Changes in fat mass and fat-free-mass are associated with incident hypertension in four population-based studies from Germany

Till Ittermann[1,3*], Nicole Werner[1*], Wolfgang Lieb[5], Benedikt Merz[6, 11], Ute Nöthlings[6], Alexander Kluttig[4,8], Daniel Tiller[8,4], Karin H. Greiser[9], Susanne Vogt[10], Barbara Thorand[4,10], Annette Peters[4,10], Henry Völzke[1,3,4], Marcus Dörr[2,3], Sabine Schipf[1,4*], Marcello R. P. Markus[2,3,4*]

* Authors contributed equally to this work.

[1]Department of Study of Health in Pomerania/Clinical-Epidemiological Research, Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany.
[2]Department of Internal Medicine B, University Medicine Greifswald, Greifswald, Germany.
[3]DZHK (German Centre for Cardiovascular Research), partner site Greifswald, Greifswald, Germany.
[4]DZD (German Center for Diabetes Research), Germany.
[5]Institute of Epidemiology and Biobank PopGen, Christian-Albrechts University of Kiel, Kiel, Germany
[6]Department of Nutrition and Food Sciences, Nutritional Epidemiology, University of Bonn, Bonn, Germany
[7]Institute of Epidemiology, Christian-Albrechts University of Kiel, Kiel
[8]Institut für Medizinische Epidemiologie, Biometrie und Informatik, Martin-Luther-University Halle-Wittenberg, Halle, Germany
[9] German Research Center for Cancer, Heidelberg, Germany
[10]Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany
[11]Department of Physiology and Biochemistry of Nutrition, Max Rubner-Institut, Federal Research Institute of Nutrition and Food, Karlsruhe, Germany

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Address for correspondence:
Till Ittermann, Dr. rer. med. habil
Institute for Community Medicine
Ernst-Moritz-Arndt-University Greifswald
Walther-Rathenau-Str. 48
D-17475 Greifswald
Germany
Phone: +49 3834-867552, Fax: +49 3834 - 8622863
Email: till.ittermann@uni-greifswald.de

Abstract:

Background We estimated the association of changes in body weight, waist circumference (WC), fat mass (FM) and fat-free mass (FFM) with changes in blood pressure and incident hypertension using data from four German population-based studies.

Methods We analyzed data from 4,467 participants, aged 21 to 82 years not taking antihypertensive medication and not having type 2 diabetes mellitus or a history of myocardial infarction at baseline and follow-up, from four population-based studies conducted in Germany. Body weight, WC, and blood pressure were measured at baseline and follow-up (median follow-up of the single studies 4 to 7 years). FM and FFM were calculated based on height-weight models derived from bioelectrical impedance studies. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Confounder-adjusted linear and logistic regressions were used to associate changes in anthropometric markers with changes in blood pressure, incident hypertension, and incident normalization of blood pressure.

Results In a pooled dataset including all four studies, increments in body weight, WC, FM, and FFM were statistically significantly associated with incident hypertension and changes in systolic and diastolic blood pressure over time. Decreases in body weight, FM, and FFM were significantly associated with incident normalization of blood pressure.

Conclusions Our data suggests that the well-established association between obesity and blood pressure levels might be more related to body composition rather than to total body weight per se. Our findings indicate that gaining or losing FFM has substantial impact on the development or reversion of hypertension.

Introduction

Obesity has reached epidemic proportions worldwide [1]. In 2008, 502 million individuals were obese [2]. These number is alarming, since obesity increases the risk for cardiovascular events, type 2 diabetes mellitus, cardiometabolic risk factors and all-cause mortality [3-7]. It was shown in the 1980ties that the prevalence of hypertension is twice as high in individuals with obesity than in those with normal weight [8]. In a more recent study conducted between 1999 and 2004, the prevalence of hypertension among US adults was 18.1% for individuals with normal weight and 52.3% for individuals with obesity grade 3 [9]. Weight reduction is already recommended in individuals with marginal overweight [10]. In a population-based cohort study including individuals not taking antihypertensive medication, a weight gain of 1 kg over a median follow-up period of 5 years was associated with an increase of 0.45 mmHg in systolic blood pressure and an increase of 0.32 mmHg in diastolic blood pressure [11]. Likewise, a weight loss of 5% was associated with a 16% decreased risk of incident hypertension in that study [11]. In line with this finding, a meta-analysis of randomized controlled trials showed that a weight loss of 1 kg was associated with a reduction of 1.05 mmHg in systolic and 0.92 mmHg in diastolic blood pressure [12].

Apart from the change in total body weight it may also be important to distinct changes in fat mass (FM) from changes in fat-free mass (FFM) to better understand the impact of changes in body composition on incident hypertension. A previous study conducted in about 1,000 individuals with a follow-up time of ten years demonstrated that a reduction in FFM was much more strongly associated with a normalization of hypertension than a reduction in FM [13]. Given the relatively low number of individuals in the latter study, we aimed to investigate the association of

changes in body weight, waist circumference, FM and FFM with changes in blood pressure, incident hypertension and incident normalization of hypertension in a large sample derived from four population-based studies conducted within Germany.

