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Combining general and central measures of adiposity to identify risk of hypertension: a cross-sectional survey in rural India

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ABSTRACT

Aim: In three socioeconomically diverse regions of rural India, we determined the optimal cut-offs for definition of overweight, the prevalence of overweight, and the relationships between measures of overweight and risk of hypertension.

Subjects and methods: Villages were randomly sampled within rural Trivandrum, West Godavari, and Rishi Valley. Sampling of individuals was stratified by age group and sex. Cut-offs for measures of adiposity were compared using area under the receiver operating characteristic curve. Associations between hypertension and definitions of overweight were assessed by logistic regression.

Results: Of 11 657 participants (50 % male; median age 45 years), 29.8 % had hypertension. Large proportions were overweight as defined by body mass index (BMI) $\geq$ 23 kg/m^2 (47.7 %), waist circumference (WC) $\geq$ 90 cm for men or $\geq$ 80 cm for women (39.6 %), waist-hip ratio (WHR) $\geq$ 0.9 for men or $\geq$ 0.8 for women (65.6 %), waist-height ratio (WHtR) $\geq$ 0.5 (62.5 %), or by BMI plus either WHR, WC or WHtR (45.0 %). All definitions of overweight were associated with hypertension, with optimal cut-offs being at, or close to, the World Health Organization (WHO) Asia-Pacific standards. Having overweight according to both BMI and a measure of central adiposity was associated with approximately twice the risk of hypertension than overweight defined by only one measure.

Conclusions: Overweight, as assessed by both general and central measures, is prevalent in rural southern India. WHO standard cut-offs are appropriate in this setting for assessing risk of hypertension. However, combining BMI with a measure of central adiposity identifies risk of hypertension better than any single measure. The risk of

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hypertension is significantly greater in those centrally and generally overweight than those overweight by a single measure.

1. Introduction

Cardiovascular disease is a leading cause of premature mortality in low-to-middle-income countries (LMICs) [1], with hypertension being the most important modifiable risk factor [2,3]. Approximately, a third of residents in rural and urban India have hypertension [4,5]. Therefore, strategies to prevent hypertension should mitigate the burden of cardiovascular disease.

Adiposity is a critical modifiable risk factor for hypertension in high-income countries (HICs) [6]. It is also an emerging risk factor in LMICs such as India, although most information comes from studies of urban populations [7–9]. Overweight can be diagnosed using a general anthropometric measurement such as body-mass-index (BMI) or by assessment of central adiposity by waist circumference (WC), waist-hip-ratio (WHR) or waist-height-ratio (WHtR) [10]. However, there is uncertainty about how to assess overweight in order to best target efforts to mitigate the burden of hypertension, both in terms of the best diagnostic index and the best cut-off values to apply. For example, in China, the optimal cut-offs for BMI and WC in their population differed from the Asia Pacific standard cut-offs for overweight developed by the World Health Organization (WHO) [11,12]. In rural India, the relative associations of these measures of overweight with prevalent hypertension have only been quantified from studies of small sample size [13,14] and the appropriateness of the Asia Pacific standard cut-offs for overweight [12], has been little explored in rural India. In addition, the potential to improve management of hypertension in rural India by targeting multiple indices of overweight and obesity has been little studied.

In response to the gaps in our knowledge described above, in the current study, we determined the prevalence of hypertension, and of overweight and obesity as assessed by anthropometric measures of general and central adiposity, in a sample of 11 657 adults within three rural regions of southern India at differing stages of the epidemiological transition. We examined various cut-offs for indices of adiposity with respect to hypertension, to determine whether the standard WHO Asia Pacific cut-offs [12] are appropriate in these settings of relative poverty and disadvantage. We then tested the hypothesis that combining measures of central and general adiposity allows for better targeting of those at risk of hypertension than use of one measure alone.

2. Methods

2.1. Study regions

This cross-sectional study was conducted across three regions in rural India; Trivandrum (Kerala), (West) Godavari (Andhra Pradesh) and the Rishi Valley (Andhra Pradesh). The three regions have varying degrees of socioeconomic status [15]. Trivandrum is the most socioeconomically advantaged region, the Rishi Valley is the most disadvantaged, and Godavari is intermediate. A total of 11 657 participants were randomly recruited from January 2014 to December 2015 (Supplementary File: Fig. S1). Power for this study was based on outcomes for a cluster randomised controlled trial (Clinical Trial Registry – India, CTRI/2016/02006678) [13] nestled within this cross-sectional study. Therefore, the sample size was larger than that required for our primary hypothesis.

