetic retinopathy reported already had the visual loss when they first detected to have T2DM[41]. This indicates that nearly half of the persons with T2DM in India are undiagnosed, and therefore, apart from other complications would have lost considerable weight by the time of diagnosis. It is reported that nearly 53% of patients may have weight loss as the presenting symptom of T2DM[42]. Given this evidence, we estimate that nearly one-fourth of the undiagnosed persons with T2DM will have weight loss and therefore will spuriously indicate that obesity may not be a significant risk factor. Using cut-off points of BMI, WC and WHR as surrogates for percentage body fat in Indians, and thereby making classifications

Table 4 Characteristics of included obesity and type 2 diabetes mellitus studies

Ref.	Year	Participants characteristics			Study characteristics		Measurements		Methodological quality of study			
		Age M (sd) in yr	Setting	Study design	Sample size	Inclusion criteria	Exposure	Outcome	Adjusting confounders	Selection bias	Measurement error	Response rate
Mohan *et al*[19]	1996	55.5 ± 11.9	Tamilnadu	Cross-sectional	1399	Individuals aged ≥ 20 yr	BMI ≥ 30 kg/m²	Diabetes (WHO criteria)	Important confounders[1] +, SBP, DBP	Not mentioned	Mentioned and discussed	90.20%
Mohan *et al*[19]	1996	55.5 ± 11.9	Tamilnadu	Cross-sectional	1399	individuals aged ≥ 20 yr	WC ≥ 90 cm	Diabetes (WHO criteria)	Important confounders[1] +, SBP, DBP	Not mentioned	Mentioned and discussed	90.20%
Kumar *et al*[20]	Published year 2008	36.4	Kolkata	Cross-sectional	2200	Policemen with (monthly income: Rs.6000-15000), age (20 and 60 yr)	BMI	T2DM	Important confounders[1] +, SBP, DBP,	Not mentioned	Mentioned and discussed	98.18%
Kumar *et al*[20]	Published year 2008	36.4	Kolkata	Cross-sectional	2200	policemen with (monthly income: Rs.6000-15000), age (20 and 60 yr)	WHR	T2DM	Important confounders[1] + SBP, DBP	Not mentioned	Mentioned and discussed	98.18%
Kumar *et al*[20]	Published year 2008	36.4	Kolkata	Cross-sectional	2200	Policemen with (monthly income: Rs.6000-15000), age: 20 and 60 yr	WC	T2DM	Important confounders[1] SBP, DBP	Not mentioned	Mentioned and discussed	98.18%
Bharati *et al*[21]	2007	20-49	Rural and urban field practice area.	Cross-sectional	1370	Adults: ≥ 20 yr	BMI > 30	T2DM (ADA classification)	Important confounders[1] + blood cholesterol, hypertension	Not mentioned	Not mentioned	100%
Bharati *et al*[21]	2007	20-49	Rural and urban field practice area	Cross-sectional	1370	Adults: ≥ 20 yr	WHR	T2DM (ADA classification)	Important confounders[1] + blood cholesterol, hypertension	Not mentioned	Not mentioned	100%
Ravindra Singh *et al*[24]	2012-13	30-39	Agra City	Cross-sectional	633	Adults: ≥ 30 yr residing in Agra City	BMI	T2DM (WHO criteria)	Important confounders[1]	Not mentioned	Not mentioned	100%
Ravindra Singh *et al*[24]	2012-13	30-39	Agra City	Cross-sectional	633	Adults: ≥ 30 yr residing in Agra City	WHR	T2DM (WHO criteria)	Important confounders[1]	Not mentioned	Not mentioned	100%
Ravindra Singh *et al*[24]	2012-13	30-39	Agra City	Cross-sectional	633	Adults: ≥ 30 yr residing in Agra City	WC (> 88 cm for female and > 102 cm for male)	T2DM (WHO criteria)	Important confounders[1]	Not mentioned	Not mentioned	100%
Ghorpade *et al*[22]	2007	35-50	Rural Tamilnadu	Cohort	1403	Adults > 25 yr of age from selected population	BMI ≥ 23	T2DM	Important confounders[1] + n work status, Alcohol intake	Mentioned	Mentioned and discussed	85%
Vijayakumar *et al*[23]	2007	30-44	Urban Kerala	Cross-sectional	1990	≥ 18 yr, residing since t 6 mo	WHR (< 0.80 in women, 0.90 in men)	T2DM (Those with diabetes, and ADA classification)	Important confounders[1] + hypercholesterolemia, elevated BP	Not mentioned	Not mentioned	82.70%

