|  |
| --- |
| **Associations of body fat and skeletal muscle with hypertension** |

Han TS, MA, MB BChir, PhD1,2, Al-Gindan YY, PhD3,4, Govan L, PhD,5 Hankey CR, PhD3, Lean MEJ, MA, MB BChir, MD, FRCP3\*

1Institute of Cardiovascular Research, Royal Holloway, University of London, Egham, UK.

2Department of Diabetes and Endocrinology, Ashford and St Peter’s NHS Foundation Trust, Chertsey, UK

3Human Nutrition, School of Medicine, University of Glasgow, Glasgow, UK.

4Department of Clinical Nutrition, Imam Abdulrahman bin Faisal University, Saudi Arabia.

5Health Economics and Health Technology Assessment, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK.

**Running title**: Fat, muscle and hypertension

**Word count**: manuscript = 2831, abstract = 250

**Number of tables**: 3, **Number of figures**: 3, **Supplemental material**: 1

**Keywords:** ageing, blood pressure, diabetes, health surveys, obesity.

**\*Corresponding author:** Dr TS Han, MA, MB BChir, PhD

Institute of Cardiovascular Research, Royal Holloway

University of London, Egham, Surrey, TW20 0EX, UK

Telephone: (UK)+01784443807, Email: thang.han@rhul.ac.uk

**ABSTRACT**

Hypertension is known to be associated with obesity, while its relationship to skeletal muscle (a marker of general health and body function), remains uncertain.We analysed population-based data of 22,591 men (mean age: 51.6±16.9yrs) and 27,845 non-pregnant women (50.6±16.9yrs) from Scottish Health Surveys (2003, 2008-2011) and Health Surveys for England (2003-2006, 2008-2013) including 2,595 non-insulin and 536 insulin treated diabetic patients. Compared with normotensive individuals (no hypertension history with normal systolic (SBP<140mmHg) and diastolic blood pressure (DBP<90mmHg)), percent body fat (BF%) was significantly higher and percent skeletal muscle (SM%) lower (*P*<0.001) in undetected (no hypertension history with raised SBP≥140 and/or DBP≥90mmHg), controlled (hypertension history with normal BP), uncontrolled (hypertension history with raised BP) and untreated hypertension. Prevalences of hypertension within BF% quintiles were 11.8, 24.8, 41.4, 56.8 and 71.6% and SM% quintiles were 67.5, 53.3, 39.5, 27.4, and 18.5%. Compared to referent groups (lowest BF% quintile or highest SM% quintile), odds ratio (age, sex, smoking, ethnicity, country, survey-year and diabetes adjusted) for having all types of hypertension in the highest BF% quintile was 5.5 (95% confidence interval=5.0-5.9) and lowest SM% quintile was 2.3 (2.2-2.5). Compared with those without diabetes, individuals with diabetes had a 2.3-2.6 fold greater risk of hypertension, independent of confounding factors and BF% or SM%. The associations of hypertension with BF% were higher than those with body mass index (BMI). In conclusion, both BF and SM should be considered when analysing results from health surveys, rather than relying on BMI which does not discriminate between the two.

**INTRODUCTION**

There is increasing interest in skeletal muscle mass and related health outcomes, especially with the population in the UK, which are ageing and becoming more obese.1,2 Muscle wasting and obesity are both age-related conditions which associate with a constellation of chronic diseases and polypharmacy.3,4 Hypertension is among the most prevalent age-related chronic diseases, affecting 29.4% of male and 26.5% of adult (≥18 years) female whites, 40.8% of male and 41.5% of female coloured people in the US between 2011 and 2014.5 Raised blood pressure (below treatment threshold) is a feature of the metabolic syndrome which is associated with an increased risk of cardiovascular disease by two to three fold6,7 and with renal complications.8

Hypertension is a ‘silent killer’7 commonly only revealed in routine health screening, which is seldom conducted below age 40 in many countries.9 Non-adherence to prescribed medications, including antihypertensives, is estimated at between 40 and 75% among older adults.10-13 Hypertension still follows the “rule of halves” in many countries; with half of all individuals with hypertension are diagnosed, but among those diagnosed, only half receive appropriate care, and only half of those treated reach treatment targets.14,15

Although the association of hypertension with body fatness is well established, little is known about its association with skeletal muscle. Both may relate to adverse lifestyles such as inactivity and smoking.

The present study was conducted to document the associations of hypertension status (normotension, undetected, adequately controlled, inadequately controlled and untreated hypertension) with body fat (BF) and with skeletal muscle (SM), assessed by validated equations using anthropometric data collected in large national surveys.

**METHODS**

**Study population**

This analysis utilized cross-sectional data from the Scottish Health Survey (SHS) collected in 2003 and 2008-2011 (n=92,216) and Health Survey for England (HSE) collected in 2003-2006 and 2008-2013 (n=140,627). The surveys followed identical methods. Subjects younger than 18 years or over 85 years were excluded as they were outside the age-range of the adult populations used to derive the equations for estimating BF and SM. Pregnant women were excluded. Among those remaining, complete-case data for anthropometric measurements, BF, SM and hypertension status were available for analysis in 22,591 men (mean age: 51.6±16.9yrs) and 27,845 women (50.6±16.9yrs).