2.2. Sample selection

Each of the three sites were divided into primary sampling units (villages, wards or hamlets) by computer generated randomisation [15,16]. In each primary sampling unit, participants were randomly selected from population censuses and stratified according to age (18–24, 25–34, 35–44, 45–54, 55–64, and >65 years) and sex, with approximately equal numbers recruited in each of the 12 categories.

2.3. Data collection

Questionnaires were administered, and anthropometric parameters and blood pressure were measured, in accordance with the World Health Organisation (WHO) STEPwise approach to surveillance (WHO STEPS) protocol [17]. No specific instructions about avoidance of alcohol, coffee, or heavy physical activity were provided to participants before they arrived for assessment.

2.4. Blood pressure

An automatic digital device (HEM-907, OMRON, Kyoto, Japan) was used to measure blood pressure (BP). Participants were asked to sit quietly for 15 min prior to measurement, with legs uncrossed. BP was measured from the right upper arm, with the arm resting at the level of the heart. To minimise risk of measurement error, at least three readings were obtained, at 3 min intervals, with a fourth or fifth measurement taken if the final two measurements varied by ≥ 10 mmHg (systolic) or ≥ 6 mmHg (diastolic). Mean systolic and diastolic pressure were defined as the averages of the final two sets of measurements.

2.5. Height and weight

Height was measured to the nearest 0.1 cm using a portable stadiometer (213, Seca, Hamburg, Germany). Weight was measured to the nearest 0.1 kg using a digital weight scale (9000SV3R, Salter, Kent, UK). To improve accuracy, participants removed footwear and heavy clothing before these measurements were taken.

2.6. Waist and hip circumference

Waist and hip circumference were assessed to the nearest 0.1 cm using a spring-loaded tension tape (Gulick M-22 C, Patterson Medical, Illinois, United States) [17]. Waist circumference was measured horizontally at the midpoint between the iliac crest and the floating rib (following expiration). Hip circumference was measured at the fullest point of the buttocks.

2.7. Questionnaires

Questionnaires were used to obtain self-reported hypertensive status, sociodemographic details, level of education, and difficulty in access to healthcare. Hard copies were scanned into *.tif* files, digitally captured and verified using Teleform Elite Version 9 software (Cardiff, San Jose, CA, USA), and uploaded into Microsoft Access. Missing data were verified with original copies and proportion of missing values were reported in results.

2.8. Clinical definitions

Hypertension was defined as mean systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, and/or self-reported treatment with and/or prescription of antihypertensive medication. WHR, BMI and WHtR were determined using standard formulae.

Measures of adiposity were dichotomised according to the WHO Asia Pacific standard cut-offs for overweight [12]. These are as follows; BMI

Table 1
Demographics, blood pressure and anthropometric measures for men and women.

Characteristics	Men[a] ($n = 5784$)	Women[a] ($n = 5852$)	P
Age (years)	45.0 (30, 60)	45.0 (30, 60)	0.80
Systolic blood pressure (mmHg)	122.5 (114.0, 134.0)	116.0 (106.5, 130.0)	<0.001
Diastolic blood pressure (mmHg)	74.5 (67.0, 82.0)	71.5 (64.5, 79.5)	<0.001
Hypertension	1650 (28.6)	1810 (30.9)	<0.001
Body mass index (BMI, kg/m^2)[b]	22.3 (19.5, 25.2)	23.3 (19.8, 27.0)	<0.001
Body mass index ≥ normal	2542 (44.0)	3013 (51.7)	<0.001
Waist hip ratio[c]	0.93 (0.87, 0.98)	0.85 (0.78, 0.91)	<0.001
Waist hip ratio ≥ normal	3682 (63.9)	3960 (68.3)	<0.001
Waist circumference (cm)[d]	83.5 (73.5, 92.3)	79.0 (68.0, 89.0)	<0.001
Waist circumference ≥ normal	1805 (31.2)	2816 (48.1)	<0.001
Waist height ratio[e]	0.51 (0.45, 0.56)	0.52 (0.45, 0.59)	<0.001
Waist height ratio ≥ normal	3901 (53.4)	3385 (57.8)	<0.001
BMI & central adiposity > normal (%)	2409 (41.6)	2836 (48.5)	<0.001

Continuous variables are presented as median (quartile 1, quartile 3). Categorical variables are presented as n (%). P-values, comparing women with men, were generated using the Mann-Whitney U test for continuous variables and the X^2 test for categorical variables. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, and/or prescription of antihypertensive medication. BMI & central adiposity > Normal was defined as body mass index ≥ 23 kg/m^2 and at least one of: waist hip ratio ≥ 0.8 for women, ≥ 0.9 for men, waist circumference ≥ 80 cm for women, ≥ 90 cm for men and/or waist height ratio ≥ 0.50.
[a] 21 missing observations for sex.
[b] 41 missing observations.
[c] 73 missing observations
[d] 64 missing observations
[e] 79 missing observations.