[1]Important confounders: Age, family history, sex, dietary habit, social economic status. As per WHO and ADA classification, diagnosis of diabetes is confirmed when fasting plasma glucose is ≥ 7 mmol/L (126 mg/dL) or 2 h plasma glucose is ≥ 11.1 mmol/L (200 mg/dL). Impaired glucose tolerance (IGT) test and impaired fasting glucose (IFG) test is considered as positive when the fasting plasma glucose is < 7 mmol/L (126 mg/dL) and 6.1 to 6.9 mmol/L (110 mg/dL to 125 mg/dL) respectively, 2 h plasma glucose is ≥ 7.8 and < 11.1 mmol/L (140 mg/dL and 200 mg/dL) and < 7.8 mmol/L (140 mg/dL) respectively. Both: Males and females; NA: Not available; ADA classification of diabetes: Fasting ≥ 126 mg/dL; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; ADA: American Diabetes Association; JNC: Joint National Committee; WHO: World Health Organization; T2DM: Type 2 diabetes mellitus; WC: Waist circumference; WHR: Waist to hip ratio; BMI: Body mass index.
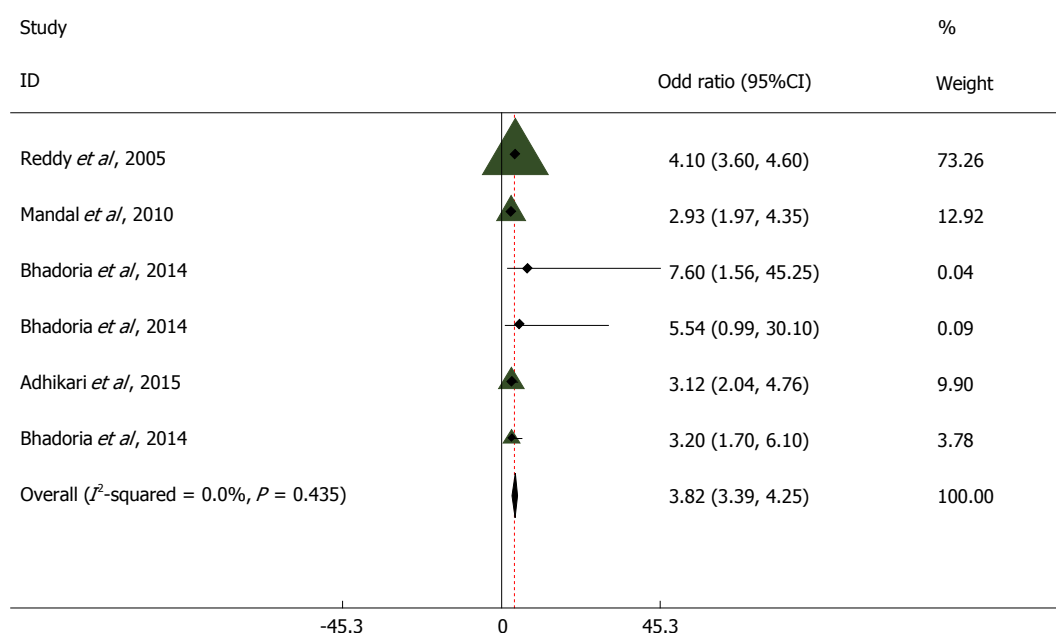
Figure 2 Meta-analysis of studies exploring association between obesity and hypertension in India.

of obesity might have underestimated the overall measures[43]. The validity of universal cut-off points for Indians is uncertain; it would be better only to treat it continuous variable[8]. Future examinations should include analysis of the data sets from these studies for a continuous association. The association of obesity with T2DM and hypertension is highly probable at lower levels than the cut-off points used in this paper. Therefore, we might have grossly underestimated the association between obesity and T2DM. Further, Survival bias might have resulted in underestimation; since, people with T2DM, who are dead, debilitated, disabled or have severe illness might not have captured by the cross-sectional studies[44]. The available evidence concurs with our finding; while the majority of persons with T2DM are obese in the west, 27% of people with diabetes in India are lean[45-47]. These individuals may have different clinical and biochemical profiles, including predisposition to microvascular complications[46-49].

Such variations in phenotype used in different studies might include inconsistencies in specific cut-points employed. It is also possible that most of the evidence from cross-sectional studies is derived from hospital-based populations and is, therefore, subject to considerable survivor bias[50]. Hence, the included participants in the final sample represent only survivors who might have had better glucose control compared to individuals with poor glucose control confounded by obesity[50]. Finally, those with T2DM may lose substantial amounts of weight from the disease and as a function of treatment[51]. Due to the cross-sectional nature of these studies, the temporality of obesity prior to the onset of T2DM cannot be established. Despite the heterogeneity, most estimates are in the same direction with only 2 studies reporting less than a null association for T2DM.