**Demographic and anthropometric assessment**

Participants were visited at home by trained nurses who recorded demographic information including age, sex, ethnicity, smoking status, medical history, and treatment by standard health and lifestyle questionnaires. Smoking status was reported in categories (never smoked, used to smoke occasionally, used to smoke regularly, current smoker). Prescriptions of drug classes for diabetes (oral antihyperglycaemic agents and/or insulin) and blood pressure (antihypertensive agents) were documented from the responses “yes” or “no”. Specific drug names were not included. The trained nurses also measured weight, height, waist and hip circumferences using calibrated instruments. Participants were asked to wear light clothing and stand upright in a relaxed position to maximal height, feet 25–30cm apart. Waist circumference (WC) was measured midway between the iliac crest and lowest rib, and hip circumference at the largest circumference around the buttocks.

**Body fat and skeletal muscle calculations**

Percentage body fat was calculated using validated published equations for men: BF% = 0.567 × WC (cm) + 0.101 × age (years) – 31.8 and for women: BF%) = 0.439 × WC (cm) + 0.221 × age (years) – 9.4.16 SM was calculated using published validated equations for men: SM (kg) = 39.5 + 0.665 × body weight (kg) − 0.185 WC (cm) − 0.418 × hip circumference − 0.08 × age (years), and for women: SM (kg) = 2.89 + 0.255 × weight (kg) − 0.175 × hip circumference (cm) − 0.038 × age (years) + 0.118 × height (cm).17 SM was expressed as percent body weight (SM%) for analysis.

**Diabetes status**

Glycated haemoglobin (HbA1c) was measured in non-fasting blood samples. Diabetes mellitus was identified firstly from participants reporting that the diagnosis had been confirmed by a doctor or a nurse, or secondly as newly diagnosed on the basis of having HbA1c >48mmol/mol (>6.5%) without previously diagnosed diabetes (n=2,595 non-insulin and 536 insulin treated).

**Blood pressure and hypertension status**

Systolic (SBP) and diastolic blood pressure (DBP) were measured on a single occasion, using an automatic sphygmomanometer (Dinamap 8100, Critikon, Tampa, FL, USA) at the first and fifth Korotkoff sounds. Participants were rested for 10-15 minutes in sitting position. The cuff size was selected according to the size of participant’s mid-upper arm circumference. History of hypertension was obtained from participants reporting whether the diagnosis had been confirmed by a doctor or a nurse. Newly identified or level of control of hypertension was assessed from SBP and DBP measured at the time of survey. Five groups of hypertension status were created: 1) “normotension” (no history of hypertension with SBP <140 mmHg and DBP <90 mmHg), 2) “undetected hypertension” (no history of hypertension with SBP ≥140 mmHg and/or DBP ≥90 mmHg), 3) “adequately controlled hypertension” (history of hypertension with SBP <140 mmHg and DBP <90 mmHg ), 4) “inadequately controlled hypertension” (history of hypertension with ≥140 mmHg and/or DBP ≥90 mmHg) and 5) “untreated hypertension” (history of hypertension without treatment, with SBP ≥140 mmHg and/or DBP ≥90 mmHg).15

## Statistical analysis

Group differences for categorical variables were assessed by chi-squared test and for continuous variables by independent t-test (between two groups) or analysis of variance, ANOVA (between more than two groups). The associations of hypertension (dependent variables) with quintiles of body mass index (BMI), WC, BF% and SM% (predictor variables) were assessed by logistic regression analysis to estimate odds ratios (OR) and 95% confidence intervals (CI). Lowest BF% quintile or highest SM% quintile was considered as referent group. Data were adjusted for age, sex, smoking status (non-smokers and current or ex-smokers), ethnicity (white Caucasians or others), survey year, country and diabetes status (no diabetes, diabetes treated with oral antihyperglycaemic agents or insulin). Missing data were handled in analysis using a ‘listwise deletion of missing data’ approach. Analyses were conducted using SPSS (version 23.0). The null hypothesis was rejected when *P*<0.05.