Methods

Study samples

For the present analyses, we combined data from four population-based longitudinal studies carried out in different regions of Germany including the Population Genetic Biobank (PopGen) from the Northwest, the Study of Health in Pomerania (SHIP) from the Northeast, the Cardiovascular Disease, Living and Ageing in Halle, Saxony-Anhalt (CARLA) from the East, and the fourth survey of the Cooperative Health Research in the Region of Augsburg, Bavaria (KORA) from the South of Germany. In total 8,746 participants aged 21 to 82 years were examined. Detailed information on study design and methods from each study has been published previously [14-18]. The response at follow-up varied between 70.7% (PopGen) and 80.7% (CARLA) and the median follow-up times between four (CARLA) and seven years (KORA).

The studies conformed to the principles of the Helsinki declaration and the studies were approved by the respective ethic committees and the public data protection offices. All participants provided a written informed consent prior to study participation.

From the 8,746 participants with available longitudinal data, we excluded individuals with the following conditions at baseline or follow-up (overlaps exist): pregnant women (n=42), type 2 diabetes mellitus (n=923), myocardial infarction (n=297), stroke (n=183), cancer (n=583), or use of antihypertensive medication (ATC

codes C02, C03, C07, C08, C09) (n=2,186). Furthermore, individuals with missing data in any of the considered variables were excluded (n=56) leading to a final sample size of 4,476 participants.

Data Collection

All participants underwent an extensive standardized medical examination. Body weight, height, and waist circumference were measured in similar way with standardized procedures in PopGen, SHIP, CARLA, and KORA. Weight was measured to the nearest 0.1 kg in light clothing and without shoes using standard digital scales. Waist circumference was measured to the nearest 0.1 cm using an inelastic tape midway between the lower rib margin and the iliac crest in the horizontal plane with the subject standing comfortably with weight distributed evenly on both feet. Waist circumference measurements varied slightly between the studies [19]. The FFM (kg) was calculated according to the formula: FFM= 5.1 * (height $[m]^{1.14}$) * (weight $[kg]^{0.41}$) for men and 5.34 * (height $[m]^{1.47}$) * (weight $[kg]^{0.33}$) for women as described by Kuch et al. [20], using height-weight models results from bioelectrical impedance analyzes [20, 21] The FM (kg) was calculated as body weight minus FFM [21]. In a recent study, our group compared FM and FFM derived by the formula with the values measured by bioelectrical impedance analysis and found excellent correlations for FM (R^2=0.92) and FFM (R^2=0.95) in 2,271 individuals [22].

Systolic and diastolic blood pressure were measured three times after an initial five-minute rest period on the right arm of seated individuals using a digital blood pressure monitor. Measurements were separated by three-minute intervals. The mean of the second and third measurements was calculated and used for the present analyses. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg at baseline and follow-up. Incident

normalization of blood pressure was defined as hypertension present only at baseline. In a sensitivity analysis we did not exclude individuals taking antihypertensive medication at follow-up and defined incident hypertension by systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or intake of antihypertensive medication.

Annual absolute changes in body weight, waist circumference, body composition and blood pressure were calculated by dividing the absolute change between baseline and follow-up through the individual follow-up time in years. By including follow-up time in the formula, we aimed to adjust for the different follow-up times in each study.

Statistical analyses

To characterize the study sample, data were reported as the median (25th and 75th percentile) for continuous variables and as percentages for categorical variables. Associations of annual changes in body composition markers (exposure) with annual changes in blood pressure values (outcome) were modeled by linear regression models adjusted for sex, age, and the mean of the baseline and follow-up values of the respective body composition marker. Annual changes in body weight were associated with incident hypertension and incident normalization of hypertensive blood pressure levels by logistic regression models adjusted for sex, age, and the mean of the two values (baseline and follow-up) of the respective body composition marker. For the analyses regarding incident hypertension, individuals with hypertension at baseline were excluded. For the analyses regarding incident normalization of blood pressure, individuals without hypertension at baseline were excluded. Pooled analyses were additionally adjusted for study. Fractional polynomials were tested for possible non-linear relationships between exposure and

outcome. To account for drop-out to follow-up inverse probability weights were applied. A p<0.05 was considered as statistically significant. Statistical analyses were performed using Stata 14.1 (Stata Corporation, College Station, TX, USA).

Results

Data of 4,476 participants from four population-based German studies aged 21 to 82 years were included in the present analyses. Participants of the CARLA study were in median older than the participants of the other studies (Supplementary Table 1). Likewise, median values of body weight, BMI, waist circumference, and FM were highest in the CARLA study. Median values of FFM were highest in PopGen and lowest in KORA and SHIP. Individuals in CARLA had in median the highest systolic and diastolic blood pressure values. The prevalence of hypertension ranged from 16.5% (KORA) to 41.1% (CARLA).

