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Both lean and fat body mass associate with blood pressure

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ABSTRACT

High body mass index (BMI) is known to be associated with elevated blood pressure (BP). The present study aims to determine the relative importance of the two components of BMI, fat mass and lean body mass index, on BP levels.

We assessed body composition with bioimpedance and performed 24 hour ambulatory BP measurements in 534 individuals (mean age 61 ± 3 years) who had no cardiovascular medication. Fat mass index and lean mass index were calculated analogously to BMI as fat mass or lean body mass (kg) divided by the square of height (m^2).

Both fat mass index and lean mass index showed a positive, small to moderate relationship with all 24 hour BP components independently of age, sex, smoking, and leisure-time physical activity. There were no interaction effects between fat mass index and lean mass index on the mean BP levels.

Adult lean body mass is a significant determinant of BP levels with an equal, albeit small to moderate magnitude as fat mass. Relatively high amount of muscle mass may not be beneficial to cardiovascular health.

Introduction

The positive relationship of body mass index (BMI) with blood pressure (BP) has been demonstrated in several large-scale observational studies [1–8]. Importantly, a causal association between BMI and hypertension has recently been verified by two Mendelian randomization studies [9,10].

Because BMI is a ratio of the total body mass (weight) and the square of height, BMI cannot discriminate fat mass from lean body mass of a person. This issue was considered among the UK Biobank participants, in whom genetically predicted fat mass index (calculated analogously to BMI as fat mass divided by height squared) was associated with hypertension, the odds ratio (OR) for hypertension being 1.12 (95% CI 1.04 to 1.20) per genetically predicted 1 kg/m^2 increase of fat mass index [10]. However, the causal association between higher genetically predicted fat-free mass index and hypertension did not quite reach statistical significance: OR 1.08 (95% CI 0.99 to 1.19) [10]. This information implies that genetic variants of fat mass influence BP levels across life course, but the role of fat-free mass is unclear. The factors that trigger disease may not be the same as those that influence it's progression [11]. Even though genetic variation in fat-free mass may not trigger elevated BP, it is possible that fat-free mass gained during life course may have an impact on BP levels in adulthood.

We had the opportunity to assess body composition and 24 hour ambulatory BP measurements (AMBP) in 534 adult individuals who had no medication affecting vasculature. To determine the relative importance of fat mass and fat-free mass on BP levels, we divided BMI into it's two components, fat mass index (FMI) and lean mass index (LMI). We hypothesized that LMI also plays a role in BP regulation.

Materials and methods

The Helsinki Birth Cohort Study (HBCS) includes 8760 men and women who were born at Helsinki University Central Hospital between the years 1934 and 1944. For the clinical study, random-number tables were used to select a subset of people from the initial epidemiological

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study cohort who were still alive and living in Finland in 1971. In order to achieve a sample size in excess of 2000 people, 2902 persons were invited, and 2003 of them visited the clinic in the years 2001-2004. The procedures used at the clinic visit have been described in greater detail previously [12]. Briefly, the subjects attended the clinic after an overnight fast. Height and weight were measured in light indoor clothing and without shoes. Height was measured to the nearest 0.1 cm, and weight to the nearest 0.1 kg. Body composition was assessed by bio-impedance, using an eight-polar tactile electrode system (InBody 3.0, Biospace Co, Ltd, Seoul, Korea). Between-day precision of InBody 3.0 has been reported to be 2.7% in a sample of individuals with a mean age of 53 years [13]. BMI, LMI and FMI were calculated as weight, lean body mass and fat mass (kg) divided by the square of height (m^2), respectively. Fat and lean mass indices were divided according to median values, and four body composition categories were created: 1) low FMI and low LMI, 2) low FMI and high LMI, 3) high FMI and low LMI, 4) high FMI and high LMI.