≥ 23 kg/m^2, WC ≥ 80 cm for women and ≥ 90 cm for men, WHR ≥ 0.80 for women and ≥ 0.90 for men, and WHtR ≥ 0.50. As we dichotomised variables, the term ‘overweight’ is used broadly to include all individuals who exceeded these cut-offs.

2.9. Statistics

Most continuous variables violated normality so are presented as medians (Quartile 1, Quartile 3). Categorical variables are presented as *n* (%). Dichotomous comparisons were made using the Mann–Whitney U test (for continuous variables) or the Chi Squared test (categorical variables).

Multivariable logistic regression was used to assess the association between risk of hypertension and each definition of overweight, with all participants adjusted for age and, when comparing between men and women, stratification by sex. The area under the receiver-operating characteristic curve (AU-ROC) was used to assess the predictive value of each regression model. To determine the interactions between the dichotomised measures of adiposity, we assessed the relative excess risk due to interaction (RERI), the attributable proportion (AP), and the Synergy Index (SI) [18]. We also conducted sensitivity analyses of these associations stratified by age and sex. Additionally, self-reported difficulty in accessing health care was used as a proxy to adjust for differences in healthcare between sites [15]. All analyses were performed using Stata 11.2 (StataCorp, College Station, Texas, United States). All figures were produced using GraphPad Prism version 8.0.0 for Macintosh (GraphPad Software, San Diego, California USA, www.graphpad.com).

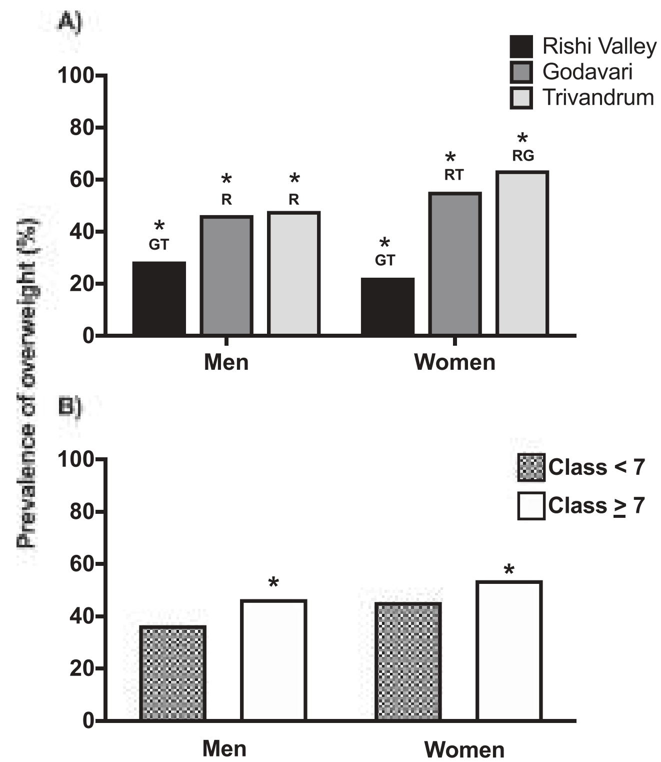

Fig. 1. Prevalence of overweight by (A) site and (B) level of education. Overweight was defined by measures of general and central adiposity. Data are presented as the proportion (%) of participants who were centrally and generally overweight based on body mass index ≥ 23 kg/m^2 and at least one central measure of adiposity above normal. Central measures of adiposity were considered above normal if waist circumference ≥ 80 cm for women or ≥ 90 cm for men, waist-hip-ratio ≥ 0.80 for women or 0.90 for men, or waist-height-ratio ≥ 0.50 for either men or women. Level of education was dichotomised as below class 7, which includes any level of schooling below class 7, including no schooling. Education of class 7 or above includes any level of education above class 7 through to tertiary education. *P*-values were generated using the χ^2 test, comparing the proportions of those who were overweight by (A) site or (B) level of education. G denotes $P \leq 0.05$ for comparison with Godavari. T denotes $P \leq 0.05$ for comparison with Trivandrum. R denotes $P \leq 0.05$ for comparison with the Rishi Valley. * denotes $P \leq 0.05$ for comparison with the opposite sex, within the same (A) site, (B) level of education. BMI; 41 missing observations. Sex; 21 missing observations. Level of education; 253 missing observations. See Supplementary Table S1 for further details.

