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ORIGINAL ARTICLE

Ambulatory blood pressure monitoring for risk stratification in obese and non-obese subjects from 10 populations

TW Hansen[1], L Thijs[2], Y Li[3,4], J Boggia[5], Y Liu[2], K Asayama[2,6], M Kikuya[6], K Björklund-Bodegård[7], T Ohkubo[8], J Jeppesen[9], C Torp-Pedersen[9], E Dolan[10], T Kuznetsova[2], K Stolarz-Skrzypek[11], V Tikhonoff[12], S Malyutina[13], E Casiglia[12], Y Nikitin[13], L Lind[7], E Sandoya[14], K Kawecka-Jaszcz[11], J Filipovský[15], Y Imai[6], J Wang[3], E O'Brien[16] and JA Staessen[2,17] on behalf of the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) Investigators[18]

Overweight clusters with high blood pressure (BP), but the independent contribution of both risk factors remains insufficiently documented. In a prospective population study involving 8467 participants (mean age 54.6 years; 47.0% women) randomly recruited from 10 populations, we studied the contribution of body mass index (BMI) to risk over and beyond BP, taking advantage of the superiority of ambulatory over conventional BP. Over 10.6 years (median), 1271 participants (15.0%) died and 1092 (12.9%), 637 (7.5%) and 443 (5.2%) experienced a fatal or nonfatal cardiovascular, cardiac or cerebrovascular event. Adjusted for sex and age, low BMI ($<20.7\,kg\,m^{-2}$) predicted death (hazard ratio (HR) vs average risk, 1.52; $P<0.0001$) and high BMI ($\geqslant 30.9\,kg\,m^{-2}$) predicted the cardiovascular end point (HR, 1.27; $P=0.006$). With adjustments including 24-h systolic BP, these HRs were 1.50 ($P<0.001$) and 0.98 ($P=0.91$), respectively. Across quartiles of the BMI distribution, 24-h and nighttime systolic BP predicted every end point ($1.13\leqslant$standardized HR $\leqslant 1.67$; $0.046\leqslant P<0.0001$). The interaction between systolic BP and BMI was nonsignificant ($P\geqslant 0.22$). Excluding smokers removed the contribution of BMI categories to the prediction of mortality. In conclusion, BMI only adds to BP in risk stratification for mortality but not for cardiovascular outcomes. Smoking probably explains the association between increased mortality and low BMI.

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INTRODUCTION

Obesity clusters with hypertension and other risk factors. Over the past few years, six mega-analyses established a J- or U-shaped relation between adverse health outcomes and body mass index (BMI).[1–6] Risk increased with both underweight and obesity.[1–6] Only one of these mega-analyses[4] included both fatal and nonfatal outcomes and considered blood pressure (BP) in the assessment of the association of cardiovascular risk with obesity. Other studies[7–12] led clinicians to believe that BP and BMI potentiate one another as predictors of cardiovascular complications. However, the interaction substantiating this hypothesis[7–14] was modeled using a linear term of BMI, which in light of the new evidence[1–6] showing a curvilinear relation between outcome and BMI is inappropriate. The Emerging Risk Factors Collaboration[4] recently demonstrated that adjustment for BP weakened the associations between cardiovascular complications and BMI. The contribution of BMI to risk over and beyond BP therefore remains insufficiently documented. None of the aforementioned studies[1–14] took advantage of the superiority of ambulatory BP measurement over conventional BP readings in the assessment of cardiovascular risk.[15] To address this gap in current knowledge, we analyzed the International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome (IDACO).[16] We studied the independent contributions of BMI and the conventional and ambulatory BP to the prediction of both fatal and nonfatal outcomes in 8467 participants randomly recruited from 10 populations.

SUBJECTS AND METHODS

Study population

At the time of writing this report, the IDACO database[16] included 12 randomly recruited population cohorts[17–26] and 12 821 participants, but information on height and weight was available in only 10 studies,

[1]Steno Diabetes Centre, Gentofte and Research Centre for Prevention and Health, Glostrup, Denmark; [2]Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium; [3]Center for Epidemiological Studies and Clinical Trials, Ruijin Hospital, Shanghai Jiantong University School of Medicine, Shanghai, China; [4]Center for Vascular Evaluation, Ruijin Hospital, Shanghai Jiantong University School of Medicine, Shanghai, China; [5]Centro de Nefrología and Departamento de Fisiopatología, Hospital de Clínicas, Universidad de la República, Montevideo, Uruguay; [6]Tohoku University Graduate School of Pharmaceutical Science and Medicine, Sendai, Japan; [7]Section of Geriatrics, Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden; [8]Department of Health Sciences, Shiga University of Medical Sciences, Otsu, Japan; [9]Copenhagen University Hospital, Copenhagen, Denmark; [10]Addenbrook's Hospital, Cambridge University Hospitals, Cambridge, UK; [11]First Department of Cardiology and Hypertension, Jagiellonian University Medical College, Kra-ków, Poland; [12]Department of Clinical and Experimental Medicine, University of Padova, Padova, Italy; [13]Institute of Internal Medicine, Novosibirsk, Russian Federation; [14]The Asociación Española Primera de Socorros Mutuos, Montevideo, Uruguay; [15]Faculty of Medicine, Charles University, Pilsen, Czech Republic; [16]The Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland and [17]The Department of Epidemiology, Maastricht University, Maastricht, The Netherlands. Correspondence: Professor JA Staessen, Studies Coordinating Centre, Laboratory of Hypertension, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Sciences, University of Leuven, Campus Sint Rafaël, Kapucijnenvoer 35, Block D, Box 7001, Leuven BE-3000, Belgium.
E-mail: jan.staessen@med.kuleuven.be
[18]The IDACO investigators are listed in Thijs *et al.*[16]
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leaving 11 167 participants.[17–24] Of those, we excluded 301 because they were younger than 18 years, 248 because their conventional BP had not been measured and 2151 because they had fewer than 10 daytime or 5 nighttime BP readings. Thus, the total number of subjects included in the present analysis totaled 8467 (for details, see expanded Methods and Supplementary Table S1 in the online data supplement).