For 24 h AMBP, oscillometric Spacelabs 90207 monitors (Spacelabs Healthcare, Issaquah, Washington, USA) were used with cuffs of appropriate size applied to the non-dominant arm. The measurement protocol for each subject included a reading once in every 30 min, except from 10 PM to 7 AM, when it included one reading in every hour. We aimed at a number of readings that meets recommendations [14] but allows maximal compliance. Pulse pressure (PP) was defined as the difference between systolic and diastolic BP. Mean arterial pressure (MAP) was calculated as DBP + (SBP – DBP)/3. Office BP was measured from the right arm while the subject was in the sitting position, and it was recorded as the mean of two successive readings from a mercury sphygmomanometer.

Leisure-time physical activity (LTPA) was assessed with the validated 12-month Kuopio Ischemic Heart Disease questionnaire [15]. Information on type, mean duration per month and mean frequency/month of LTPA was collected. We defined a specific metabolic equivalent of task (MET, 1 MET = 3.5 ml of $O_2/kg^{-1}/min^{-1}$ or 1 $kcal/kg^{-1}/h^{-1}$) for each reported activity ($n = 47$) to determine the absolute intensity of the activities. LTPA was reported as a time-weighted average intensity (TWA-MET) as previously reported [16].

Years of education, smoking status, and current medication were assessed by questionnaires.

For the present analysis, we selected only subjects ($n = 534$) who had no cardiovascular medication.

Blood samples were drawn after overnight fasting and were stored at - 70 °C prior to analysis. High sensitivity CRP (hs-CRP) was analyzed with immunoturbidimetric method using Konelab T-serie High Sensitivity-CRP analyzer (Thermo Fisher Scientific Oy, Vantaa, Finland). Interleukin-6 (IL-6) and tumor-necrosis factor-α (TNF-α) were analyzed with multiplex sandwich immunoassays. The highest between-run variation was 13% for both IL-6 and TNF-α. The amount of samples with concentrations below or above the measurement range of the analysis method were 4% for TNF-α, 5% for hs-CRP, and 50% for IL-6.

Ethical approval

Written informed consent was obtained from each subject before any procedures were carried out. The Ethics Committee for Epidemiology of Helsinki and Uusimaa Hospital District approved the study. The study met the institution's or the data curator's guidelines for protection of human subjects concerning their safety and privacy.

Statistical analysis

The descriptive statistics were presented as means with SDs or as counts with percentages. The relationship between FMI and LMI was modeled using linear regression analysis. Results were analysed using factorial (two between-subjects factors: FMI and LMI) analysis of variance (ANOVA) and logistic models. Models included main effects of FMI and LMI and their interaction. Models regarding BP values included age, sex, smoking, and LTPA as covariates. A bootstrap method was used when the theoretical distribution of the test statistics was unknown or in the case of a violation of the assumptions. Multivariate linear regression analysis was used to identify the relationship between FMI and LMI as continuous variables and the ambulatory BP components with standardized regression coefficient Beta (β). The Beta value is a measure of how strongly the predictor variable (FMI or LMI) influences the criterion (BP) variable. The Beta is measured in units of SD. Cohen's standard for Beta values above 0.10, 0.30 and 0.50 represents small, moderate and large relationships, respectively. Because both IL-6 and TNF-α values were extremely right-skewed (not normally distributed), they were transformed to normality using a van der Waerden's rank-based normalization methods [17]. Unadjusted and adjusted (partial) correlations between office and 24 h AMBP values and components of BMI were calculated by the Pearson method. Otherwise, correlation coefficients with 95% CI were calculated by the Spearman method. The normality of variables was evaluated using the Shapiro–Wilk W test. Stata 16.0 (StataCorp LP; College Station, Texas, USA) statistical package was used for the analysis.

Results

We assessed body composition and cardiometabolic risk factors including 24-hour AMBP in 534 individuals with mean age of 61 (SD 3) years, 50.4% being females. None of the subjects had any cardiovascular medication.

