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Obesity Comorbidity

Body mass index, abdominal adiposity, weight gain and risk of developing hypertension: a systematic review and dose–response meta-analysis of more than 2.3 million participants

A. Jayedi[1], A. Rashidy-Pour[2], M. Khorshidi[3] and S. Shab-Bidar[3]

[1]Food (salt) Safety Research Center, Semnan University of Medical Sciences, Semnan, Iran, [2]Laboratory of Learning and Memory, Research Center and Department of Physiology, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran, and [3]Department of Community Nutrition, School of Nutritional Science and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

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Address for correspondence: S Shab-bidar, Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, PO Box 14155/6117, Tehran, Iran.
E-mail: s_shabbidar@tums.ac.ir

Summary

Objective: This study aimed to test the association between anthropometric measures and risk of developing hypertension.

Methods: We did a systematic search using PubMed and Scopus, from inception up to January 2017. Prospective cohort studies reporting the risk estimates of hypertension for three or more quantitative categories of indices of general and abdominal adiposity were included. Summary relative risks were calculated using random-effects models.

Results: Fifty-seven prospective cohort studies were included. Summary relative risks were 1.49 (95% confidence interval [CI]: 1.41, 1.58; I^2 = 97.4%, n = 50) for a five-unit increment in body mass index, 1.27 (95%CI: 1.15, 1.39; I^2 = 95.0%, n = 14) for a 10-cm increment in waist circumference, 1.16 (95%CI: 1.09, 1.23; I^2 = 77.8%, n = 5) for weight gain equal to a one-unit increment in BMI, and 1.37 (95%CI: 1.24, 1.51; I^2 = 76.4%, n = 8) and 1.74 (95%CI: 1.35, 2.13; I^2 = 58.9%, n = 4) for a 0.1-unit increment in waist-to-hip ratio and waist-to-height ratio, respectively. The risk of hypertension increased continuously with increasing all anthropometric measures, and also along with weight gain.

Conclusion: Being as lean as possible within the normal body mass index range may be the best suggestion in relation to primary prevention of hypertension.

Keywords: Abdominal obesity, body mass index, hypertension, meta-analysis.

Abbreviations: BMI, body mass index; HTN, hypertension; NCDs, noncommunicable disease; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

Introduction

The prevalence of noncommunicable diseases (NCDs) has been spread alarmingly around the world, in both sexes and among all age subgroups (1). It has been estimated that as the leading cause of death, NCDs resulted in 38 million (68%) of the world's deaths in 2012, of which more than 40% were premature deaths under age 70 years (2). Hypertension (HTN), as one of the most important risk factors of NCDs (3) is highly prevalent in the world, and it has been estimated that the number of people with HTN will increase from 972 million at year 2000 up to more than 1.56 billion by the year 2025, especially in low-income and middle-income countries (4).

Obesity, which is generally determined by body mass index (BMI), is one the leading risk factors for HTN (5,6), and the prevalence of HTN increases with increasing BMI (7) even among low-income populations (8). However, BMI, as the most frequent anthropometric measure, does not reflect the body fat distribution, and there is some doubt

concerning it as the convenient indicator of obesity and also concerning its ability to predict the accurate risk of chronic diseases (9–11). Some evidence has indicated that indices of central adiposity including waist-to-height ratio (WHtR), waist-to-hip ratio (WHR) and waist circumference (WC) may have better predictive value in relation to the risk of HTN (12–15), although results are inconsistent (16). There is no consensus as to what anthropometric indices better predict the risk of HTN.

Additionally, uncertainty remains over the degree of the associations between different anthropometric measures and risk of HTN and about the shape of the potential non-linear dose–response relations. Previous investigations have suggested different shapes from the association between BMI and clinical outcomes (17,18), but regarding HTN, we have no such summarized evidence. It is not clearly determined whether, like the other health outcomes including all-cause mortality (19), underweight increases the risk of HTN. In addition, sex differences and geographic differences in this regard have not been properly determined yet.

Given that high blood pressure is one of the most important underlying causes of current major public health concerns including type 2 diabetes (20,21), cardiovascular disease (22–24) and chronic kidney disease (25,26), clarifying the shape of the potential non-linear dose–response relation between different anthropometric measures and risk of HTN would be of major importance in developing more detailed guidelines for primary prevention of HTN and its many unfavourable health outcomes. In addition, the extent to which weight gain increases risk of HTN is still unclear. Therefore, we aimed to conduct a systematic review and dose–response meta-analysis, using prospective cohort studies, to examine the linear and potential non-linear dose–response association between different anthropometric measures and risk of incident HTN, and also between weight gain and risk of incident HTN. To our knowledge, this is the first systematic review and meta-analysis to test the potential non-linear dose–response relations between different anthropometric measures and the risk of incident HTN.

Methods

We used the Meta-analysis of Observational Studies in Epidemiology guidelines for writing up this systematic review and reporting the results (27).

Search strategy

Systematic search was performed using PubMed and Scopus, from inception up to 25 January 2017 using a wide range of relative keywords. Systematic search included combinations of keywords relevant to general and abdominal obesity, blood pressure, HTN and study design (Table S1). The reference lists of all related articles and reviews also were searched. The search was restricted to published English articles.

Eligibility and study selection

Two independent authors (A. J. and M. K.) reviewed titles and abstracts of all studies. Prospective cohort studies were obtained and included in this review if they (1) were conducted in general population aged more than 18 years, (2) had follow-up duration more than 1 year, (3) measured and reported at least one of the anthropometric measures including baseline BMI, WHtR, WHR, WC or weight gain (represented as BMI) during the follow-up period as exposure and in at least three quantitative categories, (4) reported HTN incidence at follow-up as the outcome of interest, (5) reported risk estimates (relative risk [RR] or hazard ratio or odds ratio) and their corresponding 95% confidence interval (CI) of HTN incidence for each category of the aforementioned anthropometric measures, and (6) reported number of cases and participants/person-years in each category of anthropometric measures or reported sufficient information to estimate those numbers. Studies that reported results per unit increment in any of the mentioned anthropometric indices were also included. We excluded (1) retrospective cohorts, cross-sectional and case–control studies; (2) studies with only two categories of exposures; (3) studies that were conducted in children, adolescents and patients; and (4) studies in which the amount of increase in anthropometric measures in continuous/linear form was not exactly specified.