Median annual increases of body weight, waist circumference, and FM were highest for individuals in PopGen and SHIP (Supplementary Table 2), whereas in CARLA only slight increases were observed. Data of all regional studies demonstrated only minor annual changes in FFM. Individuals in PopGen had in median an annual increase in systolic and diastolic blood pressure of 1 and 1.5 mmHg. In contrast, individuals from the other three cohorts showed in median only a marginal annual increase in systolic and diastolic blood pressure. Incidence of untreated hypertension ranged from 6.8% (KORA) to 38.0% (PopGen), while incident normalization of blood pressure ranged from 30.4% (PopGen) to 54.1% (KORA).

In multivariable linear regression analyses, annual changes in body weight, waist circumference, FM, and FFM were positively associated with annual changes in systolic blood pressure in all of the individual studies and in the pooled sample (Table 1 and Figure 1). Associations were strongest in CARLA. Similarly, we observed

significant positive associations of annual changes in weight, waist circumference, FM, and FFM with annual changes in diastolic blood pressure in all studies and in the pooled sample (Table 1 and Figure 2).

Annual changes in body weight, waist circumference, FM, and FFM were positively associated with incident hypertension in the pooled data of the four studies (Table 2). Only change in FFM was positively associated with incident hypertension in each individual study, while annual changes in body weight, FM, and FFM were positively associated with incident normalization of blood pressure in the pooled data of the four studies. No such association was observed for annual changes in waist circumference. We observed no significant association between annual weight changes and incident normalization of blood pressure in KORA and CARLA, while annual changes in waist circumference were not significantly associated with incident normalization of blood pressure in any of the individual studies. In SHIP and PopGen a loss of FM was significantly associated with an increased chance for normalization of blood pressure, while no such association was observed in KORA and CARLA. FFM was significantly associated with incident normalization of blood pressure in PopGen. Results did not differ significantly when calculating the pooled data in a mixed effect model with study as random intercept. When forcing changes in FM, FFM and waist circumference in one regression model, we observed significant associations of changes in FM and FFM with changes in systolic (FFM: $\beta=0.58$, $p<0.001$; FM: $\beta=0.57$, $p<0.001$) and diastolic blood pressure (FFM: $\beta=0.56$, $p=0.016$; FM: $\beta=0.26$, $p=0.005$) in the pooled population, while changes in waist circumference were not significantly associated with these outcomes. Only changes in FFM were significantly associated with incident hypertension (Odds ratio=1.95, $p<0.001$), whereas only changes in FM were significantly associated with incident normalization of blood pressure (Odds ratio = 0.56, $p=0.002$).

Defining incident hypertension not only by increased blood pressure values but also by intake of antihypertensive medication at follow-up revealed no significantly different results compared to the analyses reported in Table 2. In this sensitivity analysis the odds ratios were 1.34 (95% confidence interval (CI) = 1.20 to 1.50; p<0.001) for annual change in weight, 1.18 (95% CI = 1.08 to 1.28; p<0.001) for annual change in waist circumference, 1.42 (95% CI = 1.23 to 1.63; p<0.001) for annual change in FM, and 3.40 (95% CI = 2.29 to 5.07) for annual change in FFM in the pooled sample of all four studies.

Discussion

In four population-based cohort studies from Germany consisting of individuals not taking antihypertensive medication at baseline and follow up with follow-up times between four and seven years, we observed positive associations of annual changes in body weight, waist circumference, FM, and FFM with annual changes in systolic and diastolic blood pressure. Likewise, gain of body weight, waist circumference, FM, and FFM were associated with an increased risk for incident hypertension. Losses of body weight, FM and FFM were positively associated with incident normalization of blood pressure.

Most of the previous studies on the association between changes in body weight and changes in arterial blood pressure did not consider other markers such as waist circumference, FM, or FFM [11, 12, 23-25]. All these studies reported, in agreement with our findings, positive associations of changes in total body weight with systolic and diastolic blood pressure [11, 12, 23-25]. One of the latter studies used data from SHIP, which was also integrated in our pooled analyses [11]. Another cohort study from the Netherlands with a follow-up period of five years, in which individuals taking antihypertensive medication were not excluded, reported very similar results to our

study [24]. A randomized controlled trial studied the effect of intentional weight loss on arterial blood pressure in 5,145 individuals with overweight or obesity at baseline and showed in concordance to our findings that a weight loss of 5 to 10% was associated with a 5 mmHg reduction in systolic and diastolic blood pressure [25]. Furthermore, meta-analyses of randomized controlled trials reached similar conclusions [12, 23]. In agreement with our results, data from the Framingham Heart Study demonstrated an increased chance for incident hypertension in individuals gaining weight during a follow-up of seven years [26].

We found significant positive associations of change in FM and FFM with incident hypertension and significant inverse associations with incident normalization of blood pressure. Our findings are in agreement with a previous study from our group, in which we investigated 1,145 individuals with pre-hypertension at baseline during a follow-up period of 10 years [13]. In that study, individuals evolving from pre-hypertension to hypertension during follow-up had a significant increase in FM and FFM, while individuals developing from pre-hypertension to normotension had, particularly, a significant decrease in FFM [13]. The main factors that contribute to the blood pressure values are the cardiac output (which is determined by the stroke volume and the heart rate) and the total peripheral vascular resistance [27]. An increase in FFM, which has a much higher metabolic demand than FM [27, 28], is observed in individuals that develop obesity to support the increase in FM. FFM, and not FM, seems to be the central reason for the rise in the cardiac output that leads to a raise in blood pressure levels [27, 29] in obese subjects.[30-32] Accordingly, two previous studies, one with 399 adults [33] and the other with 201 children [27], showed that FFM is a more important determinant of blood pressure levels than FM.