The relation of FMI to LMI was linear in both sexes. Correlation of FMI with LMI was $r = 0.51$ (95% CI: 0.41 to 0.59) in men and $r = 0.63$ (95% CI: 0.55 to 0.70) in women. The subjects were categorized according to medians of FMI and LMI as having ĺow FMI and low LMĺ, ĺow FMI and high LMĺ, ĥigh FMI and low LMĺ, and ĥigh FMI and high LMĺ. (Fig. 1)

Table 1 displays the baseline characteristics of the subjects according to categorization as having low or high FMI or LMI, respectively. Persons with low FMI and high LMI were mostly men whereas persons with high FMI and low LMI were mostly women. Both components of BMI showed a positive association with waist circumference and plasma triglyceride level. FMI also showed a positive association with overall body fat percentage, total cholesterol level, and hs-CRP level. FMI showed a

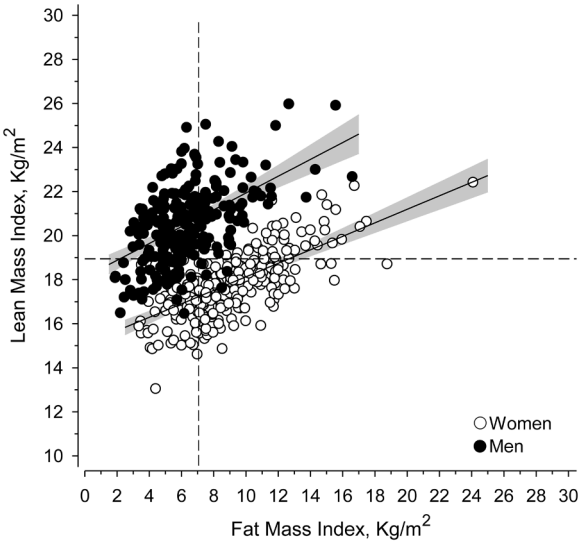

Fig. 1. The relationship between fat mass index and lean mass index in men and women. The solid lines show estimated linear regression with 95% confidence intervals. The dashed lines indicate the medians of lean mass index (LMI) and fat mass index (FMI).

Table 1
Characteristics of the subjects according to fat mass index (FMI) and lean mass index (LMI). Values are means (standard deviations) or numbers (percentages).

	FMI low		FMI high		P-value		
					Main effect		Interaction
	LMI low*N*=112	LMI high*N*=155	LMI low*N*=155	LMI high*N*=112	FMI	LMI	
Women, n (%)	69 (62)	6 (4)	151 (97)	48 (43)	<0.001	<0.001	0.74
Age, mean (SD)	61 (3)	61 (3)	61 (3)	61 (3)	0.10	0.22	0.63
Education years, mean (SD)	12.5 (3.8)	12.8 (3.8)	11.6 (3.4)	11.4 (3.5)	<0.001	0.93	0.32
BMI (kg/m^2), mean (SD)	22.5 (1.7)	26.3 (1.8)	27.1 (2.5)	31.8 (3.4)	<0.001	<0.001	0.037
WC (cm), mean (SD)							
Men	88 (7)	97 (6)	102 (5)	110 (9)	<0.001	<0.001	0.65
Women	77 (6)	83 (4)	89 (8)	103 (8)	<0.001	<0.001	0.026
Body fat-%, mean (SD)	23 (5)	21 (3)	35 (4)	34 (6)	<0.001	<0.001	0.17
Fasting glucose (mmol/l), mean (SD)	5.4 (0.7)	5.9 (1.3)	5.4 (0.8)	6.0 (1.2)	0.36	<0.001	0.68
TC (mmol/l), mean (SD)	6.0 (1.0)	5.9 (1.0)	6.3 (1.0)	6.1 (1.1)	0.003	0.047	0.34
HDL-C (mmol/l), mean (SD)							
Men	1.70 (0.49)	1.50 (0.40)	1.48 (0.31)	1.37 (0.33)	0.045	0.083	0.61
Women	1.93 (0.43)	2.03 (0.71)	1.78 (0.45)	1.62 (0.36)	0.070	0.84	0.39
Triglycerides (mmol/l), mean (SD)	1.16 (0.67)	1.37 (0.71)	1.42 (0.72)	1.72 (0.96)	<0.001	<0.001	0.50
Office BP (mmHg), mean (SD)							
SBP	139 (22)	145 (18)	146 (20)	151 (18)	<0.001	<0.001	0.78
DBP	84 (10)	90 (10)	88 (10)	93 (9)	<0.001	<0.001	0.42
PP	55 (16)	55 (13)	58 (16)	58 (15)	0.019	0.72	0.86
MAP	103 (13)	109 (11)	108 (12)	112 (10)	<0.001	<0.001	0.55
Current smoker, n (%)	29 (26)	34 (22)	29 (19)	19 (17)	0.091	0.44	0.82
LTPA, TWA-MET, mean (SD)	4.7 (1.3)	4.9 (1.1)	4.3 (0.8)	4.5 (1.3)	<0.001	0.036	0.59
hs-CRP (mg/l), mean (SD)	2.7 (6.5)	2.4 (5.0)	4.0 (6.6)	3.4 (3.4)	<0.001	0.085	0.49
TNF-α (pg/ml), median (IQR)	7.5 (5.3, 12.6)	7.9 (4.6, 11.8)	7.4 (5.3, 9.9)	7.4 (5.2, 10.0)	0.11	0.81	0.74
IL-6 (pg/ml), median (IQR)	18 (6, 113)	25 (6, 131)	15 (4, 102)	10 (4, 88)	0.047	0.86	0.71