## RESULTS

Men and women had similar mean (±SD) age (51.6 yrs ±16.9 v.s. 50.6 yrs, ±116.9), BMI (27.8 kg/m2 ±4.4 v.s. 27.4 kg/m2, ±5.5) and hip circumference (104.4 cm ±10.2 v.s. 104.1 cm ±13.9). Men were taller (174.4 cm ±7.2 v.s. 161.0 cm ±6.8, *P*<0.001) and heavier (84.7 kg ±14.8 v.s. 71.0 cm ±14.7, *P*<0.001) and had larger WC (98.8 cm ±12.2 v.s. 88.0 cm ±13.2, *P*<0.001), SM (29.7 kg ±6.2 v.s. 19.8 kg, ±3.0, *P*<0.001), SM% (35.3% of body weight ±5.3 v.s. 28.5% of body weight, ±4.3, *P* <0.001), SBP (132.0 mmHg ±16.1 v.s. 125.6 mmHg ±19.0, *P*<0.001) and DBP (75.0 mmHg ±11.2 v.s. 73.5 mmHg ±10.8, *P*<0.001) while women had higher BF than men (29.4 kg ±11.5 v.s. 25.6 kg, ±8.3, *P*<0.001) and BF% (40.4% of body weight ±7.7 v.s. 29.4% of body weight, ±7.6, *P*<0.001).

**Table 1** shows the distribution of demographic factors and prevalences of hypertension. The prevalence of hypertension increased with age, and was higher in men than in women, in current and ex-smokers than in non-smokers, in white Caucasians than in ethnic minorities and in individuals with diabetes than in those without diabetes. There were no differences in the prevalence of hypertension between England and Scotland.

The ANOVA showed that compared with normotensive individuals, BF% was significantly higher and SM% lower (*P*<0.001) in any sub-category of hypertension; undetected, adequately controlled, inadequately controlled and untreated hypertension (**Table 2**). **Figure 1** shows that compared with referent groups of normotensive individuals, BF% was significantly (*P*<0.001) higher and SM% lower in all subcategories of hypertension in men and women. For any given subcategory of hypertension, patients with diabetes had higher BF% and lower SM% than those without diabetes.

**Table 3** shows that the prevalences of any type of hypertension sub-category within BF% quintiles were 11.8, 24.8, 41.4, 56.8 and 71.6%, within SM% quintiles were 67.5, 53.3, 39.5, 27.4, and 18.5%, and within non-diabetic individuals, non-insulin treated and insulin treated diabetic individuals were 39.0, 76.4 and 70.9% respectively. There were consistently more diabetic patients with hypertension than non-diabetic individuals within each quintile of BF% (**Figure 2A**) and SM% (**Figure 2B**).

Compared to referent groups (lowest BF% quintile or highest SM% quintile), adjusted OR for having all types of hypertension in the highest BF% quintile was 5.5 (95%CI = 5.0-5.9) and in the lowest SM% quintile was 2.3 (confidence interval = 2.2-2.5). The association of BMI (OR = 4.3, 95%CI = 4.1-4.7) or WC (OR = 4.1, 95%CI = 39-4.5) with hypertension (**Supplemental material**) was lower than the association of BF% with hypertension (see above). Compared with those without diabetes, individuals with diabetes had a 1.9 to 2.6-fold increase in the risk of hypertension, independent of confounding factors and BF% or SM% (**Table 3**). Excluding patients with diabetes from analysis showed marginal changes to the results (not shown).

The proportions of hypertension in men and in women aged 18-29years = 10.4% and 2.8%, 30-39years = 14.7% and 6.5%, 40-49years = 23.8% and 14.2%, 50-59years = 33.2% and 25.9%, 60-69years = 40.4% and 38.9%, 70-79years = 44.0% and 47.1%, and 80-85years = 47.6% and 52.5%. **Figure 3** shows that the proportions of subjects with normotension fall while undetected, controlled, uncontrolled and untreated hypertension rise with increasing age (*P*<0.001).

**DISCUSSION**

In the present study, we have observed that hypertension was associated directly with BF% and inversely with SM%. Those associations remain statistically significant independently of major factors including age, sex, smoking and ethnic background as well as diabetes. Within each subcategory of hypertension, BF% was higher and SM% was lower than normotensive group while within each level of BF% and SM%, hypertension was more prevalent among those with diabetes.

Existing research often focuses on obesity and hypertension18 while the relationship between the role of SM and hypertension has received little attention. Our findings of the significant inverse association between hypertension and SM% may provide further insight into the aetiology of hypertension. A study by Ochi et al19 has shown an inverse association between arterial stiffness and thigh muscle mass in middle-aged to elderly men. We cannot deduce causal relationship between these variables from cross-sectional data but it is plausible that the relationship is bidirectional with multiple mediating factors. Ageing, chronic conditions and medications, lifestyle factors such as smoking, physical inactivity, and alcohol consumption all interplay and modulate changes in blood pressure and muscle mass.

Aside from the main results, the present study also revealed that diabetic individuals had higher BF% and lower SM% for any given hypertensive status, illustrating the complex interaction between altered body composition, insulin and hypertension. This extends our recent observations which identified the inverse association of HbA1c and type 2 diabetes with SM%.20 A combination of increased body fat and muscle wasting may lead to insulin resistance through molecular/hormonal changes in adipocytes and myocytes, and consequently hypertension.6,21 This process could be similar to Cushing’s disease, where an excessive concentration of cortisol produces central fat accumulation and skeletal muscle atrophy, accompanied by hypertension and insulin resistance/diabetes. It is most commonly accepted that hypercortisolaemia in Cushing’s disease leads to hypertension through increased insulin secretion (resulting in sodium retention) and activation of renin-angiotensin aldosterone system (resulting in increased vascular resistance).22,23 In contrast, hypertension in phaemochromocytoma is secondary to excess catecholamines24 with reduced intra-abdominal fat of brown adipose tissue origin.25 Surgical treatment of Cushing’s disease22,23 or phaeochromocytoma26 usually simultaneously cures the hypertension and also improves insulin sensitivity.