In contrast to body weight, FM, and FFM, a decrease in waist circumference was not significantly associated with normalization of blood pressure. Moreover, an increase in waist circumference was less strongly associated with incident hypertension than an increase in body weight, FM, or FFM. These findings may be explained by changes in fat composition during ageing. In the ageing process subcutaneous fat decreases accompanied by an increase in visceral fat and consequently an increase in waist circumference [34]. Thus, in the long-term, if a person reduces total body weight, FM, or FFM, he/she not necessarily decreases waist circumference [13, 34]. A second explanation for the lack of an association between change in waist circumference and normalization of blood pressure may be related to measurement error. Measuring waist circumference is much more complicated than measuring body weight and lots of different guidelines for assessment exist from different organizations such as the World Health Organization [35], the European Society Of Cardiology [36] or the US National Institutes of Health [37].

The inclusion of four large population-based studies from Germany represents a major strength of our analysis. Data on medication intake was available in all of the included studies allowing us to investigate associations in individuals free of antihypertensive treatment at baseline and follow-up. A major limitation of our study is the definition of FM and FFM by formula only, but we previously demonstrated an excellent correlation of this formula with bioelectric impedance analysis measurements in a large sample [22].

Our data suggests that the well-established association between obesity and blood pressure levels might be more related to body composition rather than to total body weight per se. Our findings indicate that gaining or losing FFM has a substantial impact on the development or reversion of hypertension.

Acknowledgement

Literature

[1] Lewis CE, McTigue KM, Burke LE, Poirier P, Eckel RH, Howard BV, et al. Mortality, health outcomes, and body mass index in the overweight range: a science advisory from the American Heart Association. Circulation. 2009;119:3263-71.

[2] Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet. 2011;377:557-67.

[3] Global BMIMC, Di Angelantonio E, Bhupathiraju Sh N, Wormser D, Gao P, Kaptoge S, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet. 2016;388:776-86.

[4] Ogden CL, Yanovski SZ, Carroll MD, Flegal KM. The epidemiology of obesity. Gastroenterology. 2007;132:2087-102.

[5] Pi-Sunyer FX. The obesity epidemic: pathophysiology and consequences of obesity. Obes Res. 2002;10 Suppl 2:97S-104S.

[6] Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. JAMA. 2003;290:1906-14.

[7] Yu E, Ley SH, Manson JE, Willett W, Satija A, Hu FB, et al. Weight History and All-Cause and Cause-Specific Mortality in Three Prospective Cohort Studies. Ann Intern Med. 2017;166:613-20.

[8] Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation. 1983;67:968-77.

[9] Nguyen NT, Magno CP, Lane KT, Hinojosa MW, Lane JS. Association of hypertension, diabetes, dyslipidemia, and metabolic syndrome with obesity: findings from the National Health and Nutrition Examination Survey, 1999 to 2004. J Am Coll Surg. 2008;207:928-34.

[10] Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res. 1998;6 Suppl 2:51S-209S.

[11] Markus MR, Ittermann T, Baumeister SE, Troitzsch P, Schipf S, Lorbeer R, et al. Long-term changes in body weight are associated with changes in blood pressure levels. Nutr Metab Cardiovasc Dis. 2015;25:305-11.

[12] Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension. 2003;42:878-84.

[13] Markus MR, Stritzke J, Siewert U, Lieb W, Luchner A, Doring A, et al. Variation in body composition determines long-term blood pressure changes in pre-hypertension: the MONICA/KORA (Monitoring Trends and Determinants on Cardiovascular Diseases/Cooperative Research in the Region of Augsburg) cohort study. J Am Coll Cardiol. 2010;56:65-76.

[14] Greiser KH, Kluttig A, Schumann B, Kors JA, Swenne CA, Kuss O, et al. Cardiovascular disease, risk factors and heart rate variability in the elderly general population: design and objectives of the CARdiovascular disease, Living and Ageing in Halle (CARLA) Study. BMC cardiovascular disorders. 2005;5:33.

[15] Holle R, Happich M, Lowel H, Wichmann HE. KORA--a research platform for population based health research. Gesundheitswesen. 2005;67 Suppl 1:S19-25.

[16] Nothlings U, Krawczak M. [PopGen. A population-based biobank with prospective follow-up of a control group]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2012;55:831-5.

[17] Scheidt-Nave C, Kamtsiuris P, Gosswald A, Holling H, Lange M, Busch MA, et al. German health interview and examination survey for adults (DEGS) - design, objectives and implementation of the first data collection wave. BMC public health. 2012;12:730.