Abbreviations: FMI, fat mass index; LMI, lean body index; BMI, body mass index; WC, waist circumference; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; LTPA, leisure-time physical activity; TWA-MET, time-weighted average intensity metabolic equivalent; hs-CRP, high-sensitivity C-reactive protein; TNF-α, tumor-necrosis factor-α; IQR, interquartile range; IL-6, interleukin-6.

negative relationship with years of education, HDL cholesterol level among males, LTPA, and IL-6 concentration. LMI was negatively associated with body fat percentage and total cholesterol level, whereas the association was positive with plasma glucose concentration and LTPA. Office measured BP components, with the exception of PP, showed a positive relationship with both FMI and LMI. The interaction between FMI and LMI was significant only for BMI and waist circumference among women.

Spearman's correlation coefficient showed only a weak positive correlation between LMI and hs-CRP level [$r = 0.15$ (95% CI: 0.06 to 0.23)], but there was no association between LMI and TNF-α [$r = -0.02$ (95% CI: -0.11 to 0.06)] or IL-6 [$r = -0.04$ (95% CI: -0.12 to 0.05)] levels.

When adjusted for age, sex, smoking, and LTPA, both FMI and LMI showed a positive association with daytime and 24 h mean BP variables except PP values. Only FMI had a main effect on night-time BP values. There were no interaction effects between FMI and LMI on the mean AMBP levels. (Table 2)

Table 3 shows correlation coefficients between the office BP and 24 h AMBP values and components of BMI. There was a statistical difference between unadjusted and adjusted (age, sex, smoking, and LTPA) office DBP and 24 h DBP regarding FMI.

In multiple regression analysis, both FMI and LMI showed a positive small-moderate relationship with all 24 h AMBP components independently of age, sex, smoking, and LTPA. (Fig. 2).

Discussion

The novel finding of this study is that adult lean body mass is a significant determinant of BP levels with an equal, albeit small to moderate magnitude as fat mass. The relationship between BP and lean body mass is positive irrespective of age, sex, smoking, and LTPA.

Given that muscle mass is the major constituent of lean body mass, it is probable that high muscle mass explains the positive relationship between high LMI and BP levels. Generally, muscle mass has been considered beneficial to health, and it is not known whether there is a threshold value above which muscle mass is no more advantageous.

Skeletal muscle cells produce and secrete cytokines called myokines. Chronically increased systemic concentrations of myokines IL-1β, IL-6, IL-8, IL-10, and TNF-α have been linked to the development of many diseases associated with inflammation and endothelial dysfunction [18]. We hypothesized that these myokines could mediate the effect of muscle mass on blood pressure. However, we found no evidence for this since LMI was not associated with IL-6, TNF-α or hs-CRP. It should be noted that IL-6 is produced and secreted only when muscle fibres contract, but TNF-α only after extremely high-intensity physical activity [19]. The laboratory tests in our study were collected in the morning before any strenuous activities, which might explain the lack of associations. Interestingly, the positive relationship between LMI and AMBP levels at daytime was not observed during night-time BP measurements. Thus, it may be possible that the elevated muscle mass *per se* does not raise BP levels, but muscle contraction and subsequent myokine release at daytime is sufficient to raise also 24 h AMBP levels. The role of muscle mass in BP regulation has recently been suggested in a Mendelian randomization analyses in which BMI, but not central adiposity, was causally associated with higher IL-6 and also ECG measures indexing left ventricular hypertrophy [9].