Data extraction and assessment for study quality

Two independent authors (A. J. and M. K.) reviewed full text of selected eligible studies and extracted the following information: first author's name, publication year, study name, country, follow-up duration, mean age and/or age range, number of participants/cases, anthropometric assessment method (measured versus self-reported), diagnosis criteria of HTN, covariates adjusted in multivariate analysis, exposure levels, and reported risk estimates and their 95% confidence interval. If in a given study results were reported as several adjustment models, the model with most covariates adjustment was selected and used. The Newcastle–Ottawa scale was used to assess the quality of included studies, and studies with more than seven stars were considered of high quality (28). Additional information was requested by correspondence. Any discrepancies were resolved through discussion under supervision of a third author (S. S.-B.).

Data synthesis and statistical analysis

The RRs and 95% CIs were considered as the effect size of all studies. Summary RRs and 95% CIs were

calculated for a five-unit increment in BMI, 10-cm increment in WC, 0.1-unit increment in WHR and WHtR and weight gain equal to a one-unit increment in BMI during the follow-up period using random-effects models (29).

The linear dose–response relation was estimated by using generalized least squares trend estimation, according to the methods developed by Greenland and Longnecker (30,31). We used the two-stage generalized least squares trend estimation method, which first estimated study-specific slope lines and then combined with studies in which the slopes were directly reported to obtain an overall average slope (31). Study-specific results were combined using a random-effect model. The median point in each category of BMI, WC, WHR, WHtR and ΔBMI was assigned to the corresponding RR for each study. If medians were not reported, we estimated approximate sex-specific medians by using the midpoint of the lower and upper bounds. If the highest or lowest categories were open ended, we considered it to have the same widths as the closest category (this method was used for all studies with categorical variables). For studies in which the reference category was not the lowest one, we recalculated risk estimates assuming the lowest category as reference (32). If studies reported results separately for men and women or other subgroups, we combined the subgroup-specific estimates using a fixed-effects model to generate an overall estimate so that each study was only represented once in the main analysis, but sex-specific results are presented separately in subgroup analyses.

Potential non-linear association was examined by modelling BMI, WC, WHR, WHtR, and ΔBMI levels using restricted cubic splines with three knots at fixed percentiles (10%, 50% and 90%) of the distribution (33). A *P*-value for non-linearity of the meta-analysis was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero. Subgroup analysis was performed based on some of the study and participant characteristics. To assess whether the results could have been affected distinctly by a single study, influence analysis was carried out with one study removed at a time. If there were several publications from the same study, the publication with the higher number of participants was included. If two different articles reported results of the same study as categorical and continuous separately, the article with the categorical model was selected for inclusion in both linear and non-linear dose–response meta-analyses. Publication bias was assessed using funnel plot asymmetry and tested by Egger's asymmetry test and Begg's test($P < 0.10$) (34). Between-study heterogeneity was explored using Cochrane's Q test of heterogeneity and I^2 statistic ($P < 0.05$), which provide the relative amount of variance of the summary effect due to the between-study heterogeneity (35). All analyses were conducted with STATA software, version 12 (Stata Corp, College Station, Texas). P values <0.05 were considered as significant.

Results

Literature search and study characteristics

As presented in Fig. S1, systematic search identified 51,808 articles, of which 16,870 were duplicates and another 34,221 were considered as non-relevant, which were excluded at initial screening of title and abstract. Of the 717 remaining articles, another 661 articles were excluded by full-text assessment. Detailed reasons for exclusions are presented in Fig. S1. We identified 56 prospective cohort studies (13,36–90), whose characteristics are presented in Table S2. One study reported results for two separate cohort studies and was regarded as two different studies (77). Results from the Aerobics Center Longitudinal Study on BMI, WC and WHR were reported in three different articles (36,69,83) and were separately included in relevant analysis. Another study (Turkish Adult Risk Factor Study) reported results on BMI and WC in two different articles (71,72) and also was separately included in relevant analysis. Two articles reported results from the Korean Genome Epidemiology Study, in which one article reported result on BMI as categorical (62) and another one reported results on BMI, WC, WHR and WHtR as continuous for men and women separately (13), and were included in relevant analysis separately. One large study was conducted among adolescents, (45) in which the age of 97–98% of participants was 18 years, and we decided to include this study. Finally, 57 prospective cohort studies with 2,343,466 participants and 216,182 incident cases of HTN were included in meta-analysis. Twenty studies were from the USA (36,39,46,47,50,52–54,57,61,63,64,69,77,81–84,88,89), 13 studies were from Europe (37,45,49,56,65,71,72,74–77,79,80), 20 studies were from Asia (13,40–44,55,58,59,62,66–68,70,73,78,85–87,90), 2 studies were from Africa (38,51), 1 study was from Mexico (60) and 1 was from Brazil (48). Baseline characteristics of included studies are presented in Table S2, and reported risk estimates in relation to different categories of anthropometric measures in each study are presented in Table S3.

Body mass index

Fifty prospective cohort studies with 2,255,067 participants and 190,320 incident cases of HTN reported results on BMI and risk of developing HTN (13,36–41,43–47,49–61,63–68,70,71,73–84,86,87,89,90). The summary RR for a five-unit increment in BMI was 1.49 (95%CI: 1.41, 1.58), with extreme heterogeneity, I^2 = 97.4%, $P_{\text{heterogeneity}}$ 0.0001 (Fig. 1). Almost all studies reported increased risk,