[18] Volzke H, Alte D, Schmidt CO, Radke D, Lorbeer R, Friedrich N, et al. Cohort Profile: The Study of Health in Pomerania. Int J Epidemiol. 2011;40:294-307.

[19] Haftenberger M, Mensink GB, Vogt S, Thorand B, Peters A, Herzog B, et al. Changes in Waist Circumference among German Adults over Time - Compiling Results of Seven Prospective Cohort Studies. Obes Facts. 2016;9:332-43.

[20] Kuch B, Gneiting B, Doring A, Muscholl M, Brockel U, Schunkert H, et al. Indexation of left ventricular mass in adults with a novel approximation for fat-free mass. J Hypertens. 2001;19:135-42.

[21] Turkbey EB, McClelland RL, Kronmal RA, Burke GL, Bild DE, Tracy RP, et al. The impact of obesity on the left ventricle: the Multi-Ethnic Study of Atherosclerosis (MESA). JACC Cardiovascular imaging. 2010;3:266-74.

[22] Markus MR, Werner N, Schipf S, Siewert-Markus U, Bahls M, Baumeister SE, et al. Changes in Body Weight and Composition Are Associated With Changes in Left Ventricular Geometry and Function in the General Population: SHIP (Study of Health in Pomerania). Circ Cardiovasc Imaging. 2017;10:e005544.

[23] Aucott L, Rothnie H, McIntyre L, Thapa M, Waweru C, Gray D. Long-term weight loss from lifestyle intervention benefits blood pressure?: a systematic review. Hypertension. 2009;54:756-62.

[24] Bot M, Spijkerman AM, Twisk JW, Verschuren WM. Weight change over five-year periods and number of components of the metabolic syndrome in a Dutch cohort. Eur J Epidemiol. 2010;25:125-33.

[25] Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care. 2011;34:1481-6.

[26] Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. Lancet. 2001;358:1682-6.

[27] Daniels SR, Kimball TR, Khoury P, Witt S, Morrison JA. Correlates of the hemodynamic determinants of blood pressure. Hypertension. 1996;28:37-41.

[28] Crandall DL, DiGirolamo M. Hemodynamic and metabolic correlates in adipose tissue: pathophysiologic considerations. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 1990;4:141-7.

[29] Messerli FH, Ventura HO, Reisin E, Dreslinski GR, Dunn FG, MacPhee AA, et al. Borderline hypertension and obesity: two prehypertensive states with elevated cardiac output. Circulation. 1982;66:55-60.

[30] Bella JN, Devereux RB, Roman MJ, O'Grady MJ, Welty TK, Lee ET, et al. Relations of left ventricular mass to fat-free and adipose body mass: the strong heart study. The Strong Heart Study Investigators. Circulation. 1998;98:2538-44.

[31] Alpert MA, Omran J, Mehra A, Ardhanari S. Impact of obesity and weight loss on cardiac performance and morphology in adults. Progress in cardiovascular diseases. 2014;56:391-400.

[32] Ortega FB, Sui X, Lavie CJ, Blair SN. Body Mass Index, the Most Widely Used But Also Widely Criticized Index: Would a Criterion Standard Measure of Total Body Fat Be a Better Predictor of Cardiovascular Disease Mortality? Mayo Clinic proceedings. 2016;91:443-55.

[33] Weinsier RL, Norris DJ, Birch R, Bernstein RS, Wang J, Yang MU, et al. The relative contribution of body fat and fat pattern to blood pressure level. Hypertension. 1985;7:578-85.

[34] Kuk JL, Saunders TJ, Davidson LE, Ross R. Age-related changes in total and regional fat distribution. Ageing Res Rev. 2009;8:339-48.

[35] World Health Organization. Waist Circumference and Waist–Hip Ratio:Report of a WHO Expert Consultation. 2008.

[36] Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37:2315-81.

[37] US National Institutes of Health. The Practical Guide Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. 2000.

Table 1   Associations of changes in anthropometric markers with changes in blood pressure.

	SHIP (n=1,730)	KORA (n=1,854)	CARLA (n=414)	Popgen (n=478)	Pooled (n=4,476)
Annual change in systolic blood pressure; β (95%-confidence interval)					
Body weight; kg/y	0.43 (0.30; 0.55)*	0.41 (0.28; 0.54)*	0.76 (0.48; 1.04)*	0.52 (0.21; 0.83)*	0.48 (0.38; 0.57)*
Waist circumference; cm/y	0.22 (0.10; 0.34)*	0.29 (0.18; 0.41)*	0.31 (0.01; 0.61)*	0.24 (0.05; 0.42)*	0.25 (0.17; 0.32)*
Fat mass; kg/y	0.55 (0.38; 0.72)*	0.53 (0.36; 0.70)*	1.00 (0.64; 1.37)*	0.64 (0.25; 1.04)*	0.61 (0.49; 0.74)*
Fat free mass; kg/y	1.35 (0.91; 1.79)*	1.76 (1.23; 2.28)*	2.81 (1.61; 4.01)*	1.67 (0.55; 2.78)*	1.66 (1.31; 2.01)*
Annual change in diastolic blood pressure; β (95%-confidence interval)					
Body weight; kg/y	0.32 (0.25; 0.40)*	0.32 (0.24; 0.40)*	0.47 (0.34; 0.60)*	0.28 (0.08; 0.47)*	0.33 (0.27; 0.38)*
Waist circumference; cm/y	0.22 (0.15; 0.29)*	0.23 (0.16; 0.30)*	0.20 (0.04; 0.36)*	0.16 (0.04; 0.28)*	0.20 (0.16; 0.25)*
Fat mass; kg/y	0.42 (0.32; 0.52)*	0.41 (0.30; 0.52)*	0.61 (0.44; 0.78)*	0.33 (0.08; 0.58)*	0.42 (0.35; 0.49)*
Fat free mass; kg/y	1.02 (0.76; 1.29)*	1.42 (1.10; 1.75)*	1.81 (1.21; 2.40)*	0.96 (0.27; 1.65)*	1.18 (0.97; 1.40)*