Our observations of increasing hypertension prevalence with age are consistent with previous reports.5 The finding that higher proportions of men than women with hypertension in the younger age groups is interesting, as the rates became approximately equal by the age of 60years, and higher among older women. This may help to explain some of the gender disparities in cardiovascular disease at different ages and supports earlier screening for hypertension (before the age of 40 years when screening usually begins).

The rates of undetected, inadequately controlled and untreated hypertension in the present study are comparable with those observed in developed countries7 and as expected, lower than middle income countries such as China.15 We found these subcategories of hypertension rise significantly with increasing age. These findings are consistent with previous reports of high non-adherence to medications (40-75%) among older adults.10-13 It is therefore important to focus research and treatment on this high risk group to elucidate the perpetual cycle of hypertension and frailty and disability arising from conditions secondary to undetected, uncontrolled or untreated hypertension such as stroke.15

**Strengths and limitations**

In the present analysis, we recognise the strengths of a large well-conducted national survey which employed well-tried standard methods, and we addressed a number of possible limitations. Some, such as the single measurement of blood pressure, and reliance on anthropometric estimates of body composition were inevitable in the context of large national surveys: these are unlikely to have introduced bias, but both methods would increase random error. For these limitations, the large study number allows confidence in the results. We used the conventional SBP and DBP cut-offs at 140 and 90 mmHg to define ‘hypertension’, at the same levels for diabetic and non-diabetic participants. We considered whether the lower treatment threshold for participants with known diabetes (130/80 mmHg in NICE guidelines27) might have affected the relationship between body composition for those on treatment with BP below 140/90. There were 842 participants with known diabetes on anti-hypertensive medication and SBP <140 and DBP <90 mmHg. Excluding these participants did not change the overall findings. We analysed all groups of participants together using two models to assess the effects of adjustments for confounding factors and diabetes on the association between blood pressure and body composition. The additional adjustment with diabetes only reduced the associations slightly, and did not change the conclusions. We have also tried excluding the diabetic group from analysis and found negligible changes to the results. Multiple logistic regression modelling allowed us to assess the associations of the main outcome measures independent of confounding factors. To avoid structural multicollinearity, we did not attempt adjusting BF% and SM% for each other since the equations to estimate these measures contain overlapping variables including age, weight, height and WC.28

Our analysis used a large dataset, with detailed measurements made using consistent methods in representative adult national populations. The populations under study included mainly white Europeans, with relatively small numbers of individuals from specific ethnic or racial origins among whom the associations may be different. Adjusting the analyses for potential confounders (age, sex and smoking) had little effect on the associations. This large dataset allowed us to examine extensively the differences in subcategories of hypertension, age and diabetes status in relation to body composition. Information on alcohol consumption and physical activity level was not available in the present study, but may have some bearing on the results. The cross-sectional study design precludes robust inference about the causal direction between variables, but there is supporting evidence from other studies that lifestyle factors including physical activity in particular probably play a large part by affecting blood pressure and also body composition.29-31 Regular exercise increases and preserves muscle mass, and also lowers blood pressure through a number mechanisms including activation of β-adrenergic system, leading to vasodilatation.32 We did not have information on specific pharmacological therapies which may have affected the relationship between body composition and blood pressure. Insulin is well recognised to promote adiposity and blood pressure, and we have examined those on insulin and on oral antihyperglycaemic drugs separately. A recent study of patients undergoing coronary bypass graft has shown that compared with patients receiving conservative insulin therapy (HbA1c between 48 and 63 mmol/mol), those receiving intensive insulin treatment (HbA1c between 32 and 48 mmol/mol) had significantly lower hospitalisation costs and resource utilisation.33 We have therefore presented diabetic patients treated with oral antihyperglycaemic agents and those with insulin separately to assess any bias introduced to the results among non-diabetic individuals. We acknowledge that other source of bias and imprecision may occur in national surveys, including inter-observer differences in recording measurements while changes in circadian rhythm may alter an individual’s anthropometry16 and blood pressure.34 Blood pressure may also be falsely raised when an individual encounters a health professional, the “white coat syndrome”. In common with most national surveys, blood pressure in our study was measured once, as cost and participant retention are important. Accuracy could in principle be improved by duplicate or triplicate measurements or by 24 or 48 hour ambulatory blood pressure monitoring,34 but these are more time-consuming, increase the burdens on participants and more expensive. There might have been some inaccuracy in self-reporting of medical conditions by the participants. However, previous studies have found questionnaire data and medical records to have good agreement for common chronic diseases that have clear diagnostic criteria including hypertension and diabetes.35

**Conclusions**

Blood pressure is inversely associated with muscle mass, as well as positively with fat mass. Estimates of both body fat and skeletal muscle mass should be considered when analysing results from health surveys (using validated anthropometric prediction equations if measurements are not possible), rather than relying on BMI which does not discriminate between the two.