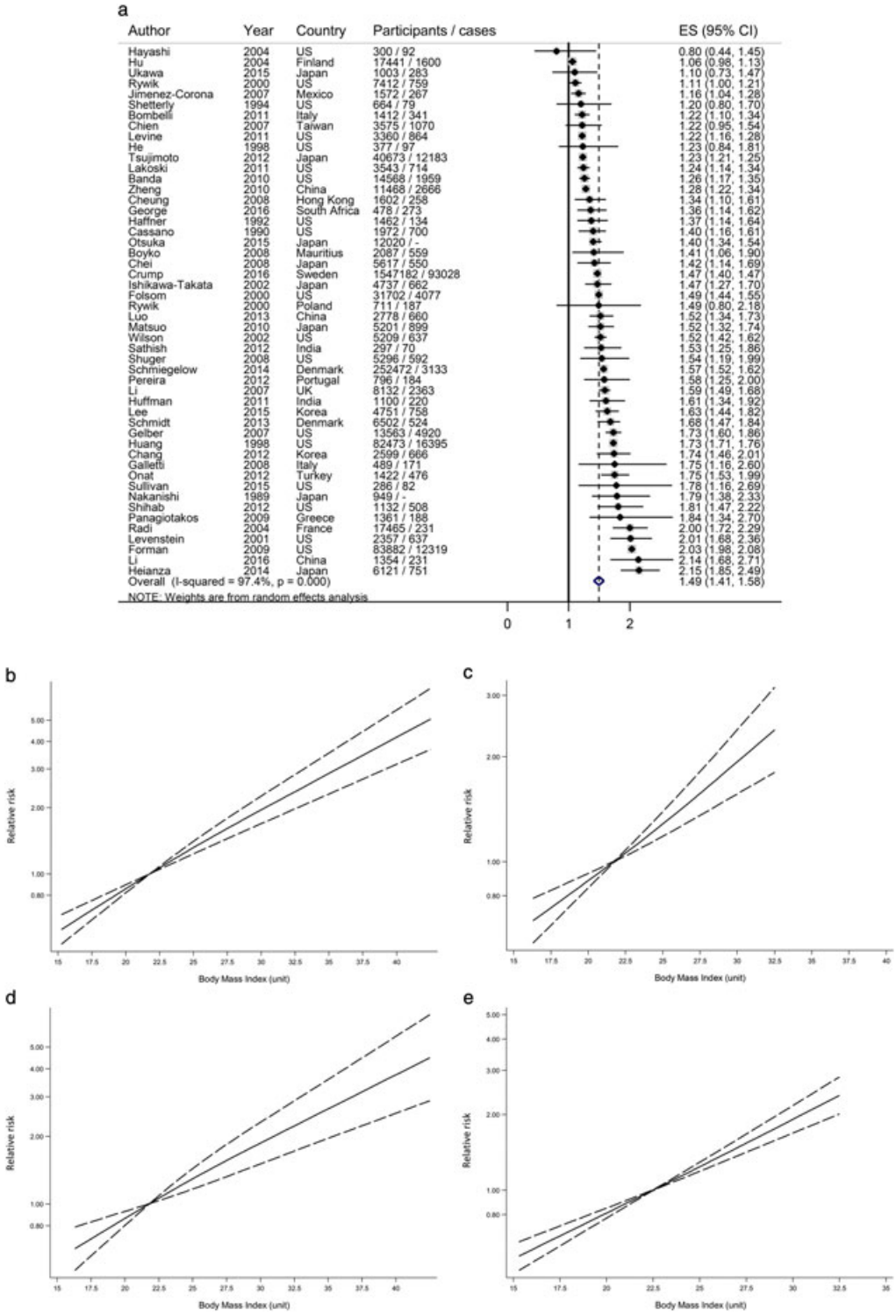

Figure 1 a) Relative risk of hypertension for a five-unit increment in body mass index. Results were combined using the random-effects model. b) Dose–response association between body mass index and risk of hypertension ($P_{\text{non-linearity}}$ = 0.04, n = 24). Solid line: relative risk. Long-dashed line: 95% confidence interval. c) Dose–response association between body mass index and risk of hypertension among men ($P_{\text{non-linearity}}$ = 0.30, n = 14). Solid line: relative risk. Long-dashed line: 95% confidence interval. d) Dose–response association between body mass index and risk of hypertension among women ($P_{\text{non-linearity}}$ = 0.39, n = 14). Solid line: relative risk. Long-dashed line: 95% confidence interval. e) Dose–response association between body mass index and risk of hypertension from studies with hypertension diagnosis criteria as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure-90 mmHg ($P_{\text{non-linearity}}$ = 0.68, n = 13). Solid line: relative risk. Long-dashed line: 95% confidence interval. [Colour figure can be viewed at wileyonlinelibrary.com]

and the results were persistently significant in all subgroups (Table 1).

Influence analysis, subgroup analysis and publication bias

Influence analysis excluding each study at a time altered the summary RR from 1.48 (95%CI: 1.40, 1.57) with the exclusion of the oil worker cohort study (66) to 1.50 (95%CI: 1.42, 1.59) with the exclusion of the Washington general clinical research centre study (53). Sequential exclusion of each study at a time did not reduce the heterogeneity, and the extreme heterogeneity persisted in all subgroups (Table 1). Significant positive association persisted in all subgroups and was stronger among men than among women (1.49, 95%CI: 1.34, 1.65; n = 21 vs 1.40, 95%CI: 1.25, 1.55; n = 15, respectively). Adjustment for baseline blood pressure attenuated the result substantially, but