The association of obesity with NCDs in India has several challenges. First, despite posing a major public health challenge, the rising prevalence of childhood obesity has received very little attention from policy makers in India. Second, compared to whites, Indians are more prone for obesity and decreased muscle mass for any proposed value of BMI[1]. With 46%[52] in the south and 50%[53] in the north, recent estimates suggest that obesity affects the unvaryingly high proportion of urban Indians, predisposing them to future NCDs. This complicates the issue since Indians within normal BMI can develop insulin resistance, metabolic syndrome, and T2DM[1]. Therefore, the severity and consequences of obesity might be grossly underestimated, including the challenge of finding an appropriate definition of obesity in Indians. The implications of obesity on the growth of the nation and future expenditures are under-valued. Given that India is projected to have 135 million individuals with generalized obesity[54], around 44 million might develop insulin resistance[55-57]. If we were to apply similar methodology employed by Popkin *et al*[57] in previous estimates, the annual costs attributable to overweight and obesity in India will surpass approximately \$100 billion in 2025.

To our estimate, this is the first meta-analysis to summarize association of obesity with hypertension and T2DM in India. Our results indicate that it is important to consider further explorations of obesity and NCD associations. Intervention and policy efforts to alleviate the adverse effects of obesity in India, including hypertension and T2DM are also needed. However, there are number of limitations to our review. First, the possibility of conclusive evidence is limited due to the availability of evidence from cohort studies. Second, there can be considerable measurement issues due to heterogeneous definitions
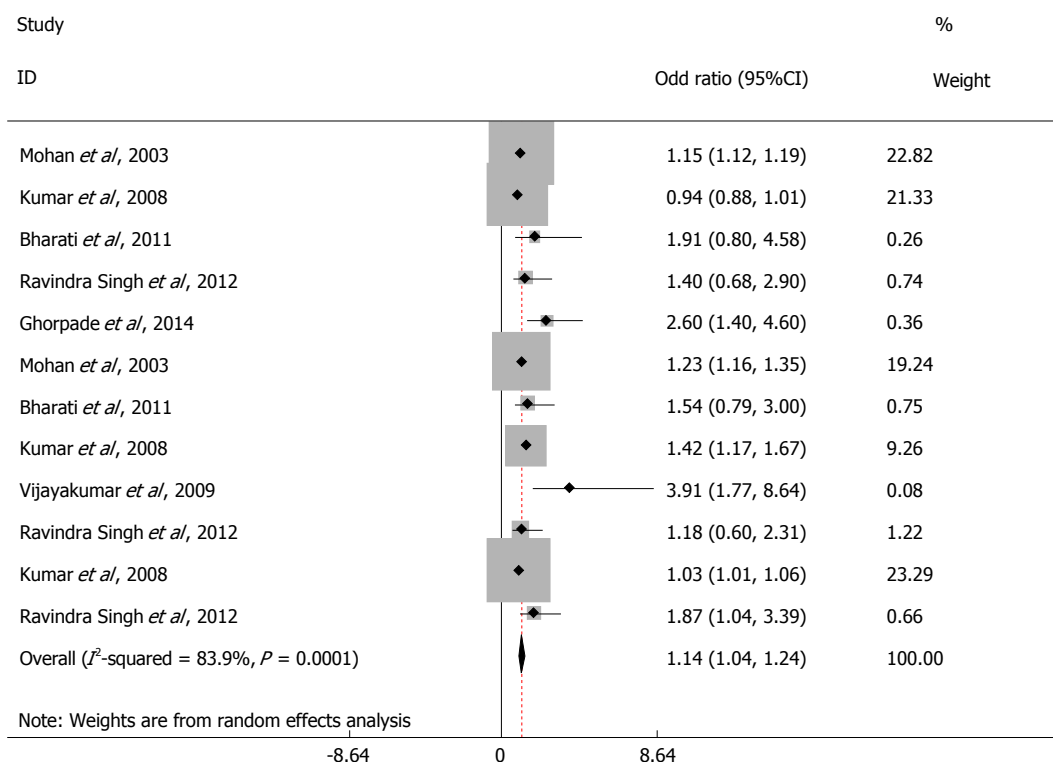
Study ID	Odd ratio (95%CI)	% Weight
Mohan *et al*, 2003	1.15 (1.12, 1.19)	22.82
Kumar *et al*, 2008	0.94 (0.88, 1.01)	21.33
Bharati *et al*, 2011	1.91 (0.80, 4.58)	0.26
Ravindra Singh *et al*, 2012	1.40 (0.68, 2.90)	0.74
Ghorpade *et al*, 2014	2.60 (1.40, 4.60)	0.36
Mohan *et al*, 2003	1.23 (1.16, 1.35)	19.24
Bharati *et al*, 2011	1.54 (0.79, 3.00)	0.75
Kumar *et al*, 2008	1.42 (1.17, 1.67)	9.26
Vijayakumar *et al*, 2009	3.91 (1.77, 8.64)	0.08
Ravindra Singh *et al*, 2012	1.18 (0.60, 2.31)	1.22
Kumar *et al*, 2008	1.03 (1.01, 1.06)	23.29
Ravindra Singh *et al*, 2012	1.87 (1.04, 3.39)	0.66
Overall (I^2-squared = 83.9%, P = 0.0001)	1.14 (1.04, 1.24)	100.00