**Contributors**

The original idea of this study was proposed by TSH and MEJL. TSH analysed the data and wrote the first draft of this paper. YYA-G, LG, CRH and MEJL edited subsequent drafts. All authors have read and approved the final version of the manuscript for submission.

**Funding**

None.

**Competing interests**

The authors declare no relevant or conflicting interests.

**REFERENCES**

1. Baumgartner RN, Wayne SJ, Waters DL, Janssen I, Gallagher D, Morley JE. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. *Obesity*. 2004;12:1995-2004.
2. Zamboni M, Mazzali G, Fantin F, Rossi A, Di Francesco V. Sarcopenic obesity: a new category of obesity in the elderly. *Nutr Metab Cardiovasc Dis*. 2008;18:388-395.
3. Sergi G, De Rui M, Sarti S, Manzato E. Polypharmacy in the elderly: can comprehensive geriatric assessment reduce inappropriate medication use? *Drugs Aging.* 2011;28:509-518.
4. Charlesworth CJ, Smit E, Lee DS, Alramadhan F, Odden MC. Polypharmacy among adults aged 65 years and older in the United States: 1988–2010. *J Gerontol A Biol Sci Med Sci.* 2015;70:989-995.
5. Yoon SS, Fryar CD, Carroll MD. Hypertension prevalence and control among adults: United States, 2011-2014. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 2015.
6. Han TS, Lean ME. A clinical perspective of obesity, metabolic syndrome and cardiovascular disease. *JRSM Cardiovasc Dis.* 2016;5:2048004016633371.
7. World Health Organization. A Global Brief on Hypertension, Silent Killer, Global Public Health Crisis. Geneva: WHO; 2013. (Document Number: WHO/ DCO/WHD/2013.2).
8. Luk AO, So WY, Ma RC, Kong AP, Ozaki R, Ng VS, Linda WL, Lau WW, Yang X, Chow FC, Chan JC, Tong PC; Hong Kong Diabetes Registry. Metabolic syndrome predicts new onset of chronic kidney disease in 5829 patients with type 2 diabetes: a 5-year prospective analysis of the Hong Kong Diabetes Registry. *Diabetes Care*. 2008;31:2357-2361.
9. Public Health England. Health matters: combating high blood pressure. Published 24 January 2017. [www.gov.uk/government/publications/health-matters-combating-high-blood-pressure/health-matters-combating-high-blood-pressure](http://www.gov.uk/government/publications/health-matters-combating-high-blood-pressure/health-matters-combating-high-blood-pressure) [accessed June, 2018].
10. Myers LB, Midence K. Adherence to treatment in medical conditions. Amsterdam, Harwood Academic, 1998.
11. Bloom BS. Daily regimen and compliance with treatment: fewer daily doses and drugs with fewer side effects improve compliance. *BMJ*. 2001;323:647.
12. Sabaté E, editor. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
13. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: A randomized controlled trial. *JAMA.* 2006;296:2563-2571.
14. Scheltens T, Bots ML, Numans ME, Grobbee DE, Hoes AW. Awareness, treatment and control of hypertension: the ‘rule of halves’ in an era of risk-based treatment of hypertension. *J Hum Hypertens.* 2007;21:99-106.
15. Han TS, Wang HH, Wei L, Pan Y, Ma Y, Wang Y, Wang J, Hu Z, Sharma P, Chen R. Impacts of undetected and inadequately treated hypertension on incident stroke in China. *BMJ Open*. 2017;7:e016581.
16. Lean ME, Han TS, Deurenberg P. Predicting body composition by densitometry from simple anthropometric measurements. *Am J Clin Nutr*.1996;63:4-14.
17. Al-Gindan YY, Hankey C, Govan L, Gallagher D, Heymsfield SB, Lean ME. Derivation and validation of simple equations to predict total muscle mass from simple anthropometric and demographic data. *Am J Clin Nutr*. 2014;100:1041-1051.