BP measurement

Methods used for conventional and ambulatory BP measurement are described in detail in the expanded Methods. Conventional BP was the average of two consecutive readings obtained either at the person's home[19,21–24] or at an examination center.[18,20,27] Portable monitors were programmed to obtain ambulatory BP readings at 30-min intervals throughout the whole day[18,25] or at intervals ranging from 15^{27} to 30^{20} minutes during daytime and from 30^{27} to 60^{20} minutes at night.

In line with current guidelines,[28,29] we defined conventional hypertension as a BP $\geqslant$140 mm Hg systolic or 90 mm Hg diastolic. The corresponding thresholds for daytime ambulatory hypertension were 135 mm Hg systolic and 85 mm Hg diastolic. Patients on antihypertensive drug treatment were classified according to the achieved BP. Normotension and sustained hypertension were a consistently normal or consistently elevated BP on conventional and ambulatory measurement.[28,29] White-coat hypertension was a raised conventional BP in the presence of a normal daytime BP.[28,29] Masked hypertension was an elevated ambulatory BP with normal conventional BP.[28,29]

Other measurements

Observers measured body height to the nearest centimeter. Participants had their body weight measured wearing light indoor clothing without shoes. BMI was calculated as weight in kilograms divided by height in meters squared. We used the questionnaires originally administered in each cohort to obtain information on each participant's medical history and smoking and drinking habits. We measured serum cholesterol and blood glucose by automated enzymatic methods. Diabetes was the use of antidiabetic drugs, a fasting blood glucose concentration of at least 7.0 mmol l^{-1},[30] a random blood glucose concentration of at least 11.1 mmol l^{-1},[30] a self-reported diagnosis or diabetes documented in practice or hospital records. Irregular heart rate was defined as an average real variability of 24-h heart rate in the highest decile ($\geqslant$12.05) (for details, see expanded Methods).

Ascertainment of events

We ascertained vital status and the incidence of fatal and nonfatal diseases from the appropriate sources in each country, as described in previous publications.[31] Fatal and nonfatal stroke did not include transient ischemic attacks. Coronary events encompassed death from ischemic heart disease, sudden death, nonfatal myocardial infarction and coronary revascularization. Cardiac events comprised coronary end points and fatal and nonfatal heart failure. The composite cardiovascular end point included all aforementioned end points plus cardiovascular mortality. In all outcome analyses, we only considered the first event within each category.

Statistical analysis

For database management and statistical analysis, we used the SAS software, version 9.3 (SAS Institute, Cary, NC, USA). For comparison of means and proportions, we applied the large-sample *z*-test and the χ^2-statistic, respectively. After stratification for cohort and sex, we interpolated missing values of BMI ($n=12$) and total serum cholesterol ($n=58$) from the regression slope on age. In subjects with unknown drinking ($n=612$) or smoking habits ($n=34$), we set the design variable to the cohort- and sex-specific mean of the codes (0,1). Statistical significance was a α-level of <0.05 on two-sided tests.

BMI in tenths of the distribution

We first explored whether a log-linear model could capture the risk associated with BMI. Using the deviation from mean coding, we computed hazard ratios (HRs) expressing the risk of death or a composite cardiovascular end point across tenths of the BMI distribution vs the overall risk in the whole study population. These HRs, stratified for cohort and adjusted for sex and age (partly adjusted) or additionally adjusted for 24-h systolic BP, serum cholesterol, smoking and drinking, history of cardiovascular disease, diabetes and use of antihypertensive drugs (fully adjusted), were plotted against the mean BMI in the corresponding decile.

BMI and BP in quartiles

Next, we assessed the contribution of BMI and BP to mortality and cardiovascular events, by cross-classifying participants by quartiles of these two risk factors and by plotting incidence rates standardized by the direct method for cohort, sex and age (<60 and $\geqslant60$ years). We compared adjusted rates using the standard normal deviate.

Adjusted Cox models and likelihood-ratio tests

In fully adjusted Cox models, we analyzed BP as a continuous variable across quartiles of BMI after checking the proportional hazards assumption by the Kolmogorov-type supremum test. We restricted these continuous analyses to systolic BP, as in middle-aged and older subjects systolic BP is a stronger risk factor than diastolic BP.[32] All models were stratified for cohort and adjusted for sex, age (treated as a continuous variable), serum cholesterol, smoking and drinking, history of cardiovascular disease, diabetes and use of antihypertensive drugs. From the Cox models, we computed 10-year absolute risk associated with BP across BMI categories. Finally, we assessed whether the contribution of BMI to risk was independent of BP or BP classification by likelihood-ratio tests. We added quartiles of BMI to models already including BP and the covariables. We evaluated the additive as opposed to synergistic effects of BP and BMI on end points by using appropriate interaction terms and likelihood-ratio tests.