Table 1 Subgroup analyses of BMI and risk of incident hypertension

		n	RR (95%CI)	I^2 (%)	$P_{heterogeneity}$
All studies		50	1.49 (1.41–1.58)	97.4	<0.0001
Sex					
Men		21	1.49 (1.34–1.65)	97.3	<0.0001
Women		15	1.40 (1.25–1.55)	98.5	<0.0001
Geographic region					
USA		18	1.48 (1.32–1.63)	97.8	<0.0001
Europe		12	1.53 (1.40–1.67)	93.8	<0.0001
Asia		17	1.49 (1.39–1.58)	86.2	<0.0001
Africa		2	1.37 (1.16–1.58)	0.0	0.84
Mexico		1	1.16 (1.04–1.28)	—	—
Follow-up duration					
<10 years		29	1.48 (1.39–1.56)	90.9	<0.0001
≥10 years		21	1.49 (1.37–1.62)	97.9	<0.0001
Assessment of weight/height					
Measured		42	1.44 (1.38–1.51)	89.6	<0.0001
Self-reported		6	1.66 (1.41–1.91)	99.0	<0.0001
Number of cases					
<500		19	1.46 (1.32–1.60)	75.1	<0.0001
500–1,000		17	1.52 (1.41–1.64)	88.1	<0.0001
≥1,000		12	1.48 (1.31–1.64)	99.3	<0.0001
Effect estimate					
OR		18	1.50 (1.33–1.67)	84.8	<0.0001
HR		19	1.50 (1.36–1.64)	98.3	<0.0001
RR		13	1.49 (1.38–1.61)	95.7	<0.0001
Criteria for HTN diagnosis (SBP/DBP)					
≥140/90		33	1.42 (1.35–1.49)	99.0	<0.0001
≥160/95		6	1.55 (1.30–1.81)	75.6	<0.0001
Self-reported		6	1.67 (1.45–1.88)	98.4	<0.0001
Population age					
<50 years		10	1.59 (1.40–1.78)	86.1	<0.0001
≥50 years		4	1.58 (1.34–1.82)	97.4	<0.0001
Study quality					
0–3 stars		—	—	—	—
4–6 stars		6	1.50 (1.42–1.59)	96.5	<0.0001
7–9 stars		44	1.45 (1.36–1.55)	98.0	<0.0001
Exclusion of participants with history of CVD	Yes	15	1.56 (1.40–1.71)	98.0	<0.0001
	No	35	1.45 (1.37–1.52)	92.4	<0.0001
Adjustment for confounders					
Baseline blood pressure	Yes	21	1.26 (1.21–1.31)	68.4	<0.0001
	No	29	1.63 (1.54–1.72)	94.8	0.0001
Physical activity	Yes	18	1.55 (1.35–1.75)	97.8	<0.0001
	No	32	1.47 (1.37–1.56)	97.2	<0.0001
Smoking	Yes	32	1.51 (1.39–1.63)	98.3	<0.0001
	No	18	1.46 (1.39–1.54)	78.9	<0.0001
Alcohol consumption	Yes	28	1.47 (1.33–1.60)	98.5	<0.0001
	No	22	1.51 (1.44–1.57)	79.1	<0.0001
Family history of HTN	Yes	14	1.42 (1.32–1.52)	90.5	<0.0001
	No	36	1.51 (1.40–1.62)	98.0	<0.0001

CVD, cardiovascular disease; DBP, diastolic blood pressure; HR, hazard ratio; HTN, hypertension; OR, odds ratio; RR, relative risk; SBP, systolic blood pressure.

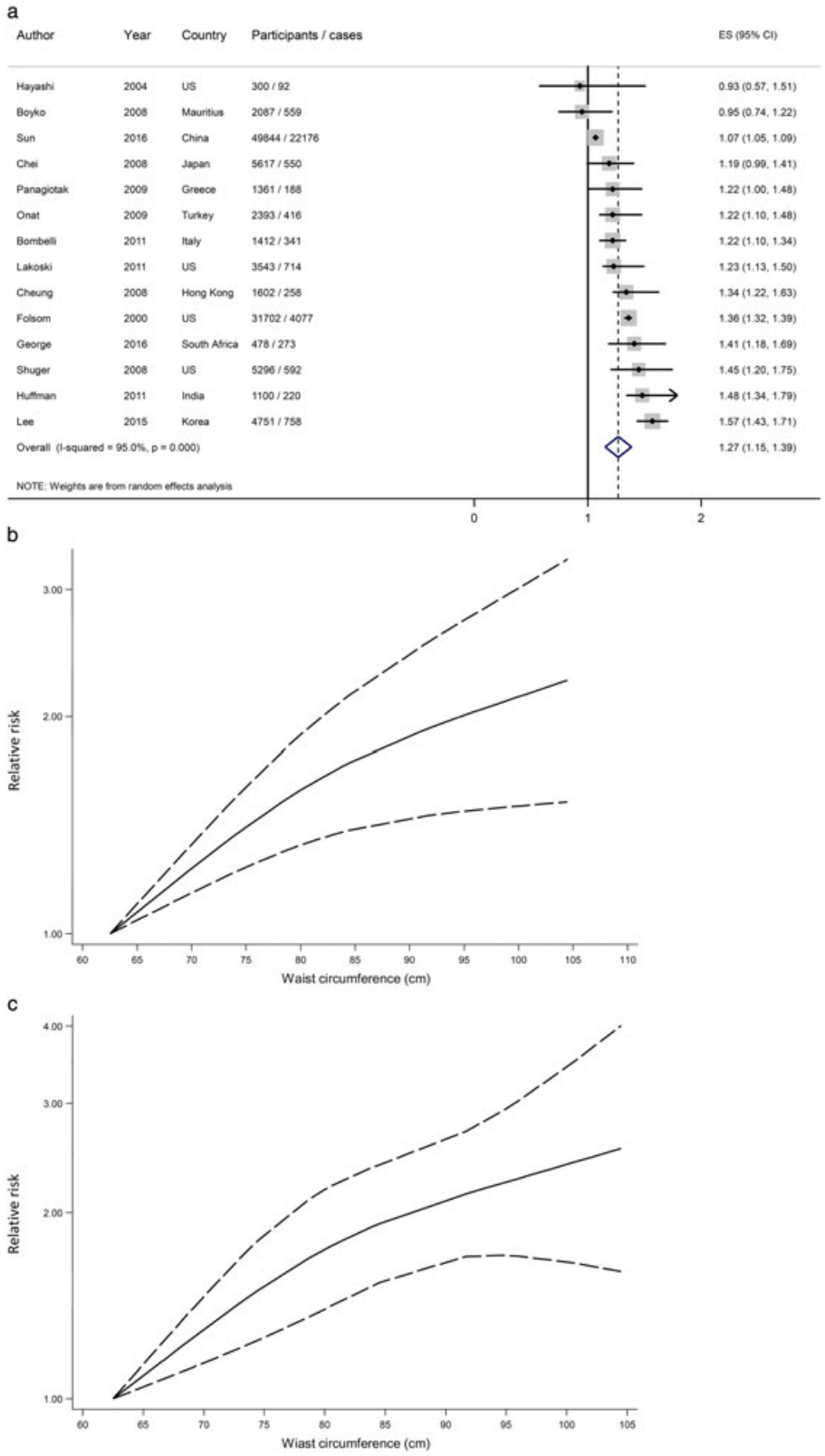

Figure 2 a) Relative risk of hypertension for a 10-cm increment in waist circumference. Results were combined using the random-effects model. b) Dose–response association between waist circumference and risk of hypertension ($P_{\text{non-linearity}} < 0.0001$, $n = 4$). Solid line: relative risk. Long-dashed line: 95% confidence interval. c) Dose–response association between waist circumference and risk of hypertension among women ($P_{\text{non-linearity}} < 0.0001$, $n = 4$). Solid line: relative risk. Long-dashed line: 95% confidence interval. [Colour figure can be viewed at wileyonlinelibrary.com]