3. Results

3.1. Prevalence of overweight

We recruited 11 657 participants, 3757 from rural Trivandrum, 4500 from Godavari and 3400 from the Rishi Valley. The mean age was 45 years and approximately half were women. More women than men had hypertension. Similarly, more women than men were overweight according to the WHO Asia Pacific standards for BMI, WHR, WC, and WHtR. Approximately 49 % of women and 42 % of men were both generally and centrally overweight (Table 1).

The proportion of those who were both centrally and generally overweight differed by site of residence. Across the three sites the smallest proportion of overweight was in the Rishi Valley for both men (28.6 %) and women (22.4 %). The largest proportion of overweight was among women in Trivandrum with 63.6 % both centrally and generally overweight (Fig. 1A; Supplementary Table S1). The proportion of centrally and generally overweight men in Trivandrum (48.0 %) was larger than in the Rishi Valley but similar to that in Godavari (46.6 %).

The proportion of those who were both centrally and generally

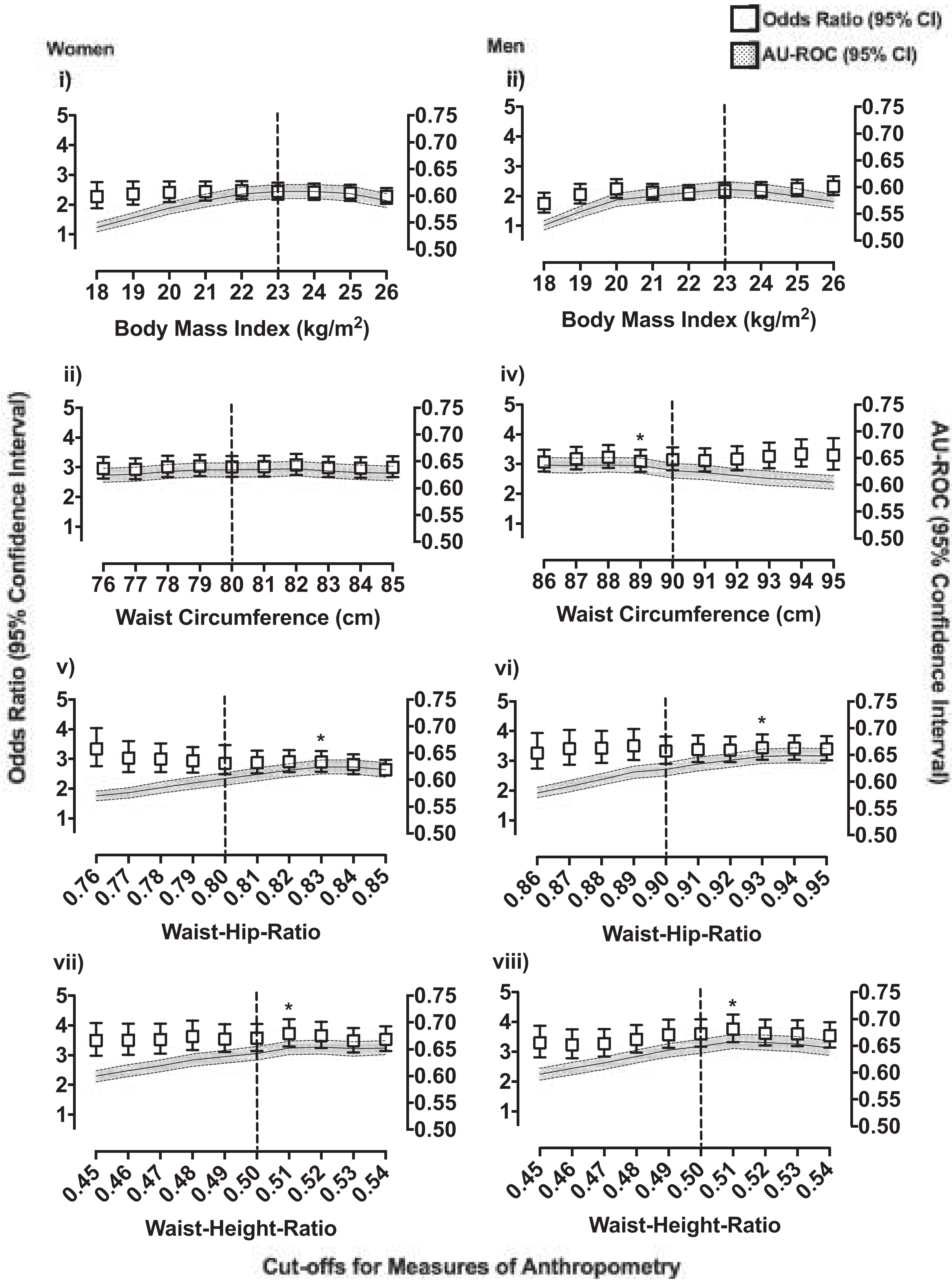

Fig. 2. Risk of hypertension at various cut-offs for measures of adiposity. Symbols show odds ratios (OR) with 95 % confidence intervals as error bars. The stippled area shows the 95 % confidence intervals for the areas under the receiver-operating characteristic curve (AU-ROC) with the point estimates joined by a solid line. The dashed vertical lines show the standard WHO Asia-Pacific cut-off for overweight for each index of adiposity. * denotes AU-ROC greater than the standard cut-off ($P \leq 0.05$) determined from χ^2. $n = 5785$ for women; $n = 5753$ for men. Sex; 21 missing observations. (i-ii) BMI; 41 missing observations. (iii-iv) WC; 64 missing observations. (v-vi) WHR; 73 missing observations. (vii-viii) WHtR; 79 missing observations. See Tables S2-S5 for details.

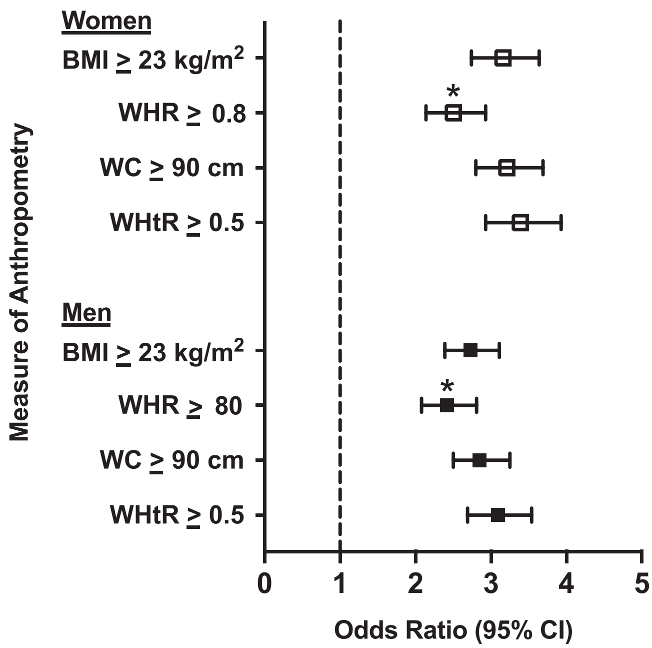