The relationship of both LMI and FMI with all 24 h AMBP components was independent of current LTPA, but it is possible that the associations could be explained by the participants' earlier LTPA. Laine et al. have shown that Finnish male former elite athletes in endurance sports (long- and middle-distance running, cross country skiing) had lower risk for hypertension than their matched controls in later life even after adjustment for present LTPA [20]. This favorable effect was not detected in groups of former athletes engaged in mixed sports (soccer, ice hockey, basketball, track and field: jumpers, sprinters, hurdles, decathletes) and power sports (boxing, wrestling, weight lifting, track and field throwers) which typically involve intensive resistance training [20]. Thus, it is reasonable to assume that resistance training in order to raise muscle mass is not advisable to BP control. In this regard, the current European recommendation for moderate-intensity resistance

Table 2
Ambulatory blood pressure and heart rate according to fat mass index (FMI) and lean mass index (LMI). Adjusted for age, sex, smoking, and leisure-time physical activity. Values are means (standard deviations).

	FMI low		FMI high		P-value		
					Main effect		Interaction
	LMI low	LMI high	LMI low	LMI high	FMI	LMI	
Daytime (mmHg)							
SBP	125 (14)	131 (12)	128 (13)	133 (13)	0.009	0.019	0.75
DBP	77 (9)	83 (8)	78 (9)	83 (9)	0.003	0.020	0.45
PP	48 (11)	48 (7)	50 (10)	50 (9)	0.27	0.20	0.81
MAP	94 (10)	99 (9)	96 (10)	100 (10)	0.002	0.025	0.57
Night-time (mmHg)							
SBP	112 (14)	116 (11)	116 (13)	120 (14)	<0.001	0.054	0.89
DBP	67 (8)	70 (8)	67 (8)	71 (9)	0.003	0.24	0.95
PP	46 (10)	46 (6)	49 (9)	49 (9)	0.014	0.064	0.78
MAP	83 (10)	86 (9)	85 (9)	88 (10)	<0.001	0.15	0.91
24-hour (mmHg)							
SBP	121 (14)	126 (11)	124 (12)	129 (13)	0.001	0.024	0.94
DBP	74 (8)	79 (7)	74 (8)	79 (8)	<0.001	0.045	0.68
PP	47 (10)	47 (6)	49 (9)	50 (9)	0.097	0.13	0.78
MAP	89 (9)	94 (8)	91 (9)	95 (9)	<0.001	0.024	0.78
Heart rate (beats/min)							
Daytime	75 (10)	72 (10)	75 (8)	77 (11)	0.001	0.47	0.003
Night-time	65 (8)	63 (9)	66 (9)	67 (12)	<0.001	0.97	0.11
24-hours	72 (9)	69 (9)	72 (8)	74 (11)	<0.001	0.48	0.004

Abbreviations: FMI, fat mass index; LMI, lean mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure

Table 3
Unadjusted and adjusted correlations (Pearson) between office and 24-hour blood pressure values and components of body mass index. Adjusted for age, sex, smoking, and leisure-time physical activity.

	Systolic BP		Diastolic BP	
	Office	24 h	Office	24 h
FMI				
Crude	0.19 (0.11 to 0.27)	0.10 (0.02 to 0.19)	0.14 (0.05 to 0.22)	-0.06 (-0.14 to 0.03)***
Adjusted	0.22 (0.14 to 0.30)	0.19 (0.09 to 0.28)	0.24 (0.16 to 0.31)	0.10 (0.02 to 0.18)***
LMI				
Crude	0.16 (0.07 to 0.24)	0.15 (0.06 to 0.23)	0.15 (0.07 to 0.23)	0.10 (0.02 to 0.19)
Adjusted	0.17 (0.09 to 0.26)	0.15 (0.07 to 0.24)	0.16 (0.07 to 0.24)	0.10 (0.02 to 0.18)

