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

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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 4467 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.

1. 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 1000 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.

2. Methods

2.1. 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 8746 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 8746 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 = 2186). Furthermore, individuals with missing data in any of the considered variables were excluded (n = 56) leading to a final sample size of 4476 participants.

2.2. 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 = $5.1 * (\text{height [m]})^{1.14} * (\text{weight [kg]})^{0.41}$ for men and $5.34 * (\text{height [m]})^{1.47} * (\text{weight [kg]})^{0.33}$ 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 2271 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.

2.3. 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).

3. Results

Data of 4476 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 Fig. 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 Fig. 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

Table 1

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

	SHIP (n = 1730)	KORA (n = 1854)	CARLA (n = 414)	Popgen (n = 478)	Pooled (n = 4476)
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.

systolic (FFM: β = 0.58, p < 0.001; FM: β = 0.57, p < 0.001) and diastolic blood pressure (FFM: β = 0.56, p = 0.016; FM: β = 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.

4. 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 5145 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].
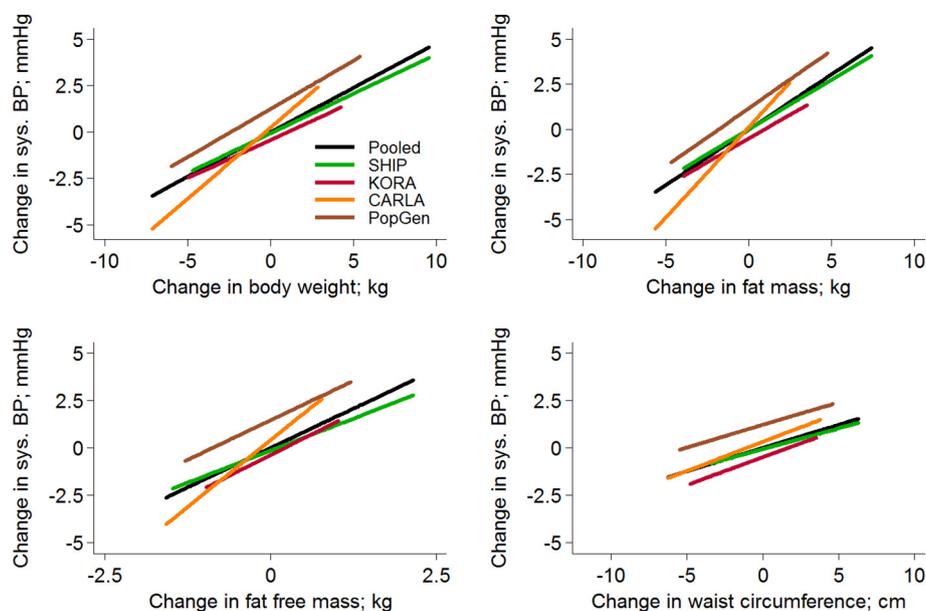

Fig. 1. Associations between annual changes in anthropometric markers and annual changes in systolic blood pressure adjusted for confounding in the individual studies and in the pooled sample.
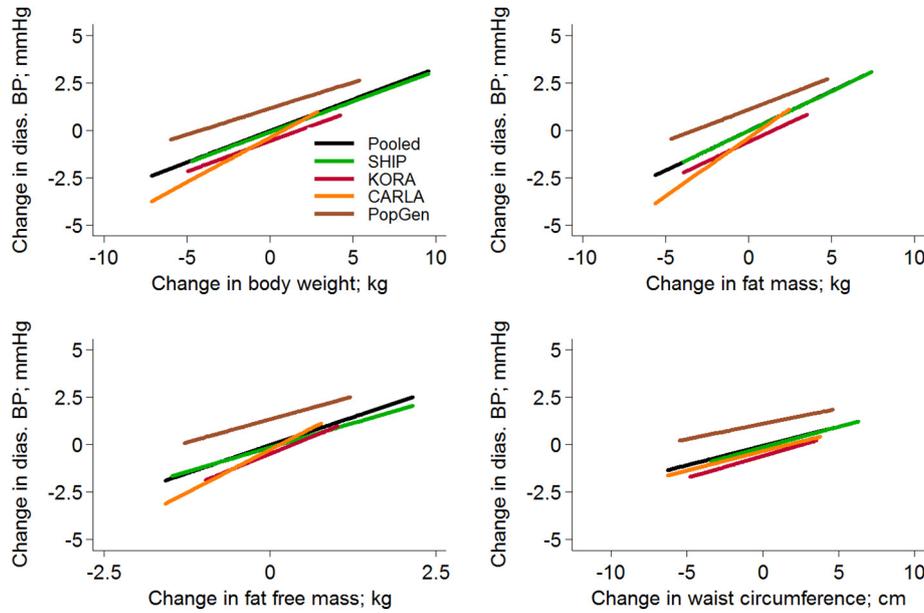
Fig. 2. Associations between annual changes in anthropometric markers and annual changes in diastolic blood pressure adjusted for confounding in the individual studies and in the pooled sample.

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 1145 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

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

	SHIP	KORA	CARLA	Popgen	Pooled
N for incident hypertension	1273	1549	244	320	3386
N for incident normalization	457	305	170	158	1090
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;
* $p < 0.05$.

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.

Conflict of interest

We have nothing to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.035.

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