Fig. 3. Risk of hypertension for central and general measures of adiposity. Data are presented as odds ratios (95 % confidence intervals) for risk of hypertension for various measures of adiposity. Dashed line denotes line of null effect. BMI = body mass index; WHR = waist-hip-ratio; WHtR = waist-height-ratio; WC = waist circumference. * denotes $P \leq 0.05$ for comparison between BMI and the various measures of central overweight. $n = 5785$ for women; $n = 5753$ for men. Sex; 21 missing observations. BMI; 41 missing observations. WHR; 73 missing observations WC; 64 missing observations. WHtR; 79 missing observations. See Supplementary Table S6 for details.

overweight differed by level of education for men and women (Fig. 1B; Supplementary Table S1). More men (46.6 %) and women (53.8 %) with education of at least class 7 were both centrally and generally overweight than men (36.6 %) or women (45.5 %) with schooling less than class 7.

3.2. Associations between hypertension and various cut-offs for overweight

We assessed the associations of various cut-offs of BMI, WC, WHR and WHtR with hypertension (Fig. 2; Supplementary Tables S2-S5). The optimal associations between each index of overweight and hypertension, as assessed both by the magnitude of the odds ratio and the AU-ROC, was at, or close to, the WHO Asia Pacific standard cut off [12]. The exception to this was WHR, where the AU-ROC was greater for a higher cut-off of 0.93 for men and 0.83 for women than the WHO Asia Pacific standard cut-offs of 0.90 (men) and 0.80 (women). Conversely, a lower cut-off for WC for men of 89 cm had a higher AU-ROC than the standard cut-off of 90 cm (Fig. 2). Nevertheless, the ORs for hypertension estimated using these alternative cut-offs did not vary from those generated from the WHO Asia Pacific standard cut-offs. Thus, the WHO Asia Pacific standard cut-offs for overweight appear to be appropriate for estimating risk of hypertension in these rural populations in South India.