RESULTS

Baseline characteristics

The study population consisted of 5363 Europeans (63.3%), 1666 Asians (19.7%) and 1438 South Americans (17.0%). The 8467 participants included 3978 women (47.0%) and 3757 patients with hypertension on conventional BP measurement (44.4%), of whom 1819 (48.4%) were on antihypertensive drug treatment. Age averaged 54.6 (s.d., 15.1) years and BMI 25.5 (4.2) kg m^{-2}. The mean conventional BP was 131.5 (20.6) mm Hg systolic and 79.9 (11.6) mm Hg diastolic. For the 24-h BP, these values were 124.3 (14.3) and 73.9 (8.5) mm Hg, respectively. Of the participants, 4213 (49.8%) had normotension and 867 (10.2%), 1181 (14.0%) and 2206 (26.1%) had white-coat, masked or sustained hypertension, respectively. At enrolment, 2430 participants (28.7%) were current smokers and 4109 (48.5%) reported intake of alcohol. The prevalence of smoking was higher among patients with masked hypertension than in normotensive people (37.6% vs 30.2%; $P<0.001$).

Table 1 lists the baseline characteristics of the whole study population by quartiles of BMI. Across quartiles, all characteristics were significantly different ($P<0.05$), with the exception of conventional heart rate ($P=0.17$). Participants with a higher BMI were older, had higher BPs, were more likely to be European, male, nonsmoking and diabetic (Table 1). BMI was lower ($P<0.0001$) in smokers (832 women and 1598 men) than nonsmokers (3137 women and 2866 men). BMI averaged 24.9 vs 25.2 kg m^{-2} in women and 25.2 vs 26.3 kg m^{-2} in men.

Incidence of events

In the overall study population, median follow-up was 10.6 years (5th to 95th percentile interval, 2.5–17.9 years). Across cohorts, median follow-up ranged from 2.5 years (2.3–2.6) in China to 17.6 years (5.1–20.1 years) in Belgium. During 88 666 person-years of follow-up, 1271 participants died (14.3 per 1000 person-years) and 1092 experienced a fatal or nonfatal cardiovascular complication (12.8 per 1000 person-years). The cause of death was cardiovascular in 500 participants, noncardiovascular in 732, renal failure in 18 and unknown in 39. Considering cause-specific first cardiovascular events, the incidence of fatal and nonfatal stroke amounted to 132 and 362, respectively. Cardiac events consisted of 186 fatal

Table 1. Baseline characteristics of participants

Characteristic	*Quartiles of BMI*			
Limits, kg m^{-2}	*⩽22.6*	*>22.6–⩽25.1*	*>25.1–⩽27.9*	*>27.9*
Number with characteristic (%)				
All subjects in category	2117	2117	2117	2116
European	1100 (52.0)	1344 (63.5)	1444 (68.2)	1475 (69.7)
Asian	753 (35.6)	449 (21.2)	338 (16.0)	126 (6.0)
South American	264 (12.4)	324 (15.3)	335 (15.8)	515 (24.3)
Women	1274 (60.2)	966 (45.6)	835 (39.4)	903 (42.7)
White-coat hypertension	167 (7.9)	181 (8.6)	248 (11.7)	271 (12.8)
Masked hypertension	259 (12.2)	297 (14.0)	328 (15.5)	297 (14.0)
Sustained hypertension	287 (13.6)	448 (21.2)	627 (29.6)	844 (39.9)
Smokers	712 (33.7)	635 (30.1)	549 (26.1)	534 (25.4)
Drinking alcohol	906 (45.1)	1040 (53.3)	1085 (56.3)	1078 (54.8)
Diabetes	95 (4.5)	116 (5.5)	154 (7.3)	222 (10.5)
History of cardiovascular disease	136 (6.4)	162 (7.7)	213 (10.1)	215 (10.2)
Antihypertensive treatment	323 (15.3)	374 (17.7)	481 (22.7)	641 (30.3)
Diuretic	98 (4.7)	122 (5.8)	166 (7.9)	257 (12.2)
Beta-blocker	89 (4.3)	122 (5.8)	162 (7.7)	242 (11.5)
ACE inhibitor	43 (2.1)	77 (3.7)	112 (5.3)	171 (8.1)
Calcium channel blocker	139 (6.7)	153 (7.3)	189 (9.0)	197 (9.4)
Other antihypertensive drug	21 (9.9)	22 (1.0)	26 (1.2)	47 (2.2)
Mean (s.d.) of characteristic				
Age, years	50.4 (17.3)	54.3 (15.2)	57.1 (13.6)	56.7 (13.0)
Serum cholesterol, mmol l^{-1}	5.2 (1.1)	5.6 (1.1)	5.8 (1.1)	5.9 (1.2)
Conventional measurements				
Systolic BP, mm Hg	124.1 (19.8)	128.9 (20.0)	134.6 (19.9)	138.5 (19.4)
Diastolic BP, mm Hg	74.8 (10.6)	78.2 (11.1)	81.6 (11.1)	85.2 (10.9)
Heart rate, b.p.m.	71.5 (11.2)	69.2 (11.3)	69.6 (11.3)	71.7 (11.8)
Ambulatory measurements				
24-h systolic BP, mm Hg	119.3 (13.6)	122.5 (13.5)	126.4 (13.9)	128.9 (14.3)
24-h diastolic BP, mm Hg	71.3 (8.2)	72.9 (8.1)	75.1 (8.5)	76.2 (8.3)
24-h heart rate, b.p.m.	72.6 (8.8)	71.5 (9.0)	71.6 (9.0)	73.2 (9.6)
Daytime systolic BP, mm Hg	125.4 (14.3)	129.1 (14.4)	133.1 (15.1)	135.2 (15.3)
Daytime diastolic BP, mm Hg	76.2 (8.8)	77.9 (8.8)	80.2 (9.2)	81.3 (9.0)
Nighttime systolic BP, mm Hg	108.7 (14.6)	110.9 (14.3)	114.3 (14.9)	117.0 (15.8)
Nighttime diastolic BP, mm Hg	62.6 (9.1)	63.9 (8.7)	65.8 (9.3)	66.9 (9.3)