Linear regression models adjusted for baseline values of age and sex, and for the mean of baseline and follow-up values of the respective anthropometric marker;

*p <0.05

Table 2   Associations of changes in anthropometric markers with incident hypertension.

	SHIP	KORA	CARLA	Popgen	Pooled
N for incident hypertension	1,273	1,549	244	320	3,386
N for incident normalization	457	305	170	158	1,090
Incident hypertension; odds ratio (95%-confidence interval)					
Weight; kg/y	1.30 (1.07; 1.58)*	1.54 (1.20; 1.99)*	1.56 (1.07; 2.27)*	1.24 (0.98; 1.57)	1.34 (1.18; 1.53)*
Waist circumference; cm/y	1.05 (0.90; 1.22)	1.35 (1.06; 1.72)*	1.22 (0.92; 1.61)	1.25 (1.05; 1.50)*	1.16 (1.05; 1.28)*
Fat mass; kg/y	1.39 (1.08; 1.80)*	1.69 (1.22; 2.34)*	1.68 (1.03; 2.75)*	1.29 (0.95; 1.74)	1.42 (1.20; 1.68)*
Fat free mass; kg/y	2.61 (1.36; 5.02)*	7.97 (2.83; 22.45)*	8.51 (1.90; 38.09)*	2.44 (1.04; 5.73)*	3.26 (2.05; 5.19)*
Incident normalization of blood pressure; odds ratio (95%-confidence interval)					
Weight; kg/y	0.72 (0.58; 0.89)*	0.80 (0.59; 1.08)	0.89 (0.65; 1.21)	0.59 (0.40; 0.87)*	0.74 (0.64; 0.86)*
Waist circumference; cm/y	0.91 (0.76; 1.10)	0.97 (0.75; 1.27)	1.01 (0.78; 1.31)	0.90 (0.81; 1.00)	0.89 (0.12; 1.66)
Fat mass; kg/y	0.62 (0.47; 0.82)*	0.75 (0.51; 1.12)	0.87 (0.59; 1.30)	0.53 (0.33; 0.86)*	0.68 (0.56; 0.86)*
Fat free mass; kg/y	0.53 (0.26; 1.09)	0.36 (0.11; 1.20)	0.55 (0.17; 1.74)	0.16 (0.05; 0.57)*	0.42 (0.25; 0.69)*

Logistic regression models adjusted for baseline values of age and sex, and for the mean of baseline and follow-up values of the respective anthropometric marker;