summary RR still remained significant (summary RR: 1.26; 95%CI: 1.21, 1.31). Detailed results for subgroup analyses are provided in Table 1. Egger's asymmetry test (P = 0.58) and Begg's test (P = 0.55) did not show sign of publication bias, but the funnel plot seemed to be asymmetric (Fig. S2).

Systematic search identified 24 prospective cohort studies with sufficient information for inclusion in non-linear dose–response meta-analysis (36,40,41,46,47,50,56,57,59,62,66–68,75,76,78–80,82,83,86,87,89,90), and the result suggested a significant dose-dependent association between BMI and risk of HTN ($P_{\text{non-linearity}}$ = 0.04), in which the risk increased continuously with increasing BMI from a baseline of 15 kg m^{-2} up to more than 40 kg m^{-2}, even within the normal BMI range (Fig. 2). The results were the same with the main analysis among men ($P_{\text{non-linearity}}$ = 0.30, n = 14; Figure 1c) and women ($P_{\text{non-linearity}}$ = 0.39, n = 14; Fig. 1d), and also in different geographic regions (Figs S3–S5). Thirteen studies used systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg as HTN diagnosis criteria (50,59,62,66–68,75,76,78,86,87,89,90), and meta-analysis showed a steeper increase in the risk in comparison with the main analysis ($P_{\text{non-linearity}}$ = 0.68, Fig. 1e).

Waist circumference

Fourteen prospective cohort studies with 111,370 participants and 31,214 incident cases of HTN were included in the analysis of WC and risk of incident HTN (13,37,38,41,43,46,51,53,58,61,72,74,83,85). Summary RR for a 10-cm increment in WC was 1.27 (95%CI:

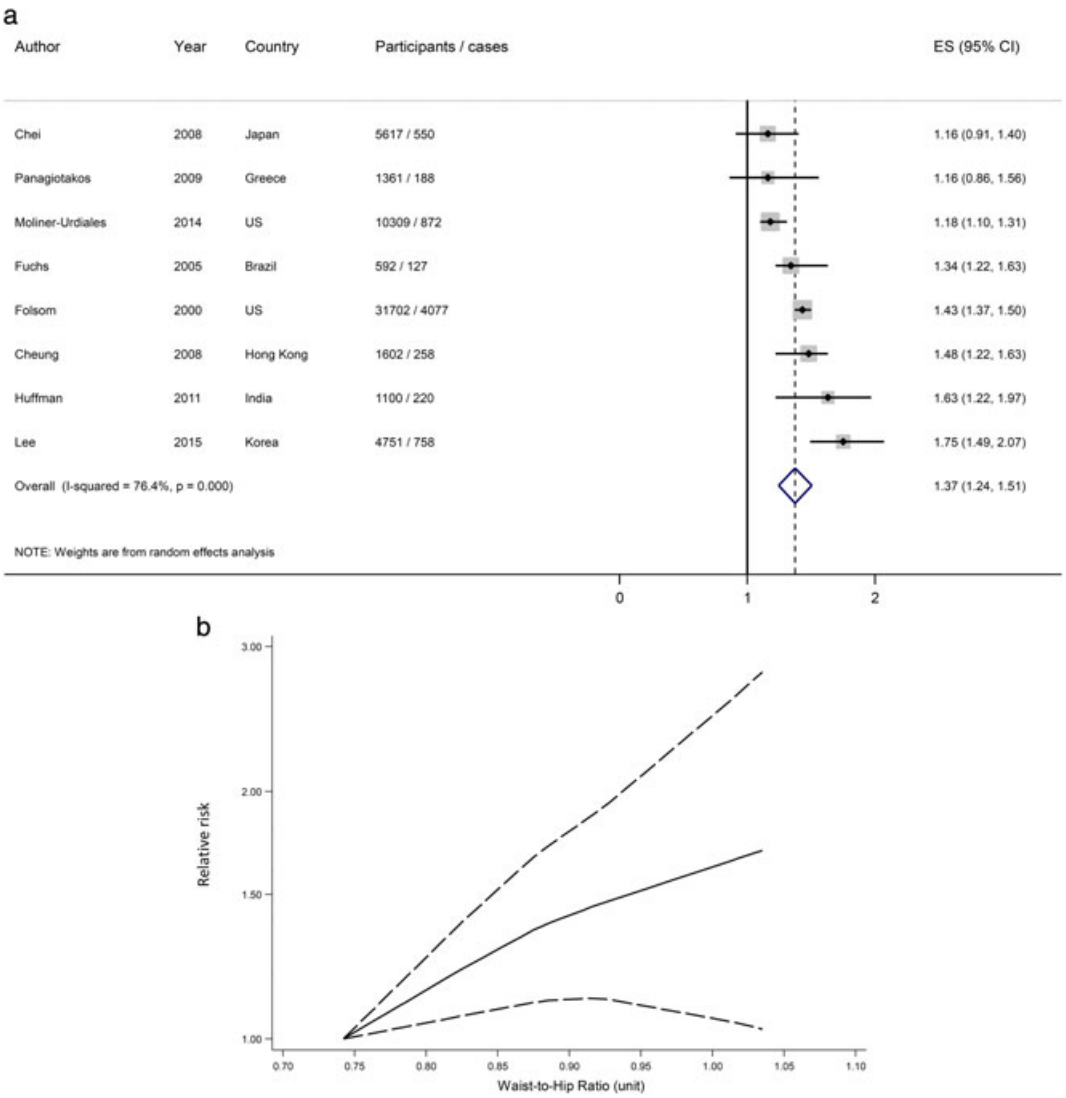

Figure 3 a) Relative risk of hypertension for a 0.1-unit increment in waist-to-hip ratio. Results were combined using the random-effects model. b) Dose–response association between waist-to-hip ratio and risk of hypertension ($P_{\text{non-linearity}}$ = 0.45). Solid line: relative risk. Long-dashed line: 95% confidence interval. [Colour figure can be viewed at wileyonlinelibrary.com]

1.15, 1.39), with extreme heterogeneity, I^2 = 95.0%, $P < 0.0001$ (Fig. 3).