18. Rahmouni K, Correia ML, Haynes WG, Mark AL. Obesity-associated hypertension: new insights into mechanisms. *Hypertension.* 2005;45:9-14.
19. Ochi M, Kohara K, Tabara Y, Kido T, Uetani E, Ochi N, Igase M, Miki T. Arterial stiffness is associated with low thigh muscle mass in middle-aged to elderly men. *Atherosclerosis.* 2010;212:327-332.
20. Han TS, Al-Gindan Y, Hankey CR, Lean MEJ. Associations of BMI, waist, body fat and skeletal muscle with type 2 diabetes and HbA1c in adults. 35th Annual Meeting of the American Society for Metabolic and Bariatric Surgery. *Surg Obes Relat Dis*. 2018 Nov (in press) [Abstract: T-P-3107].
21. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. *Diabetes Care.* 2009;32(suppl 2):S157-S163 .
22. Sacerdote A, Weiss K, Tran T, Noor BR, McFarlane SI. Hypertension in patients with Cushing’s disease: pathophysiology, diagnosis, and management. *Curr Hypertens Rep.* 2005;7:212-218.
23. Pivonello R, De Leo M, Cozzolino A, Colao A. The treatment of Cushing's disease. *Endocr Rev*. 2015;36:385-486.
24. Zuber SM, Kantorovich V, Pacak K. Hypertension in pheochromocytoma: characteristics and treatment. *Endocrinol Metab Clin North Am.* 2011;40:295-311.
25. Lean ME. Brown adipose tissue in humans. *Proc Nutr Soc.* 1989;48:243-56.
26. Wiesner TD, Bluher M, Windgassen M, Paschke R. Improvement of insulin sensitivity after adrenalectomy in patients with pheochromocytoma. *J Clin Endocrinol Metab*. 2003;88:3632-3636.
27. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. www. nice.org.uk/guidance/ng28 (accessed June 2018).
28. Jagpal HS. Multicollinearity in structural equation models with unobservable variables. *Journal of Marketing Research*. 1982:431-439.
29. Han TS, Bijnen FC, Lean ME, Seidell JC. Separate associations of waist and hip circumference with lifestyle factors. *Int J Epidemiol.* 1998;27:422-430.
30. Newby PK, Muller D, Hallfrisch J, Qiao N, Andres R, Tucker KL. Dietary patterns and changes in body mass index and waist circumference in adults. *Am J Clin Nutr*. 2003;77:1417-1425.
31. Han TS, Lee DM, Lean ME, Finn JD, O'Neill TW, Bartfai G, Forti G, Giwercman A, Kula K, Pendleton N, Punab M, Rutter MK, Vanderschueren D, Huhtaniemi IT, Wu FC, et al; EMAS Study Group. Associations of obesity with socioeconomic and lifestyle factors in middle-aged and elderly men: European Male Aging Study (EMAS). *Eur J Endocrinol.* 2015;172:59-67.
32. Santulli G, Ciccarelli M, Trimarco B, Iaccarino G. Physical activity ameliorates cardiovascular health in elderly subjects: the functional role of the β adrenergic system. *Front Physiol*. 2013;12:209.
33. Cardona S, Pasquel FJ, Fayfman M, Peng L, Jacobs S, Vellanki P, Weaver J, Halkos M, Guyton RA, Thourani VH, Umpierrez GE. Hospitalization costs and clinical outcomes in CABG patients treated with intensive insulin therapy. *J Diabetes Complications*. 2017;31:742-747.
34. Hermida RC, Ayala DE, Fontao MJ, Mojón A, Fernández JR. Ambulatory blood pressure monitoring: importance of sampling rate and duration-48 versus 24 hourr-on the accurate assessment of cardiovascular risk. *Chronobiol Int*. 2013;30:55-67.
35. Haapanen N, Miilunpalo S, Pasanen M, Oja P, Vuori I. Agreement between questionnaire data and medical records of chronic diseases in middle-aged and elderly Finnish men and women. *Am J Epidemiol*. 1997;145:762-769.