*$p < 0.05$

Figure 1 Associations between annual changes in anthropometric markers and annual changes in systolic blood pressure adjusted for confounding in the individual studies and in the pooled sample.
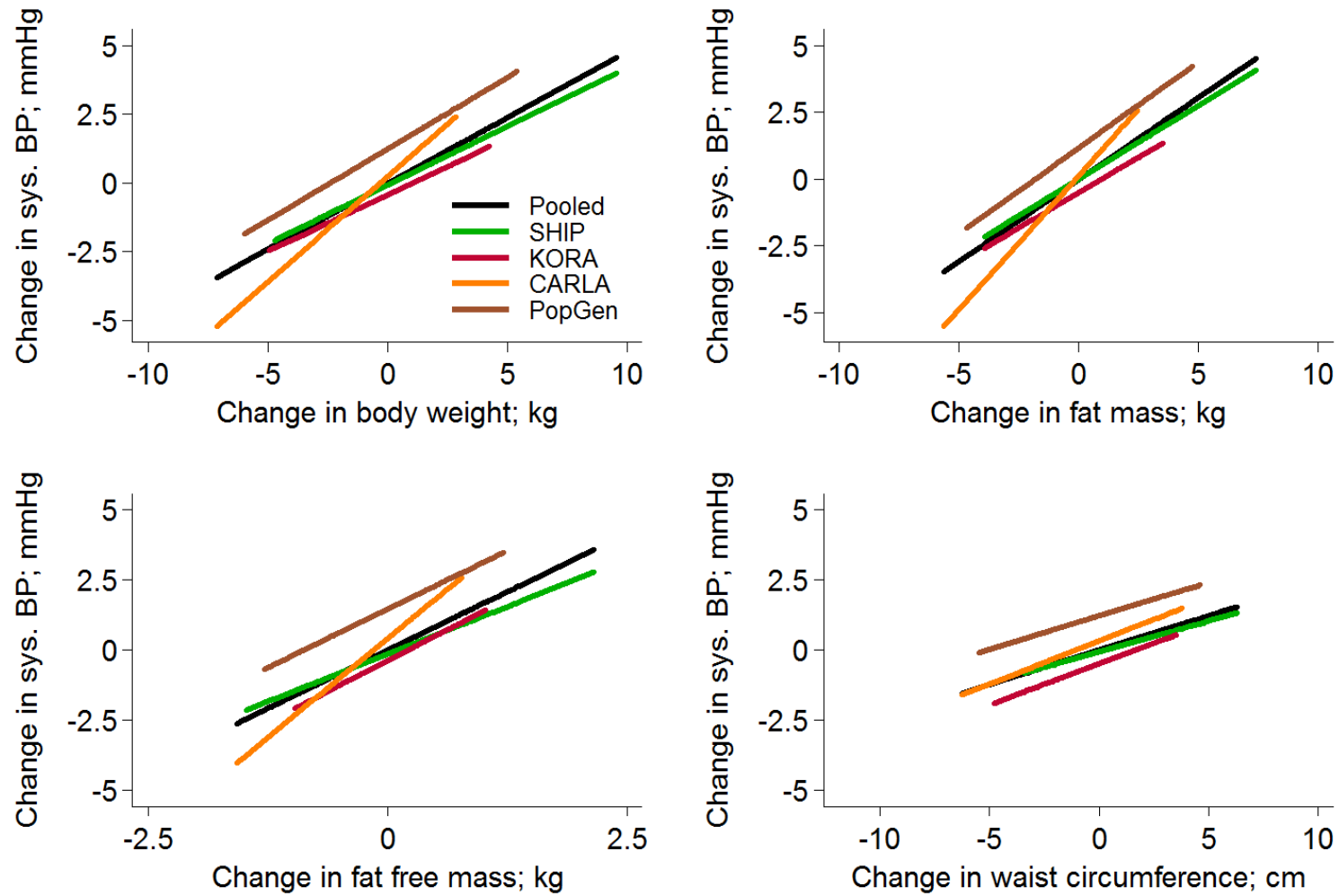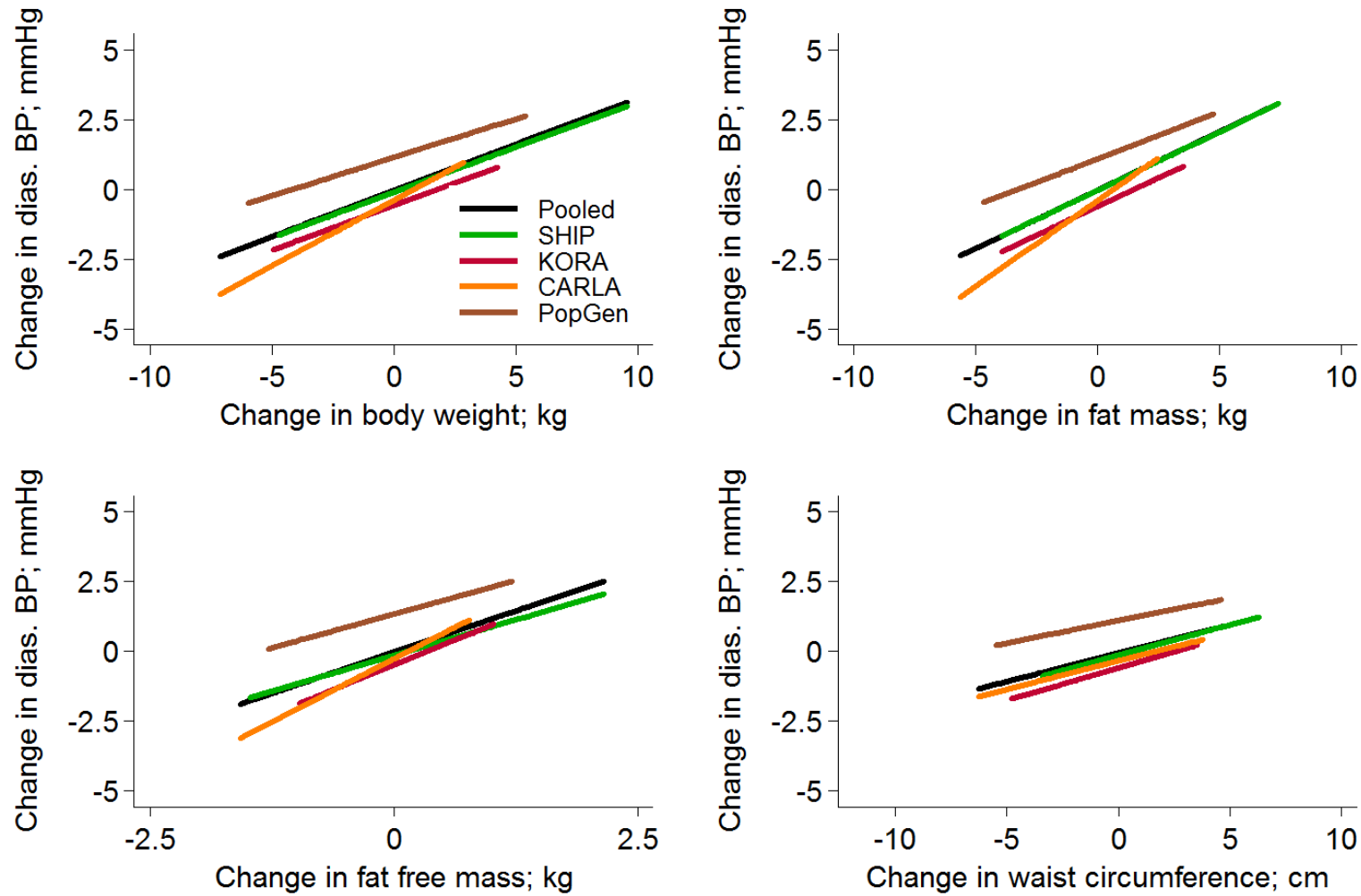
Figure 2 Associations between annual changes in anthropometric markers and annual changes in diastolic blood pressure adjusted for confounding in the individual studies and in the pooled sample.