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; BP, blood pressure; b.p.m., beats per minute. Definition of BP categories: normotension, conventional BP $<140/<90$ mm Hg and daytime BP $<135/<85$ mm Hg; white-coat hypertension, conventional BP $\geqslant 140/\geqslant 90$ mm Hg and daytime BP $<135/<85$ mm Hg; masked hypertension, conventional BP $<140/<90$ mm Hg and daytime BP $\geqslant 135/\geqslant 85$ mm Hg; and sustained hypertension, conventional BP $\geqslant 140/\geqslant 90$ mm Hg and daytime BP $\geqslant 135/\geqslant 85$ mm Hg. Trends across quartiles were significant ($P<0.05$) for all characteristics with the exception of conventional heart rate ($P=0.17$).

and 451 nonfatal events, including 80 fatal and 217 nonfatal cases of acute myocardial infarction, 66 deaths from ischemic heart diseases, 13 sudden deaths, 27 fatal and 169 nonfatal cases of heart failure and 65 cases of surgical or percutaneous coronary revascularization.

BMI as risk predictor

Figure 1 shows the partly and the fully adjusted HRs of death or a composite cardiovascular end point across tenths of the BMI distribution. Compared with the overall risk in the whole study population, the partly adjusted risk of mortality was higher in the lowest tenth of the BMI distribution (HR, 1.52; 95% confidence interval (CI), 1.28, 1.80; $P<0.0001$), whereas it was significantly lower in the sixth (HR, 0.83; 95% CI, 0.70, 0.99; $P=0.03$) and seventh (HR, 0.79; 95% CI, 0.66, 0.94; $P=0.007$) decile groups. In fully adjusted models, the risk of death remained higher in the lowest tenth (HR, 1.50; 95% CI, 1.26, 1.78; $P<0.0001$) and lower in the seventh decile group (HR, 0.78; 95% CI, 0.66, 0.94; $P=0.010$). With regard to the composite cardiovascular end point, the partly adjusted risk associated with BMI was higher in the top tenth of the distribution (HR, 1.27; 95% CI, 1.07, 1.50; $P=0.006$). However, full adjustment removed significance of BMI (HR, 1.00; 95% CI, 0.84, 1.19; $P=0.99$).

BMI and BP as combined risk factors

Figure 2 and Supplementary Figure S1 shows the standardized incidence of death and composite cardiovascular end points by cross-classifying participants by quartiles of the distributions of BMI and 24-h systolic BP and conventional systolic BP, respectively. Within each BMI quartile ($P\leqslant 0.004$) with the exception of the highest ($P\geqslant 0.35$), rates increased with higher 24-h systolic BP.

With stratification for cohort and adjustments applied for sex, age, serum cholesterol, smoking and drinking, history of cardiovascular disease, diabetes and antihypertensive drug treatment, the 24-h and nighttime systolic BPs consistently predicted every end point under study across all quartiles of BMI ($P\leqslant 0.046$) (Tables 2 and 3). Conventional and daytime systolic BP were weaker predictors not reaching significance ($P\geqslant 0.068$) in some of the quartiles of BMI in relation to all-cause mortality (Table 2) or cardiovascular mortality or fatal combined with nonfatal cardiac