Influence analysis, subgroup analysis and publication bias

The association was significant only among women (summary RR: 1.33, 95%CI: 1.19, 1.48; I^2 = 92.0%, n = 6) compared with men (summary RR: 1.30, 95%CI: 0.90, 1.71; I^2 = 93.1%, n = 3). Influence analysis removing each study at a time changed the summary RR from 1.24 (95%CI: 1.13, 1.36) with the exclusion of the Korean Genome Epidemiology Study (13) to 1.30 (95%CI: 1.22, 1.38) with the exclusion of the Kailuan Study (85). The heterogeneity did not disappear when each study was sequentially excluded from the pooled analyses. A significant positive relationship persisted in all subgroups, but not among men and African studies. Subgroup analyses suggested region, number of cases and adjustment for main confounders as the potential sources of the heterogeneity (Table S4). There was no evidence of publication bias with Egger's asymmetry test (P = 0.27) or Begg's test (P = 0.10), but the funnel plot seemed to be asymmetric (Fig. S6).

Four studies were eligible for inclusion in non-linear dose–response meta-analysis (41,46,83,85), and the results showed that there was a non-linear association between waist circumference and risk of HTN ($P_{\text{non-linearity}}$ 0.0001, Fig. 2b), with a steeper increase in risk at lower levels of waist circumference. Analysis of women yielded a relatively similar result with the main analysis ($P_{\text{non-linearity}} <$ 0.0001, n = 4; Fig. 2c).

Waist-to-hip ratio

Eight studies involving 57,007 participants and 7,050 incident cases of HTN were identified on the association between WHR and the risk of HTN (13,41,43,46,48,58,69,74). The results showed that a 0.1-unit increment in WHR was associated with 37% higher risk of HTN (summary RR: 1.37, 95%CI: 1.24, 1.51), with high heterogeneity, I^2 = 76.4%, $P_{\text{heterogeneity}} < 0.0001$ (Fig. 4).

Sensitivity analysis, subgroup analysis and publication bias

Summary RR for a 0.1-unit increment in WHR was 1.35 (95%CI: 1.03, 1.65; I^2 = 84.6%, $P_{\text{heterogeneity}}$ = 0.002; n = 3) among men and 1.31 (95%CI: 1.13, 1.48; I^2 = 77.4%, $P_{\text{heterogeneity}}$ = 0.04; n = 4) among women. Summary RR altered from 1.33 (95%CI: 1.21, 1.46) with the exclusion of the Korean Genome Epidemiology Study (13) to 1.41 (95%CI: 1.29, 1.54) with the exclusion of the Aerobics Center Longitudinal Study (69). Sequential exclusion of each study at a time did not make the heterogeneity disappear. Subgroup analyses resulted in significant association across most of the subgroups and yielded history of cardiovascular disease, number of cases and adjustment of main confounders as the potential sources of the heterogeneity (Table S5). Egger's asymmetry test (P = 0.84) and Begg's test (P = 1.00) did not show any evidence of publication bias, but funnel plot showed some evidence of asymmetry (Fig. S7). There was no evidence of a non-linear association between WHR and risk of HTN ($P_{\text{non-linearity}}$ = 0.45, Fig. 3b).

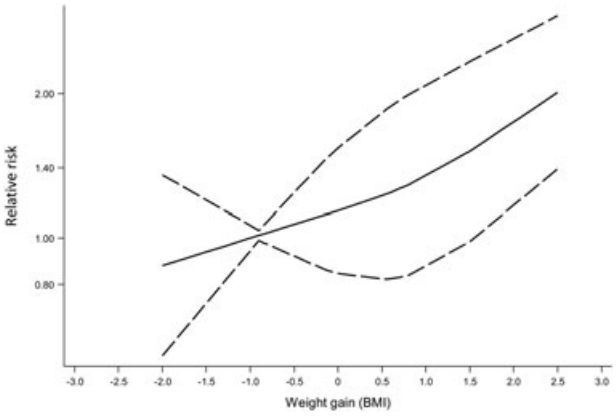

Figure 4 Dose–response association between weight gain (represented by body mass index [BMI]) and risk of hypertension ($P_{\text{non-linearity}}$ = 0.58, n = 5). Solid line: relative risk. Long-dashed line: 95% confidence interval.

Waist-to-height ratio

Four studies with 18,910 participants and 1,769 incident cases of HTN were included in the analysis of WHtR and the risk of HTN (13,41,51,74). Summary RR for a 0.1-unit increment in WHtR was 1.74 (95%CI: 1.35, 2.13), with moderate-to-high evidence of heterogeneity, I^2 = 58.9%, $P_{\text{heterogeneity}}$ = 0.06 (Fig. S8).

Sensitivity and subgroup analysis

Summary RR ranged from 1.56 (95%CI: 1.23, 1.89; I^2 = 2.2%, $P_{\text{heterogeneity}}$ = 0.36) with the exclusion of the Korean Genome Epidemiology Study (13) to 1.88 (95%CI: 1.51, 2.25; I^2 = 42.7%, $P_{\text{heterogeneity}}$ = 0.17) with the exclusion of the Osaka and Ibaraki Prefecture cohort study (41). Summary RR was 1.99 (95%CI: 0.93, 3.35; I^2 = 89.3%, $P_{\text{heterogeneity}}$ = 0.002; n = 2) among men and 1.68 (95%CI: 1.26, 2.09; I^2 = 69.2%, $P_{\text{heterogeneity}}$ = 0.04; n = 3) among women. Only one study reported sufficient information (41), so we could not test the potential non-linear dose–response relation. Publication bias tests were not performed ($n < 10$).