Supplementary Table 1 Baseline characteristics of the study populations.

	SHIP (n = 1730)	KORA (n = 1854)	CARLA (n = 414)	Popgen (n = 478)
Age; years	40 (32; 51)	42 (34; 52)	56 (51; 63)	52 (43; 60)
Males; %	803 (46.4)	873 (47.1)	232 (56.0)	262 (54.8)
Systolic blood pressure; mmHg	126 (116; 138)	121 (111; 131)	134 (124; 147)	130 (120; 140)
Diastolic blood pressure; mmHg	80 (74; 87)	78 (72; 84)	84 (78; 91)	80 (70; 80)
Pulse pressure; mmHg	45 (39; 52)	43 (37; 49)	49 (44; 58)	50 (40; 60)
Body weight; kg	74 (64; 85)	74 (64; 84)	76 (66; 85)	75 (67; 86)
Body mass index; kg/m^2	25.3 (22.8; 28.0)	25.6 (23.0; 28.3)	26.1 (23.8; 28.6)	25.0 (22.5; 27.5)
Waist circumference; cm	83 (74; 93)	87 (78; 96)	95 (86; 101)	89 (79; 97)
Fat mass; kg	21.9 (17.0; 27.8)	22.3 (17.3; 27.9)	22.6 (17.9; 28.3)	22.0 (16.9; 27.1)
Fat free mass; kg	50.4 (43.8; 59.2)	50.4 (43.5; 58.8)	52.8 (43.9; 59.5)	55.2 (45.7; 61.7)
Hypertension; %	457 (26.4)	305 (16.5)	170 (41.1)	158 (33.1)

Data are expressed as median, 25th, and 75th percentile (continuous data) or as absolute numbers and percentage (categorical data).

Supplementary Table 2   Yearly changes of anthropometric markers and blood pressure.

	SHIP (n = 1730)	KORA (n = 1854)	CARLA (n = 414)	Popgen (n = 478)
Systolic blood pressure; mmHg	-0.1 (-1.5; 1.4)	-0.4 (-1.5; 0.6)	-0.1 (-2.3; 1.9)	1.5 (-0.9; 3.8)
Diastolic blood pressure; mmHg	0.1 (-0.9; 1.0)	-0.4 (-1.1; 0.3)	-0.5 (-1.7; 0.6)	1.0 (0.0; 2.3)
Pulse pressure; mmHg	-0.1 (-1.2; 1.0)	0.0 (-0.7; 0.8)	0.5 (-1.2; 1.7)	0.3 (-1.4; 2.0)
Body weight; kg	0.4 (0.0; 0.9)	0.2 (-0.2; 0.7)	0.1 (-0.5; 0.6)	0.3 (-0.2; 0.9)
Waist circumference; cm	0.7 (0.1; 1.4)	0.4 (-0.1; 0.9)	0.1 (-0.7; 0.8)	1.0 (0.1; 1.7)
Fat mass; kg	0.3 (0.0; 0.7)	0.2 (-0.1; 0.5)	0.1 (-0.3; 0.5)	0.4 (0.0; 0.8)
Fat free mass; kg	0.1 (-0.1; 0.3)	0.1 (0.0; 0.2)	0.0 (-0.2; 0.1)	0.0 (-0.2; 0.1)
Incident Hypertension; %	185 (14.5)	106 (6.8)	44 (18.0)	120 (38.0)
Normalization of hypertension	185 (40.5)	165 (54.1)	56 (32.9)	49 (30.4)

Data are expressed as median, 25th, and 75th percentile (continuous data) or as absolute numbers and percentage (categorical data).