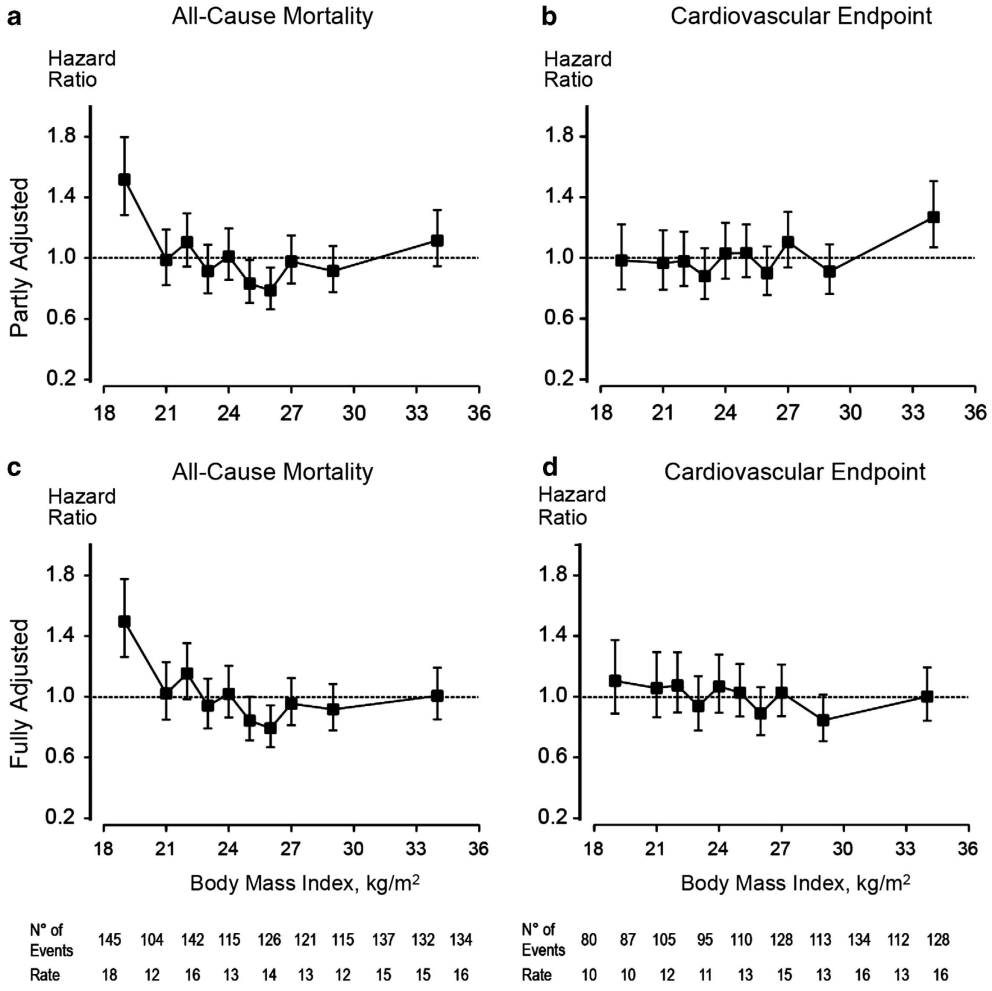

Figure 1. Hazard ratios (95% confidence intervals) expressing the risk of death (**a**, **c**) or of a composite cardiovascular end point (**b**, **d**) in tenths of the BMI distribution vs the overall risk in the whole study population. The data markers are centered on the means in each tenth. Hazard ratios were stratified for cohort and either partly adjusted for sex and age (**a**, **b**) or additionally adjusted for 24-h systolic BP, serum cholesterol, smoking and drinking, history of cardiovascular disease, diabetes and use of antihypertensive drugs (**c**, **d**).

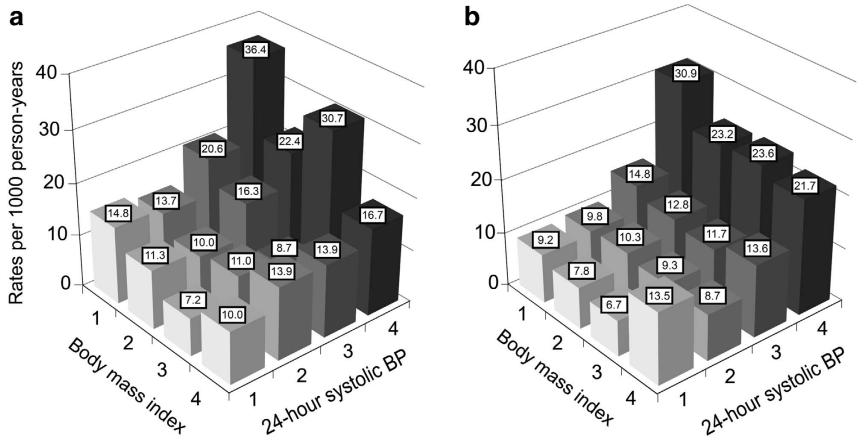

Figure 2. Incidence of death (**a**) or of a composite cardiovascular end point (**b**) by cross-classification of BMI and 24-h systolic BP categorized into quartiles. The incidence rates were standardized for cohort, sex and age (<60 and ⩾60 years). Within each BMI quartile ($P \leqslant 0.004$) with the exception of the highest ($P \geqslant 0.35$), rates increased with higher 24-h systolic BP.

events (Table 3). Although accounting for BP, total mortality was the only outcome that remained associated with BMI categories (Table 2), because of higher risk in the low quartile (HR⩾1.23; $P \leqslant 0.001$) as opposed to lower risk in the medium–high quartile (HR⩽0.84; $P \leqslant 0.001$). For fatal combined with nonfatal cardiovascular end points (Table 3), both overall and cause-specific, BMI did

Table 2. Hazard ratios for total mortality in relation to category of BMI and systolic BP

	Quartiles of BMI					
Limits, kg m^{-2}	*⩽22.6*	*>22.6–⩽25.1*	*>25.1–⩽27.9*	*>27.9*	*P-Con*	*P-Int*
Conventional BP						
BMI	1.23 (1.11, 1.37)‡	0.99 (0.90, 1.09)	0.84 (0.76, 0.92)‡	0.99 (0.89, 1.09)	<0.0001	0.64
Systolic BP	1.18 (1.05, 1.33)†	1.10 (0.97, 1.25)	1.11 (0.97, 1.26)	1.11 (0.98, 1.25)		
24-h BP						
BMI	1.24 (1.12, 1.38)‡	1.00 (0.91, 1.10)	0.83 (0.75, 0.92)‡	0.97 (0.91, 1.10)	<0.0001	0.91
Systolic BP	1.13 (1.01, 1.27)*	1.21 (1.08, 1.35)†	1.17 (1.03 1.32)†	1.12 (1.01, 1.25)*		
Daytime BP						
BMI	1.23 (1.11, 1.37)‡	0.99 (0.90, 1.09)	0.83 (0.76, 0.92)‡	0.98 (0.89, 1.09)	<0.0001	0.86
Systolic BP	1.10 (0.98, 1.23)	1.16 (1.03, 1.30)*	1.09 (0.97, 1.23)	1.04 (0.89, 1.16)		
Nighttime BP						
BMI	1.23 (1.11, 1.36)‡	1.00 (0.91, 1.10)	0.84 (0.76, 0.92)‡	0.97 (0.88, 1.07)	<0.0001	0.89
Systolic BP	1.14 (1.03, 1.27)*	1.22 (1.11, 1.35)†	1.21 (1.09, 1.35)†	1.14 (1.04, 1.24)†		

Abbreviations: BMI, body mass index; BP, blood pressure. Hazard ratios (95% confidence intervals) for BMI express the risk of death ($n = 1271$) associated with each quartile vs the average risk in the whole population. Hazard ratios for BP are calculated within each quartile of BMI and express the risk associated with a 1 s.d. increase in the conventional (20.6 mm Hg), 24-h (14.3 mm Hg), daytime (15.2 mm Hg) or nighttime (15.3 mm Hg) systolic BPs. All models were stratified for cohort and included, in addition to BMI and BP, sex, age, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes and treatment with antihypertensive drugs. Significance of the hazard ratios: *⩽0.05; †⩽0.01; and ‡⩽0.001. *P*-Con denotes the significance of the likelihood ratio testing the contribution of BMI quartiles to the prediction of death over and beyond BP and *P*-Int expresses the significance of the interaction between BP and BMI.