Statistical significance calculated using Sidak-adjusted probabilities *p<0.05, **p<0.01, *** p<0.001**Abbreviations**: BP, blood pressure; FMI, fat mass index; LMI, lean mass index

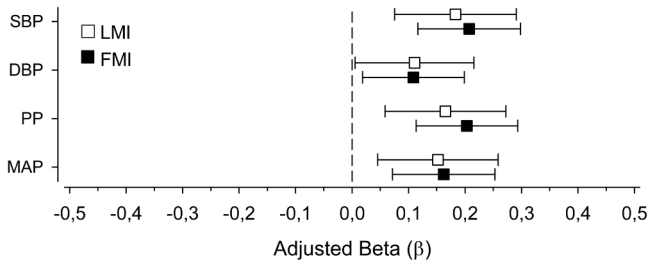

Fig. 2. Magnitude of the simultaneous effect of lean mass index (LMI) and fat mass index (FMI) as continuous variables on the ambulatory blood pressure components. Beta (β) values with 95% confidence intervals were adjusted for age, sex, smoking, and leisure-time physical activity.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure

training as an adjunct to aerobic exercise seems to be appropriate [21].

Recently, a report from the Health Professionals Follow-up Study utilized estimates of body fat mass and muscle mass derived from validated anthropometric prediction equations [22]. Compared with men in the lowest fifth of predicted fat or lean body mass, those in the highest fifth had hazard ratios of 1.67 (95 % CI 1.47 to 1.89) or 1.11 (95 % CI 0.99 to 1.24) for cardiovascular death, respectively [22]. Although the association of predicted lean body mass and mortality from cardiovascular disease did not quite reach statistical significance (P value for trend 0.10) [22], the results give support to our finding that high muscle mass may not be beneficial to cardiovascular health. It must also be noted that, although difficult to prove definitely, the relationship between fat mass and lean mass may partly be a result of the extra load caused by excess fat mass. This load serves as a long-term training stimulus leading to higher muscle mass and strength [23].

There is also evidence that lipid depots within muscle cells (intramyocellular lipid, IMCL) are associated with risk of arterial stiffness and may thus be a risk factor for elevated BP [24]. Identification of IMCL droplets is possible with proton magnetic resonance spectroscopy but not with the bioimpedance method used in our study.

It appears unlikely that the other components of lean body mass, i.e. bones and organs, might contribute to the association of BP and LMI. Of note, the magnitude of the effect of both LMI and FMI on BP levels was only small to moderate in our study. According to the Poiseuilleś law, the diameter of an artery plays by far the greatest role of all factors determining the rate of blood flow through a vessel [25]. Thus, body dimensions rather than body mass components, may have the major impact on BP levels. Indeed, we have shown in this study population that the relationship between BP and height is independent of BMI up to a BMI level of 27–28 kg/m^2 [26]. BMI diminishes the impact of height on body size by dividing body mass by the square of height. Another important limitation of BMI is that persons with high lean body mass and low body fat mass – who are mostly men – may be regarded as overweight or obese without an excess of body fat mass. Our results suggest that in persons without cardiovascular disease needing medication, body mass is not a major determinant of BP level.

This study is cross-sectional, which prevents us to define any causal relationships between LMI or FMI and BP levels. There is the potential for instrument bias in the bioimpedance analyses for FMI and LMI. However, the multifrequency bioimpedance technology used in our study with palm and sole electrodes has been shown to be sufficiently accurate at the group level also in the age group of our study participants [27]. The age range of our study participants was 57–70 years, which limits the generalization of the results to other age groups. However, by using AMBP we were able to measure circadian BP levels, and by excluding patients with vasoactive medications we could observe exclusively the relation between BP and body composition.

Conclusions

Both components of BMI, i.e. lean body mass and fat mass, have a positive but only small to moderate association with daytime and 24 h AMBP components. Relatively high muscle mass may not be beneficial to BP regulation. The current European recommendation for moderate-intensity resistance training as an adjunct to aerobic exercise seems to be appropriate [21].

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Declarations of Competing Interest

None.

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