**LEGENDS**

**Figure 1.** Boxplots of the median and interquartile ranges and whiskers represent the 5th and 95th percentiles of percent body fat (BF%) by hypertension status in men (A) and in women (B) and percent skeletal muscle (SM%) by hypertension in men (C) and in women (D). Solid line indicates the median of referent normotensive non-diabetic group and dashed line indicates the median of referent normotensive diabetic group. Analysis of variance (ANOVA) for differences between groups: *P*<0.001, *post hoc* test: *P*<0.001 compared with referent normotensive group.

**Figure 2.** Proportions of hypertensive individuals with diabetes and those without diabetes in different quintiles of percent body fat (BF%) (A) and percent skeletal muscle (SM%) (B).

**Figure 3.** Proportions of subjects in different hypertension categories according to 10-year age bands in men (A) and women (B).

**Table I.** Distribution of hypertension among demographic factors and hypertension (known and newly diagnosed with systolic blood pressure ≥140 or diastolic blood pressure ≥90mmHg) in 50,436 adults without diabetesaged 18-85 years old.

|  |  |  |
| --- | --- | --- |
|  | Men (n=22,591) | Women (n=27,845) |
|  | n (% of study cohort) | Prevalence of hypertension within group | χ2 test | n (% of study cohort) | Prevalence of hypertension within group | χ2 test |
| **Total** | 22,591 (100%) | 45.4% |  | 27,845 (100%) | 37.9% | <0.001 |
| **Age (years)** |  |  |  |  |  |  |
| 18-29 | 2,915 (12.9%) | 14.5% | <0.001 | 3,830 (13.8%) | 8.1% | <0.001 |
| 30-39 | 3,612 (16.0%) | 22.0% | 4,851 (17.4%) | 13.8% |
| 40-49 | 4,146 (18.4%) | 35.6% | 5,393 (19.4%) | 24.6% |
| 50-59 | 4,243 (18.8%) | 52.6% | 5,019 (18.0%) | 43.1% |
| 60-69 | 4,208 (18.6%) | 65.7% | 4,761 (17.1%) | 62.7% |
| 70-79 | 2,808 (12.4%) | 69.5% | 3,176 (11.4%) | 77.0% |
| 80-85 | 659 (2.9%) | 73.5% | 815 (2.9%) | 79.0% |
| **Smoking status** |  |  |  |  |  |  |
| Non-smokers | 5,418 (24.0%) | 40.8% | <0.001 | 6,885 (24.7%) | 36.6% | 0.005 |
| Current and ex-smokers | 3178,161 (76.0%) | 46.9% | 20,942 (75.3%) | 38.3% |
| **Ethnicity** |  |  |  |  |  |  |
| White Caucasians | 19,709 (87.2%) | 46.8% | <0.001 | 24,207 (86.9%) | 39.3% | <0.001 |
| Others | 2,882 (12.8%) | 35.9% | 3,638 (13.1%) | 28.6% |
| **Country** |  |  |  |  |  |  |
| England | 17,584 (77.8%) | 45.2% | 0.131 | 21,533 (77.3%) | 37.8% | 0.276 |
| Scotland | 5,007 (22.2%) | 46.1% | 6,312 (22.7%) | 38.2% |
| **Co-morbidity** |  |  |  |  |  |  |
| No diabetes | 20,904 (92.5%) | 42.9% | <0.001 | 26,401 (94.8%) | 35.9% | <0.001 |
| T2D (known + newly diagnosed) | 1,421 (6.3%) | 77.3% | 1,174 (4.2%) | 75.4% |
| Insulin treated diabetes | 266 (1.2%) | 55.9% | 270 (1.0%) | 65.9% |

**Table II.** Analysis of variance (ANOVA) of adiposity and skeletal mass by different categories of blood pressure in 50,436 adult males and females.

|  |  |  |
| --- | --- | --- |
|  | Mean ±SD | ANOVA |
| **All subjects, n (%)** | Normotension(referent)29,628 (58.7%) | Undetected hypertension6,217 (12.3%) | Controlled hypertension8,071 (16.0%) | Uncontrolled hypertension4,730 (9.4%) | Untreated hypertension1.790 (3.5%) | p-value |
|  |  |  |  |  |  |  |
| **Men, n (%)** | **12,328 (54.6%)** | **3,302(14.6%)** | **3,786 (16.8%)** | **2,249 (10.0%)** | **926 (4.1%)** |  |
| Age (years) | 45.1 ±15.9 | 55.1 ±15.7 | 60.4 ±14.1  | 63.6 ±12.3 | 60.0 ±14.1 | <0.001 |
| SBP (mmHg) | 123.6 ±9.2 | 149.9 ±12.1  | 126.1 ±9.5 | 154.4 ±13.3 | 149.3 ±10.5  | <0.001 |
| DBP (mmHg) | 71.2 ±8.5 | 84.8 ±10.9 | 71.7 ±9.6 | 84.0 ±12.6 | 81.9 ±9.9 | <0.001 |
| Body mass index (kg/m2) | 26.8 ±4.1 | 28.5 ±4.3 | 29.2 ±4.5 | 29.5 ±4.5 | 29.2 ±4.4 | <0.001 |
| Waist circumference cm) | 95.4 ±11.5 | 100.8 ±11.3 | 103.6 ±11.8  | 104.7 ±11.7 | 103.7 ±11.6 | <0.001 |
| BF% (% body weight) | 26.8 ±7.2 | 30.9 ±6.7 | 33.1 ±7.0  | 34.0 ±6.7 | 33.1 ±6.7 | <0.001 |
| SM% (% body weight) | 36.7 ±5.5 | 34.5 ±4.6 | 33.3 ±4.6  | 32.7 ±4.4 | 33.6 ±4.5  | <0.001 |
|  |  |  |  |  |  |  |
| **Women, n (%)** | **17,300 (62.1%)** | **2,915 (10.5%)** | **4,285 (15.4%)** | **2,481 (8.9%)** | **864 (3.1%)** |  |
| Age (years) | 44.0 ±14.9 | 59.8 ±13.8 | 59.7 ±15.1 | 65.4 ±12.4 | 63.5 ±12.3 | <0.001 |
| SBP (mmHg) | 116.1 ±10.9 | 150.9 ±14.2 | 124.2 ±10.4 | 155.6 ±15.3 | 151.0 ±13.8 | <0.001 |
| DBP (mmHg) | 70.3 ±8.5 | 84.8 ±10.7 | 71.7 ±9.5 | 82.6 ±12.4 | 81.1 ±10.5 | <0.001 |
| Body mass index (kg/m2) | 26.2 ±5.0 | 28.8 ±5.7  | 29.5 ±5.8 | 29.8 ±5.5 | 29.2 ±5.4 | <0.001 |
| Waist circumference cm) | 84.6 ±12.2 | 91.9 ±12.9 | 94.0 ±13.3 | 94.6 ±12.5 | 93.2 ±12.8 | <0.001 |
| BF% (% body weight) | 37.5 ±6.9 | 44.1 ±6.1 | 45.0 ±7.0 | 46.6 ±5.9 | 45.6 ±6.1 | <0.001 |
| SM% (% body weight) | 29.6 ±4.3 | 27.0 ±3.6 | 26.7 ±3.7  | 26.1 ±3.4  | 26.4 ±3.3 | <0.001 |