Weight gain

Five prospective cohort studies with 134,247 participants and 4,984 incident cases of HTN reported sufficient information on the association between weight gain during the follow-up period and subsequent risk of HTN (42,77,80,88). Summary RR of HTN for weight gain equal to one-unit increment in BMI was 1.16 (95%CI: 1.09, 1.23), with high heterogeneity, I^2 = 77.8%, $P_{\text{heterogeneity}}$ = 0.001 (Fig. S9). Influence analysis removing each study at a time altered the association from 1.14 (95%CI: 1.07, 1.21) with the exclusion of National Runners' Health Study (88) to 1.19 (95%CI: 1.14, 1.23) with the exclusion of the Atherosclerosis Risk in Communities Study (77), and the later study explained much of the heterogeneity (I^2 = 14.5%, $P_{\text{heterogeneity}}$ = 0.32). Weight gain was associated with worse prognosis among men (summary RRs: 1.20, 95%CI: 1.05, 1.36; I^2 = 87.5%, n = 3) than among women (summary RRs: 1.13, 95%CI: 1.04, 1.22; I^2 = 82.2%, n = 4). There was a linear association between weight gain and risk of HTN ($P_{\text{non-linearity}}$ = 0.58, Fig. 4).

Discussion

Principal findings

The present study is the first document that systematically evaluated the linear and non-linear dose–response relations between indices of general and abdominal adiposity and the risk of developing HTN. Linear dose–response meta-analysis indicated that the risk of HTN increased by 49% per a five-unit increment in BMI, by 27% per 10-cm increment in waist circumference and by 37% and 74% per 0.1-unit increment in waist-to-hip ratio and waist-to-height ratio, respectively. In addition, weight gain equal to a one-unit increment in BMI was associated with 16% higher risk of HTN, with worse prognosis among men. Subgroup analysis by sex resulted in a stronger positive relationship among men in analyses of BMI and WHR, but in analyses of waist circumference and WHtR, a significant positive relationship was found only among women. Adjustment for baseline blood pressure attenuated the associations in analysis of all measures of adiposity, but summary results still remained significant, which indicated that all measures of adiposity increases risk of HTN independent of baseline blood pressure.

When results were stratified based on an anthropometric assessment method, a greater risk was observed in self-reported subgroup compared with measured. Generally, self-reported assessment of anthropometric measures tends to underestimate the BMI (91), which may result in a weaker effect size. However, only six studies used self-reported BMI (46,47,50,56,57,63), of which four studies were large-scale prospective cohorts in the US, making it possible to obtain stronger effect size. Additionally, the number of studies with the self-reported method was substantially lower than the measured method (6 vs 42); thus, it may be hard to compare the effect sizes conveniently across anthropometric assessment methods.

Non-linear dose–response meta-analysis found a significant dose-dependent relation between BMI and the risk of HTN, such that the risk increased continuously with increasing BMI, even within the normal BMI range. The results were the same with overall analysis in analysis of men and women, although concerning BMI levels above ~32 kg m^{-2} among men, we have no data to include and future investigations may be needed to examine the risk of HTN for a BMI >32 kg m^{-2} among men. We also could test the non-linear relation in different geographic regions, which yielded nearly the same results. Results of the non-linear dose–response meta-analysis across all subgroups clearly indicated that lean people experience lower risk of HTN, but owing to the greater rate of mortality in the underweight populations in comparison with the normal-weight ones (18,92), these results should be interpreted with caution. The better description for our findings may be that having a weight within the healthy weight range and towards the lower end of the normal-weight range may be the best suggestion in relation to primary prevention of HTN. A significant curve linear association was observed in analysis of waist circumference, but the association seemed to be linear in analysis of waist-to-hip ratio and weight gain.

Dose–response meta-analysis suggested that the risk of HTN increased with a somewhat steeper trend with increasing BMI, in comparison with waist circumference and waist-to-hip ratio. However, the number of studies and participants/cases was very low in analyses of waist circumference and waist-to-hip ratio in comparison with BMI, making it hard to compare the dose–response relations across adiposity measures. In addition, the highest value of waist circumference (105 cm) was not far from the lower limit of severe abdominal obesity in men (102 cm). This is partially because, of the four included studies, two studies included only women (46,83) and another two studies included both sexes (41,85); thus, concerning waist circumference levels of more than 105 cm, we have no data to include. Additionally, analysis of women resulted in a relatively similar result with the main analysis; thus, the shape of the dose–response association between the waist circumference and risk of HTN may represent more the association among women than among general population, and as a result, generalization of the results to the whole population should be made with caution.

In comparison with other studies, no systematic review has assessed the linear and non-linear dose–response relations between anthropometric measures and the risk of HTN. Seo *et al.* (93), using data from 19 cohort studies,

indicated that both BMI > 30 kg m^{-2} and waist circumference > 102/88 cm are strongly associated with higher risk of HTN. Another meta-analysis of 19 prospective and cross-sectional studies assessed the discriminatory power of general and abdominal anthropometric indices in distinguishing adults with HTN and indicated that higher BMI, WC and WHtR are associated with higher risk of HTN, with the best discriminatory power for WHtR (12). Our results are in line with these findings and indicated that the risk of HTN increased with increasing all indices of general and abdominal adiposity.

Subgroup analysis resulted in a greater effects size in subgroup of studies with the exclusion of participants with a history of cardiovascular disease at baseline, in analyses of BMI and waist circumference. This may partially be due to the higher presence of comorbidities in studies without exclusion of cardiovascular patients at baseline, which in turn might misleadingly hide the harmful effects of adiposity. Much interestingly, subgroup analysis resulted in a non-significant association among men in analyses of waist circumference (n = 3) and WHtR (n = 2). The lack of significant association among men can mainly be attributed to the results of the Osaka and Ibaraki prefecture cohort study in Japan (41), in which the results may have been limited by the low number of participants/cases and weak statistical power. However, the number of included studies was very low to obtain a definitive conclusion in this regard.