Table 3. Adjusted standardized hazard ratios for cardiovascular events for systolic BP by BMI in quartiles

	Quartiles of BMI					
Limits, kg m^{-2}	*⩽22.6*	*>22.6–⩽25.1*	*>25.1–⩽27.9*	*>27.9*	*P-Con*	*P-Int*
Cardiovascular mortality (n = *500)*						
Conventional	1.20 (0.98, 1.48)	1.26 (1.04, 1.53)†	1.39 (1.15, 1.68)‡	1.42 (1.20, 1.69)‡	0.68	0.88
24-h	1.24 (1.03, 1.49)*	1.50 (1.27, 1.77)‡	1.41 (1.18, 1.67)‡	1.31 (1.12, 1.53)‡	0.67	0.49
Daytime	1.16 (0.96, 1.40)	1.52 (1.27, 1.82)‡	1.29 (1.08, 1.55)†	1.19 (1.00, 1.41)*	0.65	0.27
Nighttime	1.30 (1.09, 1.54)‡	1.35 (1.17, 1.56)‡	1.36 (1.16, 1.59)‡	1.29 (1.13, 1.47)‡	0.81	0.93
Fatal and nonfatal cardiovascular events (n = *1092)*						
Conventional	1.21 (1.05, 1.39)†	1.22 (1.06, 1.39)†	1.33 (1.18, 1.51)‡	1.29 (1.14, 1.46)‡	0.49	0.95
24-h	1.41 (1.24, 1.60)‡	1.39 (1.23, 1.56)‡	1.35 (1.21, 1.33)‡	1.35 (1.22, 1.49)	0.27	0.83
Daytime	1.33 (1.17, 1.52)‡	1.37 (1.21, 1.56)‡	1.29 (1.15, 1.45)	1.28 (1.15, 1.43)‡	0.31	0.79
Nighttime	1.39 (1.23, 1.57)‡	1.27 (1.15, 1.41)‡	1.30 (1.17, 1.44)‡	1.27 (1.16, 1.40)	0.60	0.52
Fatal and nonfatal cardiac events (n = *637)*						
Conventional	1.06 (0.84, 1.34)	1.18 (0.98, 1.41)	1.26 (1.08, 1.48)‡	1.22 (1.05, 1.41)†	0.16	0.87
24-h	1.20 (1.00, 1.45)*	1.24 (1.06, 1.46)‡	1.31 (1.13, 1.52)‡	1.30 (1.15, 1.48)‡	0.21	0.98
Daytime	1.13 (0.94, 1.37)	1.26 (1.06, 1.50)‡	1.29 (1.11, 1.50)‡	1.25 (1.09, 1.43)‡	0.19	0.96
Nighttime	1.21 (1.02, 1.44)*	1.17 (1.01, 1.36)*	1.26 (1.10, 1.44)‡	1.23 (1.10, 1.37)‡	0.25	0.89
Fatal and nonfatal stroke (n = *443)*						
Conventional	1.38 (1.15, 1.67)‡	1.41 (1.15, 1.72)‡	1.47 (1.21, 1.79)‡	1.43 (1.15, 1.77)‡	0.34	0.95
24-h	1.66 (1.38, 2.00)‡	1.67 (1.42, 1.97)‡	1.38 (1.16, 1.64)‡	1.64 (1.37, 1.95)‡	0.13	0.34
Daytime	1.60 (1.32, 1.93)‡	1.63 (1.35, 1.96)‡	1.29 (1.08, 1.53)†	1.53 (1.27, 1.85)‡	0.21	0.22
Nighttime	1.56 (1.31, 1.87)‡	1.44 (1.26, 1.65)‡	1.29 (1.11, 1.51)‡	1.52 (1.31, 1.77)‡	0.18	0.43

Abbreviations: BMI, body mass index; BP, blood pressure. Hazard ratios (95% confidence intervals) are calculated within quartiles of BMI and express the risk associated with a 1 s.d. increase in the conventional (20.6 mm Hg), 24-h (14.3 mm Hg), daytime (15.2 mm Hg) or nighttime (15.3 mm Hg) systolic BPs. The hazard ratios were stratified for cohort and adjusted for sex, age, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes and treatment with antihypertensive drugs. Significance of the hazard ratios: *⩽0.05; †⩽0.01; ‡⩽0.001. *P*-Con denotes the significance of the likelihood ratio testing the contribution of BMI quartiles to the prediction of risk over and beyond BP and *P*-Int expresses the significance of the interaction between BP and BMI.

not contribute to risk over and beyond BP ($P \geqslant 0.13$). Furthermore, the interaction terms between systolic BP and BMI in relation to all of the end points under study were nonsignificant ($0.22 \leqslant P \leqslant 0.98$).