3.3. Risk of hypertension for central and general measures of adiposity

Regardless of the index used, adiposity was positively associated with risk of hypertension (Fig. 3; Supplementary Table S6). The risk of hypertension in those classified as overweight was similar for BMI, WC and WHtR for both men and women. However, based on AU-ROC analyses, in men BMI was better associated with risk of hypertension [AU-$ROC_{BMI,}$ 0.810 (0.802 – 0.819)] than WHR [AU-$ROC_{WHR,}$ 0.800 (0.792–0.808); $P < 0.001$]. A similar pattern was seen in women [AU-$ROC_{BMI,}$ 0.810 (0.802–0.818) versus AU-ROC_{WHR}, 0.800 (0.792–0.808); $P = 0.04$].

3.4. Additive association between BMI and measures of central adiposity

Having overweight, as defined by the WHO Asia Pacific standard cut-off for each of the four anthropometric indices, was positively associated with the risk of hypertension, independent of age (Fig. 4). A stronger association was observed when a central measure of adiposity (WC, WHR or WHtR) was added to BMI than when any single measure of adiposity was used (Fig. 4; Supplementary Tables S7-S9). For example, in women, there was an approximately 2-fold greater risk of hypertension when both BMI and WHtR were greater than normal [OR, 3.99 (3.40–4.67); $P < 0.001$] than when only WHtR was greater than normal [OR 1.95 (1.54–2.46); $P < 0.001$] (Fig. 4). Similar patterns were also observed in men and when stratified by age < or ≥ 60 years. In addition, the predictive potential (AU-ROC) of an additive interaction model of BMI combined with a waist measure was greater than that of BMI alone (Supplementary Table S10).

There was a pattern of greater risk of hypertension for any given measure of adiposity in Godavari than in Rishi Valley or Trivandrum independent of age (Supplementary Table S11), even after adjustment for self-reported difficulty in accessing healthcare (Supplementary Table S12).

4. Discussion

In three diverse populations in rural India, individuals categorised as overweight using a combination of both BMI $\geq$ 23 kg/m^2 and a measure of central adiposity were at considerably greater risk of hypertension than those categorised as overweight using only one of these indices. The additive effect of combining measures of general and central adiposity on risk of hypertension was independent of age and sex. We also found that overweight and obesity are highly prevalent, and that the WHO Asia Pacific standard cut-offs for measures of overweight [12] are appropriate for identifying risk of hypertension in these settings of relative disadvantage in rural India. These findings provide impetus for utilisation of both BMI and a central measure of adiposity, dichotomised using the WHO Asia Pacific standard cut-offs for overweight [12], to inform management of hypertension in rural India.

Nearly half of adults had both BMI and a measure of central adiposity in the overweight or obese range in these rural regions of Southern India. These findings are consistent with those from other LMICs and highlight the growing prevalence of overweight in these populations [19–21]. Thus, even in rural India, where under-nutrition has historically been considered a more significant contributor to the burden of disease than over-nutrition [21], there is considerable potential for adiposity to contribute to the burden of cardiometabolic disease.

Socioeconomic position (SEP) appears to be a major factor underlying overweight in rural southern India, since the prevalence of overweight varied with level of education and with the stage of epidemiological transition across these three socioeconomically diverse regions. Individuals in Trivandrum, the most socioeconomically advantaged of the three regions, were more commonly centrally and generally overweight than in the other two sites. Furthermore, those in the Rishi Valley, the most socioeconomically disadvantaged of the three regions, were less commonly centrally and generally overweight than those in the other two sites. In rural India, individual measures of SEP based on income or educational attainment were found to be positively associated with BMI and WHR and also with the risk of hypertension [15]. Similar patterns have been observed in other LMICs [20,22]. Thus, adiposity may be an important mediator of the positive association between SEP and the risk of hypertension in rural India and other LMIC settings, in contradistinction to its role as an important mediator of the