Note: Weights are from random effects analysis

-8.64   0   8.64

Figure 3 Meta-analysis of studies exploring association between obesity and type 2 diabetes mellitus in India.

in different population subgroups. Third, a standard definition of what constitutes "obesity" in Indians remains elusive and therefore, combining different measures of obesity might have led to misclassifications in this study. Also, in the absence of India specific cut-off points, inability to treat obesity as a continuous variable might have underestimated the association between obesity and T2DM. Finally, the reliance on cross-sectional studies may be particularly susceptible to biases, including survivor bias and therefore restricts causal inference.

Obesity is an important driver of NCDs in India. The current stage of the obesity epidemic presents an opportunity for policy and intervention efforts related to prevention. This opportunity necessitates developing a clear strategy for the control of NCDs through rigorous screening and management. The adverse effects of obesity cannot be assessed without robust documentation of obesity indicators throughout the life course. The increasing prevalence of obesity, hypertension, and diabetes in India has enormous implications for the healthcare system. Policymakers, Government officials, and public health professionals can focus policy and intervention efforts on obesity as an important risk factor to prevent NCDs like diabetes and hypertension.

ARTICLE HIGHLIGHTS

Research background
It is well known that hypertension and type 2 diabetes mellitus (T2DM) are the major non-communicable diseases (NCDs) leading to catastrophic complications and death in India. It is important to investigate the role of modifiable risk factors such as obesity resulting in NCDs. The authors are

aware that the risk factors seldom act in isolation and it is important to alleviate the impact of their confluence. It is therefore important to determine the significance of risk contribution by individual risk factor like obesity. Available evidence suggests strong associations between obesity and NCDs. However, none of the earlier reviews have specifically evaluated the role of obesity in the etiology of hypertension and T2DM in India.

Research motivation
As obesity is one of the key NCD's and risk factor for the majority of other NCD's in India, the authors need to provide evidence to show its association with other major diseases like hypertension and T2DM. By exhibiting the evidence and its association, preventive measures can be taken for route cause of disease.

Research objectives
To perform a meta-analysis of the association of obesity with hypertension and T2DM in India among adults to assess potential causal factors and improve prevention and control measures for these NCDs.

Research methods
The authors have followed rigorous methodology in doing comprehensive meta-analysis with a predefined protocol. The authors entered and analysed data using the Cochrane Collaboration's Review Manager software version 5 for Windows (Cochrane Collaboration, Oxford, England), and subsequently entered into a spreadsheet and re-analysed data using the "metan" command of STATA 11 version for Mac. The authors have used the RevMan for developing flow chart according PRISMA guidelines, and also assessed the methodological quality of studies. The authors found that the pooled estimate between obesity and hypertension and the heterogeneity around this estimate which indicating low variability among the included studies. The pooled estimate from all studies showed a statistically significant association between obesity and T2DM. The authors observed considerable heterogeneity among these estimates of studies.

Research results
The results shows that the association of obesity and hypertension is strongly positive and T2DM moderately positive compared with healthy non-obese

adults in India. This study provides evidence regarding the putative role of obesity and its impact on NCDs. This also coincides with the observed trend of increasing prevalence of hypertension in India across different risk groups for obesity.

Research conclusions

The current stage of the obesity epidemic presents an opportunity for policy and intervention efforts related to prevention. This opportunity necessitates developing a clear strategy for the control of NCDs through rigorous program management at national and state levels. The increasing prevalence of obesity, hypertension, and diabetes in India has enormous implications for the healthcare system. Policy makers, government officials, and public health professionals can focus policy and intervention efforts on obesity as an important risk factor to prevent NCDs like diabetes and hypertension.

Research perspectives

Study provides with experience of route cause associated with major NCD's like hypertension and T2DM. As the evidence suggested obesity is associated with these NCD's, it is the time to think regarding preventive aspect of obesity to prevent future outcome. With limited earlier statistically proved evidence, the current meta-analysis the association of obesity with hypertension and T2DM in India proved the statistical significance association of obesity with major NCD's such as T2DM and hypertension with high degree of variability and substantial heterogeneity. Results provided the possible common risk factors for the NCD's and made a way for the researchers to think of the research on interventional measures to prevent obesity in coming future. Research involving Randomized Controlled Trials nested within cohort for the prevention of obesity will provide affirmation of fruitful interventions which can be included in future evidence based policy formulation.

ACKNOWLEDGMENTS

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