*Post hoc* test using LSD for differences between normotension group (referent) and hypertensive groups of different treatment status: *P*<0.001.

**Table III.** Associations of sex-specific percent body fat (BF%) quintiles or percent skeletal muscle (SM%) quintiles with hypertension in 22,591 men and 27,845 women.

|  |  |  |
| --- | --- | --- |
|  | **Group differences** | **Logistic regression to assess the risk for having hypertension** |
|  | **Model 1: Adjusted for age, sex, smoking, ethnicity, survey year and country‡** | **Model 2 Adjusted for age, sex, smoking, ethnicity, survey year, country and diabetes§** |
| **Body fat** | **n** | **Rates of hypertension (%)** | ***p*†** | **OR (95% CI)** | ***p*** | **OR (95% CI)** | ***p*** |
| BF% quintile 1 (% weight): M <23.1, F <33.4 (referent) | 10087 | 11.8 | <0.001 | 1 | -- | 1 | -- |
| BF% quintile 2 (% weight): M = 23.1-27.4, F = 33.4-38.1 | 10085 | 24.8 | 1.48 (1.37-1.61) | <0.001 | 1.48 (1.37-1.61) | <0.001 |
| BF% quintile 2 (% weight): M = 27.4-31.2, F = 38.1-42.4 | 10088 | 41.4 | 2.39 (2.21-2.59) | <0.001 | 2.38 (2.20-2.58) | <0.001 |
| BF% quintile 4 (% weight): M = 31.2-35.6, F = 42.4-47.2 | 10087 | 56.8 | 3.58 (3.31-3.89) | <0.001 | 3.52 (3.25-3.82) | <0.001 |
| BF% quintile 5 (% weight): M ≥35.6, F ≥47.2 | 10089 | 71.6 | 5.83 (5.36-6.35) | <0.001 | 5.45 (5.00-5.93) | <0.001 |
| No diabetes (referent) | 47,305 | 39.0 | <0.001 | -- | -- | 1 |  |
| Diabetes on oral antihyperglycaemic agents | 2,595 | 76.4 | -- | -- | 1.93 (1.74-2.13) | <0.001 |
| Insulin treated diabetes | 536 | 70.9 | -- | -- | 2.33 (1.87-2.89) | <0.001 |
| **Skeletal muscle** |  |  |  |  |  |  |  |
| SM% quintile 5 (% weight): M ≥38.2, F ≥31.4 (referent) | 10087 | 18.5 | <0.001 | 1 | -- | 1 | -- |
| SM% quintile 4 (% weight): M = 36.0-38.2, F = 29.0-31.4 | 10087 | 27.4 | 1.17 (1.09-1.25) | <0.001 | 1.17 (1.09-1.26) | <0.001 |
| SM% quintile 3 (% weight): M = 34.0-36.0, F = 27.2-29.0 | 10088 | 39.5 | 1.45 (1.35-1.56) | <0.001 | 1.45 (1.35-1.56) | <0.001 |
| SM% quintile 2 (% weight): M = 31.6-34.0, F = 25.1-27.2 | 10087 | 53.3 | 1.84 (1.71-1.98) | <0.001 | 1.83 (1.70-1.97) | <0.001 |
| SM% quintile 1 (% weight): M <31.6, F <25.1 | 10087 | 67.5 | 2.41 (2.23-2.61) | <0.001 | 2.32 (2.15-2.51) | <0.001 |
| No diabetes (referent) | 47,305 | 39.0 | <0.001 | -- | -- | 1 | <0.001 |
| Diabetes on oral antihyperglycaemic agents | 2,595 | 76.4 | -- | -- | 2.43 (2.20-2.69) | <0.001 |
| Insulin treated diabetes | 536 | 70.9 | -- | -- | 2.60 (2.11-3.21) | <0.001 |

†χ2 test for group difference; ‡Model 1: adjusted for age, sex, smoking, ethnicity, survey year and country; **§**Model 2: as in model 1 with additional adjustment for diabetes.

**Figure 1**

(A)



(B)



(C)



(D)



**Figure 2.**

(A)



(B)



**Figure 3.**

(A)



(B)