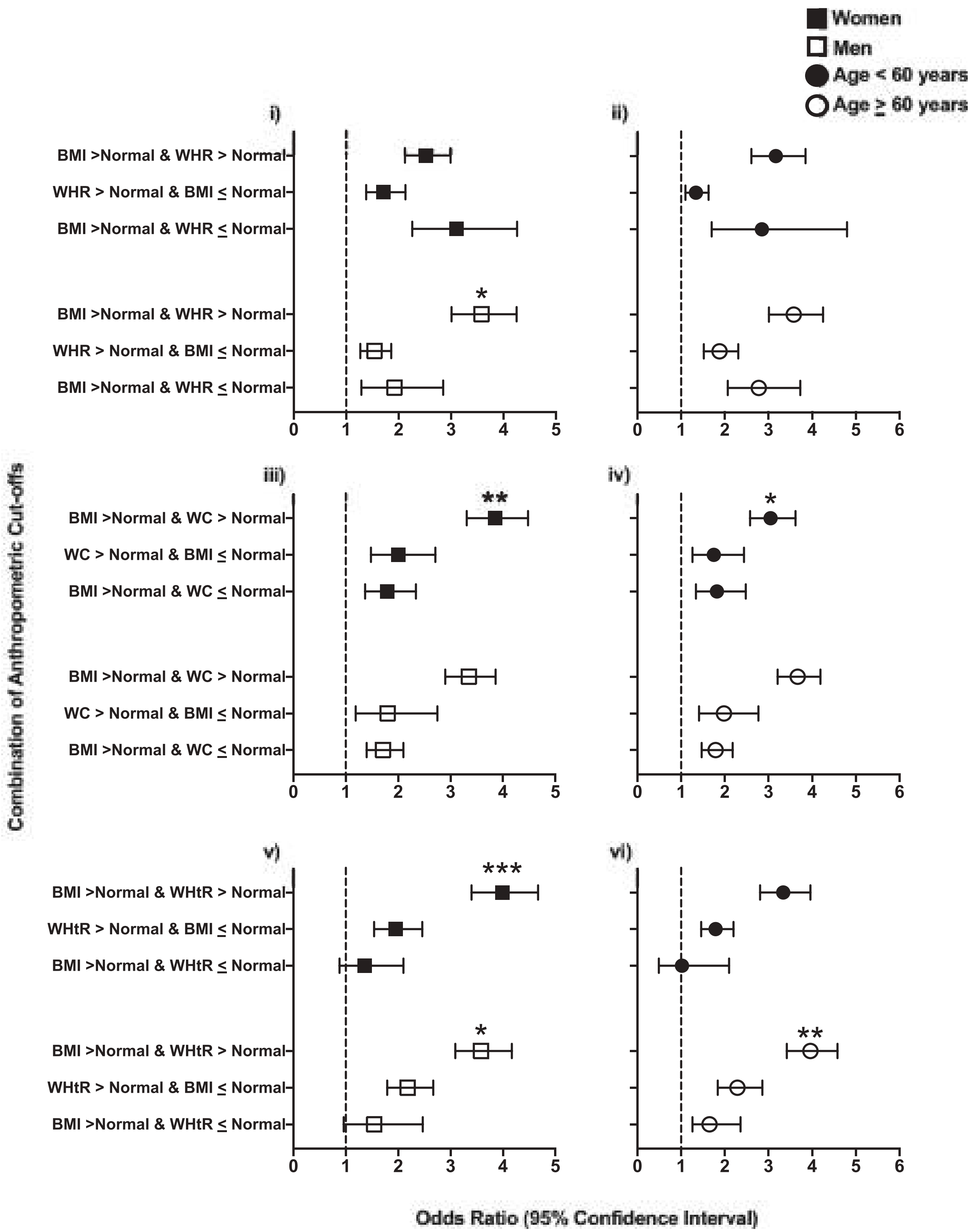

Fig. 4. Age-adjusted odds-ratios for the association of hypertension with individual and combined measures of adiposity. BMI = body-mass-index; WHR = waist-hip-ratio; WHtR = waist-height-ratio; WC = waist circumference. Cut offs for normal: BMI < 23 kg/m^2; WHR < 0.8 women and < 0.9 for men; WC < 80 cm for women and 90 cm for men; WHtR < 0.50. * denotes $P \leq 0.05$ for relative excess risk due to interaction (RERI), attributable proportion (AP) and/or synergy index (SI); ** denotes $P \leq 0.01$ for RERI, AP and/or SI; *** denotes $P \leq 0.001$ for RERI, AP and/or SI. $n = 5794$ for women; $n = 5753$ for men; $n = 8580$ for those aged < 60 years; $n = 2980$ for those aged $\geq$ 60 years. Sex; 21 missing observations. BMI; 41 missing observations. WHR; 73 missing observations. WC; 64 missing observations. WHtR; 79 missing observations. (i-ii) BMI and WHR; (iii-iv) BMI and WC; (v-vi) BMI and WHtR. See Supplementary Tables S7-S9 for details.

negative association between SEP and the risk of hypertension in HICs [23]. Our current analysis does not provide insight into the factors that mediate the obesogenic influence of higher SEP in settings of relative disadvantage. However, there is evidence that adoption of more sedentary occupations rather than the more active occupation of farming, in those of higher SEP, may be important [15].

Adiposity is an established risk factor for hypertension [24]. Accordingly, we found that, independent of age and sex, individuals who were overweight according to any anthropometric measure were at a greater risk of hypertension than those who were not overweight. However, there remains considerable uncertainty regarding the best way to assess adiposity within the context of risk of hypertension, particularly in rural regions of LMICs. Our current work addressed two critical questions that are relevant to this issue: (1) what are the cut-offs that should be used to best identify individuals at risk of hypertension? and (2) which measure or combination of measures of adiposity best reflects the risk of hypertension?