Mechanisms

Adiposity, as a chronic condition, has been identified as a well-known risk factor for development of HTN. Higher body fat mass, in both children and adults, is associated with low-grade inflammatory status and insulin resistance (94,95), which in turn are highly associated with the risk of HTN (96). Activation of the sympathetic nervous system is another consequence of adiposity (97), which plays a key role in the development of HTN (98).

Strength and limitations

The present study has several strengths. This is the first study that systematically assessed the linear and non-linear dose–response relation between baseline anthropometric measures and the future risk of incident HTN. We included a high number of studies, especially in the analysis of BMI, with more than 2.2 million participants and around a 190,000 incident cases of HTN, which enabled us to test the non-linear relation across sex and geographic region subgroups with an acceptable statistical power. We could find a strong positive relation for all anthropometric measures even after adjustment for main confounding variables. We could conduct several subgroup analyses on the basis of some of the study and participant characteristics. We only included prospective cohort studies to reduce the potential confounding effects of selection bias, recall bias and reverse causation bias. We also could appropriately show how weight gain would increase risk of HTN.

We also were faced with some limitations, which should be noted when interpreting the results. Our main limitation was the low number of studies in the analysis of WHtR, which limited us to test the potential non-linear dose–response relation and publication bias and to conduct subgroup analysis. We also had few studies to test the non-linear relation for WC and WHR. Therefore, the number of included studies varies substantially across adiposity measures and it may be hard to compare the effect size of adiposity on HTN across adiposity measures. Second, the results were accompanied with extreme heterogeneity in analyses of BMI and WC and high heterogeneity in analyses of WHR and weight gain. In analysis of BMI, extreme heterogeneity persisted in all subgroups, and the interpretation of the results was limited by heterogeneity. However, almost all included studies reported significant positive association; therefore, the observed heterogeneity may possibly be due to the difference in effect size of included studies, and not because of the lack or presence of an association, such that all but one study reported risk estimates above 1 in analysis of BMI. However, the observed heterogeneity, at least in part, may be due to different adjustment models, different cut-offs to categorize anthropometric measures, geographic disparities and different definitions of HTN in different studies. In analysis of waist circumference, the extreme heterogeneity was reduced among US and European studies, and subgroup analyses suggested region, number of cases and adjustment for main confounders as the potential sources of heterogeneity. Third, only one study adjusted results for salt intake, and none of them took renal function into account. Thus, without considering these confounding variables, we may have a biased conclusion. Fourth, funnel plots appeared to be asymmetric in analyses of BMI, WC and WHtR. Thus, the magnitude of the associations may have been affected by publication bias, which in turn might result in overestimating the risk. Fifth, all included studies reported and used baseline anthropometry to examine the associations, and only two studies performed additional analysis using BMI as a time-dependent variable (68,82), which yielded nearly the same results with the main analysis. Thus, we could not conveniently examine the potential effects of the changes in BMI over the follow-up period on the results. The results showed that the risk of HTN increases along with weight gain; thus, future investigations may be needed to address the association between anthropometric measures and risk of HTN considering the potential changes in body size over the follow-up. Finally, only two studies were from Africa. Therefore, the generalization of the results to Africans should be made with caution.

Conclusion

The present study conferred strong evidence regarding the association between greater mass and future risk of HTN and indicated that the future risk of HTN increased continuously with increasing all indices of general and abdominal adiposity and also along with weight gain. Being as lean as possible within the normal-weight range may be a good suggestion in relation to primary prevention of HTN. It may be helpful to test the relations with considering potential changes over the follow-up period to better clarify the associations.

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No separate funding was necessary for undertaking this systematic review.

Conflict of interests

No conflict of interest was declared.

Author contributions

S. S.-B. and A. R. P. conceived and designed the study. A. J. and M. .K conducted systematic search, screened articles, selected eligible articles and extracted information from eligible studies. A. J., S. S. –B. and A. R. P. performed analysis and interpreted results. All authors contributed to writing, reviewing or revising the paper. S. S.-B. is the guarantor. All authors have read and approved the final manuscript. All authors had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article. https://doi.org/10.1111/obr.12656

Table S1. Search strategy to find the relevant articles for inclusion in meta-analysis of general and abdominal adiposity and risk of hypertension.
Table S2. Baseline characteristics of included studies in meta-analysis of general and abdominal adiposity and risk of hypertension.
Table S3. Reported risk estimates of hypertension in included studies in meta-analysis of general and abdominal adiposity and risk of hypertension.
Table S4. Subgroup analyses of waist circumference and risk of incident hypertension.
Table S5. Subgroup analyses of waist-to-hip ratio and risk of incident hypertension.

Figure S1. Literature search and study selection process for inclusion in meta-analysis of anthropometric measures and risk of developing hypertension.
Figure S2. Funnel plot of the relative risks of 50 studies on body mass index and risk of hypertension. Begg's test $P = 0.55$, Egger's test $P = 0.58$. Log RR: natural logarithm of relative risk. SE: standard error.
Figure S3. Dose–response association between body mass index and risk of hypertension in US ($P_{\text{non-linearity}} = 0.47$, $n = 8$).
Figure S4. Dose–response association between body mass index and risk of hypertension in Europe ($P_{\text{non-linearity}} = 0.15$, $n = 5$).
Figure S5. Dose–response association between body mass index and risk of hypertension in Asia ($P_{\text{non-linearity}} = 0.35$, $n = 11$).
Figure S6. Funnel plot of the relative risks of 14 studies on waist circumference and risk of hypertension. Begg's test $P = 0.10$, Egger's test $P = 0.27$. Log RR: natural logarithm of relative risk. SE: standard error.
Figure S7. Funnel plot of the relative risks of eight studies on waist-to-hip ratio and risk of hypertension. Begg's test $P = 1.00$, Egger's test $P = 0.84$. Log RR: natural logarithm of relative risk. SE: standard error.
Figure S8. Relative risk of hypertension for a 0.1-unit increment in waist-to-height ratio. Results were combined using random-effects model.
Figure S9. Relative risk of hypertension for weight gain equal to one-unit increment in BMI. Results were combined using random-effects model.

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