Figure 3 and Supplementary Figure S2 shows the fully adjusted 10-year absolute risk for total mortality and the composite cardiovascular end point in relation to 24-h systolic BP and conventional systolic BP across categories of BMI. For clarity, we

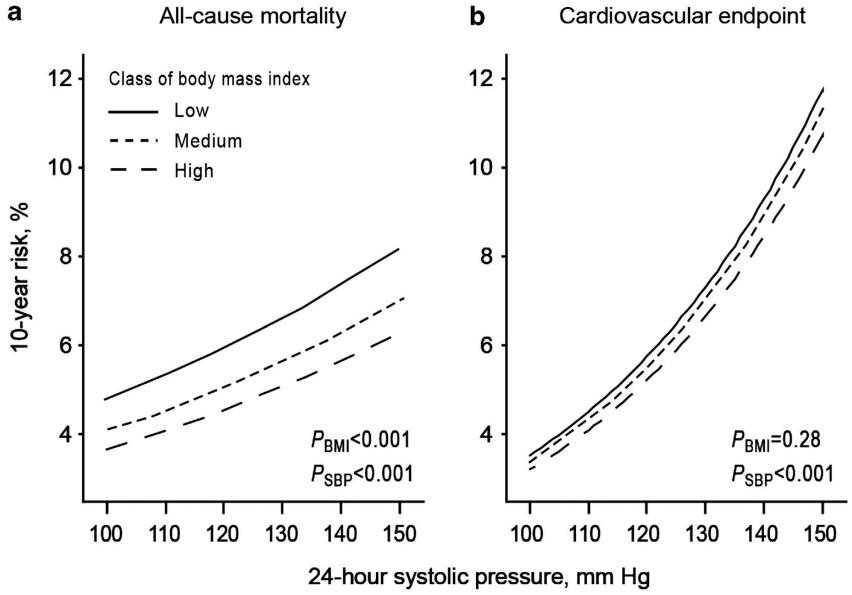

Figure 3. Absolute 10-year risk of death (**a**) or a composite cardiovascular end point (**b**) in relation to 24-h systolic BP in classes of body mass index. For clarity, the second and third quartile of BMI were combined, because the risk functions were coincident. Risk estimates were stratified for cohort and adjusted for sex, age, serum cholesterol, smoking and drinking, history of cardiovascular disease, diabetes and antihypertensive drug treatment. *P* values are for the independent contributions to risk of BMI and 24-h systolic BP.

combined in this plot the medium–low and medium–high BMI quartiles, because these two risk functions were coincident. The absolute risk of death or a composite cardiovascular end point increased with 24-h systolic BP and conventional systolic BP ($P<0.001$), whereas the BMI categories only added to the prediction of total mortality ($P\leqslant0.033$), but not cardiovascular events ($P\leqslant0.53$).

BMI and BP categories as combined risk factors

In participants with normotension or white-coat, masked or sustained hypertension, the prevalence of smoking was 30.1, 16.6, 37.4 and 26.2%, respectively. Supplementary Table S2 shows the HRs for total mortality and the composite cardiovascular end point in relation to white-coat, masked and sustained hypertension across quartiles of BMI. The HRs express the risk vs the normotensive subgroup and are stratified for cohort and adjusted for the aforementioned covariables. The *P*-value for trend in these HRs across categories of BMI was only significant ($P=0.015$) for masked hypertension in relation to mortality (HRs from low to high BMI category, 1.66 ($P=0.001$), 1.46 ($P=0.032$), 1.04 ($P=0.85$) and 0.76 ($P=0.20$), respectively.

Sensitivity analyses

We analyzed total mortality in relation to 24-h systolic BP across quartiles of BMI in subgroups to assess the potential influences of ethnicity, sex, antihypertensive drug treatment, smoking and irregular heart rhythm (Supplementary Table S3). Results were confirmatory in analyses stratified for ethnicity, sex or irregular heart rhythm. However, BMI category no longer added to the prediction of death by 24-h systolic BP in nonsmokers and in participants not on treatment with antihypertensive drugs at baseline ($P\geqslant0.11$).

DISCUSSION

Our subject-level meta-analysis of population samples representing 10 countries and 3 continents is the first study that clarifies how fatal and nonfatal outcomes are independently associated with BMI and BP, 2 inter-related risk factors, while making use of both conventional and ambulatory BP measurement. First, we confirmed that the association between total mortality and BMI is curvilinear, with the highest death rates at the lower tail of the BMI distribution and the lowest risk around or slightly above the median. Second, BMI does not predict cardiovascular mortality or fatal combined with nonfatal cardiovascular complications over and beyond BP. Third, the aforementioned observations were consistent irrespective of the technique of BP measurement. In line with the literature, 24-h and nighttime BP tended to behave as stronger predictors of outcome than the conventional or daytime BP. Fourth, we clarified whether BMI adds to the prediction of total mortality over and beyond BP; this is likely due to the higher prevalence of smoking among lean people.

Several recently published mega-analyses[1–6] all reported a J- or U-shaped relation between total[1–6] or cause-specific[2,4,5] mortality, but only one report accounted for BP, conventionally measured. The Emerging Risk Factor Collaboration pooled individual data from 221 934 people recruited in 17 countries. With adjustment applied for sex, age and smoking, the HR for cardiovascular disease associated with a BMI of $\geqslant20\,kg\,m^{-2}$ was 1.23 (95% CI, 1.17, 1.29). After further adjustment for baseline systolic BP, history of diabetes and total and HDL cholesterol, the HR was 1.07 (95% CI, 1.03, 1.11). Addition of information on BMI to a cardiovascular disease risk prediction model containing conventional risk factors did not improve risk discrimination (C-index change—0.0001). In line with our current observations, the consortium concluded that BMI did not improve cardiovascular disease risk prediction in people in developed countries when systolic BP, diabetes and total and HDL cholesterol are accounted for.[4]