The optimal AU-ROC for risk of hypertension, of cut-offs of the various measures of adiposity, did not vary substantially from the WHO Asia Pacific standard cut-off values [12]. Similarly, Verma and colleagues [25] found the WHO Asia Pacific standard cut-offs for BMI to be appropriate for Asian Indian populations, although they did not assess cut-offs for measures of central adiposity. We conclude that, while there is some evidence that these standard cut-offs may not be optimal for China [11,26], they appear to be appropriate for rural India.

Although all indices of adiposity were positively associated with hypertension, BMI was a marginally better predictor than WHR. This could possibly be due the greater risk of measurement error and subjective differences in the measurement of waist circumference compared with BMI. However, we were unable to detect differences in the strength of association with hypertension between BMI and other measures of central adiposity (WC and WHtR). These findings are consistent with those from previous studies in a range of settings, in which measures of general adiposity were found to be marginally better associated with risk of hypertension than were measures of central adiposity [27,28]. However, the potential to better target those at risk of hypertension by combining measures of general and central adiposity has not been studied to a significant extent, particularly in settings of disadvantage such as rural Southern India.

Most importantly, our findings show that individuals in rural Southern India with combined central and general adiposity are at greater risk of hypertension than those with only central or only general adiposity. This finding appears to apply regardless of the measure of central adiposity (WC, WHR, or WHtR) used. Similar observations were made in rural China, although in a relatively small sample of 1275 adults [29]. We are not aware of any previous investigation of this issue in urban and/or rural India. Central obesity, a marker of unhealthy adiposity with visceral fat distribution, has been strongly associated with cardiovascular risk, even in the absence of an unhealthy BMI [30, 31]. Therefore, our findings provide impetus for consideration of measures of both general and central adiposity in management of patients at risk of hypertension-related cardiovascular disease in rural India.

A limitation of this study was that we could not adjust for some potential confounders, including diet and physical activity. The cross-sectional nature of our work also precluded generation of information regarding the mechanistic links between obesity and hypertension. Strengths include the large age- and sex-stratified sample from three socioeconomically diverse regions of rural India, which increases the generalisability and applicability of our findings to rural India. We used stringent methods for data collection, guided by the WHO-STEPs protocol [17].

In conclusion, in rural Southern India, those who are overweight as defined by both central and general indices of adiposity are at considerably greater risk of hypertension than those defined as overweight by only a central or general index. This provides impetus for simultaneous deployment of measures of both central adiposity and general adiposity to improve management of those at risk of hypertension-related cardiovascular disease in these populations.

Ethics approval

This project was approved by the ethics committees at each of the study sites, Monash University, and the Indian Council of Medical Research.

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CRediT authorship contribution statement

Amanda G Thrift, Brian Oldenburg, Clara K Chow, Rohina Joshi, Nihal Thomas, Kavumpurathu R Thankappan, Pallab K Maulik, Velandai K Srikanth, Ajay Mahal and Roger G Evans: Conceptualization, Methodology, Funding acquisition. **Matthew Kaye, Rathina Srinivasa Ragavan, Jordan Ismail and Simin Arabshahi:** Data curation and cleaning. **Kamakshi Kartik, Kartik Kalyanram, Oduru Suresh, and Gomathyamma K Mini:** Resources, data curation. **Matthew Kaye and Michaela Riddell**: Data interpretation. **Amanda Thrift, Rathina Srinivasa Ragavan, Jordan Ismail and Roger Evans:** Methodology, Planning data analyses. **Rathina Srinivasa Ragavan and Jordan Ismail:** Formal analysis. **Rathina Srinivasa Ragavan:** Writing – Original draft preparation. **Rathina Srinivasa Ragavan, Amanda Thrift and Roger Evans:** Writing – Reviewing and editing. All authors approved the final manuscript before submission.

Declaration of Competing Interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no support from any organization for the submitted work (apart from funding as outlined above). CKC, AGT, and RGE also report grants from the National Health & Medical Research Council (NHMRC; Australia) outside the submitted work; CKC, AGT, and RGE also report grants from the National Heart Foundation of Australia outside the submitted work. RKG reports research grants from the European Commission and the Polish Ministry of Science and Higher Education, outside the submitted work. RKG reports being a shareholder of Ajanta Pharma Limited, Divi's Laboratories Limited, and NATCO Pharma Limited. There are no other relationships or activities that could appear to have influenced the submitted work.

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Consent to participate

Informed consent was obtained from all individual participants included in the study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.orcp.2023.04.005.

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