Prospective Studies Collaboration[2] conducted a subject-level meta-analysis of 57 prospective studies with 894 576 participants (mean age 46 years; 39% women) recruited in western Europe (63.3%), North America (29.1%) and Japan (7.6%). Associations between baseline BMI and mortality were estimated with stratification for study, sex, age and smoking. These investigators intentionally did not adjust for BP, blood lipids or diabetes, because these risk factors represent intermediary mechanisms by which BMI affects cardiovascular mortality. In both sexes, mortality was lowest at about 22.5–25.0 $kg\,m^{-2}$. Above this range, each 5 $kg\,m^{-2}$ higher BMI was associated with a 30% and 40% increase

in total and cardiovascular mortality, respectively. Below the range of 22.5–25.0 kg m^{-2}, BMI was associated inversely with overall mortality, mainly because of strong inverse associations with respiratory disease and lung cancer. At all levels of BMI, the risk of death was approximately twice as high in smokers than in nonsmokers.[2] In contrast to the approach taken by the Prospective Studies Collaboration,[2] we chose to account for a comprehensive set of covariables, including BP, blood lipids and diabetes, because the goal of our analysis was to assess the relative contributions of BMI and BP to adverse outcomes.

Our findings support the hypothesis that the excess mortality associated with low BMI might be at least partially caused by smoking. Smokers have lower BMI than nonsmokers and are at high risk of cardiovascular and noncardiovascular disease. Smokers compared with nonsmokers have a life expectancy that is on average 10 years shorter.[33] Smoking acutely stimulates the sympathetic nervous system.[34] The acute hemodynamic responses to smoking include increases in heart rate and BP. They occur within 1–2 min of the act of smoking and last for 30 min or longer. The BP rise in response to smoking can only be picked up by intermittent or continuous BP monitoring.[35] The conventional BP is usually measured after a smoking-free interval. On average, smokers have a slightly lower conventional BP than nonsmokers, because of the reduction in sympathetic activity in the intervals between smoking[36] and the development of tolerance to catecholamines.[37] For these reasons, as in our current study, smoking is more prevalent among masked hypertensive patients than normotensive people.[35] Thus, use of ambulatory BP monitoring not only refined BP measurement but also provided insight into the mechanism potentially underlying the higher mortality in lean persons.

Several studies[7–14] addressed the additive or synergistic roles of BMI and BP as joined risk factors. Sample size ranged from 1727[8] to 1.1 million[10] participants. However, several issues render a straightforward interpretation of these studies difficult. First, in some studies the method to measure the conventional BP was not reported in detail[8,13] or only one cuff size was used in nonobese and obese participants.[12,13] Applying standard cuffs to upper arms with a girth of >32 cm leads to overestimation of BP.[28] Some studies exclusively enrolled overweight and obese participants,[9] young Swedish men drafted into military service[10] or excluded women.[7,8,13] Most previous reports[7–9,12] addressing the interaction between BMI and BP only considered fatal outcomes. In all the aforementioned studies,[7–14] investigators addressed the joined effects of BMI and BP on adverse outcomes by testing the interaction terms. Results were contradictory, as studies varyingly reported that the interaction between BMI and BP on outcome was positive,[10,11] nonsignificant[13,14] or negative.[7–9,12] The models used in the aforementioned studies[7–14] assumed a log-linear association between mortality and BMI, which, based on the recent evidence from the mega-studies,[1–6] is not the case. To address this problem of nonlinearity, in the current study we subdivided BMI into quartiles and applied the likelihood-ratio test, which does not imply any particular shape of the relation between the outcome and risk variables under study. The absence of interaction between BMI and BP in relation to outcome suggests that BMI does not modify the risk associated with BP.

The current study must be interpreted within the context of its strengths and limitations. Strong points are the relatively large sample, the availability of both fatal and nonfatal outcomes in unbiased population samples and the use of ambulatory BP monitoring, which is state-of-the art in the assessment of BP status.[28] BMI in our study was measured and not self-reported as in some other articles.[3,38] Weaker points are that we did not have any information on central obesity and that we did not collect a biomarker of smoking, such as serum cotinine. However, the Emerging Risk Factors Collaboration[4] demonstrated that in multivariable-adjusted analyses, the risk of a cardiovascular end point increased equally with BMI, waist circumference and the waist-to-hip ratio and that these three measures of obesity carried approximately the same risk information. This observation actually argues against the proposition based on studies with coronary heart disease[39] or myocardial infarction[40] as outcome that measures of central obesity should replace BMI as the anthropometric measure of choice in risk assessment.

Our findings have implications for clinical practice and research. First, our study adds to the growing evidence that out-of-office BP monitoring should be applied more widely in day-to-day practice and clinical research. Second, all patients with hypertension should be treated to same BP level irrespective of BMI. The ACCOMPLISH investigators recently suggested that hypertension in normal weight and obese patients might be mediated by different mechanisms.[41] They reported that thiazide-based treatment provided less cardiovascular protection in normal weight than obese patients, whereas amlodipine-based therapy was equally effective across BMI subgroups.[41] However, most hypertensive patients require multiple drug classes to be controlled, and in our current study the risk associated with BP was similar across a wide BMI range. We[42] and others[43] have suggested that attained BP rather than drug class explains the benefit associated with BP lowering treatment.

In conclusion, although obesity and hypertension cluster, BMI only adds to BP in risk stratification for total mortality but not for any cardiovascular outcomes. Smoking is a confounder factor at least partially explaining the association between increased mortality and low BMI.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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