

Physical activity, arterial hypertension and waist circumference in men from Warmia and Masuria region in Poland

Aktywność fizyczna, nadciśnienie tętnicze i obwód pasa u mężczyzn z województwa warmińsko-mazurskiego w Polsce

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Abstract

Introduction. Regular physical activity is a recognized method of non-pharmacological prevention many chronic diseases. The aim of this study was to evaluate the prevalence of physical activity and abdominal obesity in 631 randomly selected men from Warmia and Masuria region in Poland.

Material and methods. 631 men from the Warmia and Mazury region in age of 19–82 years (47.2 ± 13.7 years) were examined between Dec 2014 and Dec 2016. Participants completed standardized questionnaire. Anthropometric measurements were performed. BP was measured. In serum of 398 participants glucose and lipidogram were measured. Analyses were performed separately for three groups depending on time of physical activity in week: ACT+ (meet WHO physical activity recommendations ≥ 150 min/week), ACT+/- (do not meet WHO recommendations < 150 min/week and ≥ 50 min/week) and ACT — (do sport occasionally or never). Two groups were performed depending on the BP: AHT+ (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or antihypertensive therapy) and AHT — (BP values $< 140/90$ mmHg and no antihypertensive therapy).

Results. ACT-, ACT+/- and ACT+ accounted respectively for 53%, 24% and 23%, AHT+ for 55.6% and men with waist circumference ≥ 94 cm for 63.9% of studied population. In ACT- increased BP was measured more frequently in comparison with ACT+. In ACT+ waist circumference, DBP and HR were lower and PP was higher in comparison to ACT-. Laboratory tests results did not differ between all three groups of respondents. It was observed that group of participants with waist circumference < 94 cm had lower values of blood pressure parameters in comparison to participants with waist circumference ≥ 94 cm.

Conclusions. Only 1 out of 4 men in Warmia and Masuria region in Poland meets the WHO physical activity recommendations, 64% of them have abdominal obesity and more than a half had measured increased values of arterial blood pressure. These findings reveal increased risk of CVD and mortality among men in Warmia and Masuria region comparing to population of Poland and Europe.

Key words: exercise, obesity, Poland

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Streszczenie

Wstęp. Regularna aktywność fizyczna jest uznawana za jedną z metod niefarmakologicznej prewencji wielu chorób przewlekłych. Badanie przeprowadzono w celu oceny odsetka osób uprawiających sport i częstości występowania otyłości brzusznej w grupie 631 losowo wybranych mężczyzn z województwa warmińsko-mazurskiego.

Materiał i metody. W okresie od grudnia 2014 r. do grudnia 2016 r. przebadano 631 mężczyzn zamieszkających w województwie warmińsko-mazurskim, w wieku 19–82 lat ($47,2 \pm 13,7$ r.). Uczestnicy badania wypełniali wystandardyzowany kwestionariusz. Przeprowadzono pomiary antropometryczne. Zmierzono również ciśnienie tętnicze. U 398 osób oznaczono stężenie glukozy oraz lipidów we krwi. Analizy przeprowadzono oddzielnie w 3 grupach wydzielonych na podstawie czasu poświęconego na aktywność fizyczną w ciągu tygodnia: ACT+ (osoby, u których poziom aktywności fizycznej jest zgodny z zaleceniami WHO i wynosi ≥ 150 min/tydz.), ACT+/- (osoby o aktywności fizycznej mniejszej niż zalecana przez WHO — < 150 min/tydz. ≥ 50 min/tydz.) i ACT (osoby uprawiające sport okazjonalnie lub w ogóle nieuprawiające sportu). Wyróżniono również dwie grupy w zależności od wartości ciśnienia tętniczego: grupa AHT+ (ciśnienie skurczowe ≥ 140 mmHg i/lub ciśnienie rozkurczowe ≥ 90 mmHg lub przyjmowanie leków przeciwnadciśnieniowych) i grupa AHT- (wartości ciśnienia tętniczego wynoszące $< 140/90$ mmHg i niestosowanie leczenia przeciwnadciśnieniowego).

Wyniki. Grupy ACT-, ACT+/- i ACT+ stanowiły odpowiednio 53%, 24% i 23% badanej populacji, do grupy AHT+ zakwalifikowano 55,6% mężczyzn, a obwód pasa wynoszący ≥ 94 cm stwierdzono u 63,9% uczestników badania. U mężczyzn w grupie ACT- częściej uzyskiwano podwyższone wartości w pomiarach ciśnienia tętniczego niż w grupie ACT+. W grupie ACT+ obwód pasa, skurczowe ciśnienie tętnicze i częstość akcji serca były niższe, a ciśnienie tętna wyższe niż w grupie ACT-. Wyniki badań laboratoryjnych nie różniły się istotnie między 3 grupami. Stwierdzono, że mężczyźni z obwodem pasa wynoszącym < 94 cm mieli niższe ciśnienie tętnicze niż osoby, u których ten parametr wynosił ≥ 94 cm.

Wnioski. Tylko co 4. mężczyzna w województwie warmińsko-mazurskim utrzymuje poziom aktywności fizycznej zgodny z zaleceniami WHO, u 64% badanych występowała otyłość brzuszna, a u ponad połowy stwierdzono podwyższone wartości ciśnienia tętniczego. Powyższe wyniki wskazują na zwiększone ryzyko chorób sercowo-naczyniowych i zgonu wśród mężczyzn zamieszkujących ten region w stosunku do populacji Polski i Europy.

Słowa kluczowe: ćwiczenia fizyczne, otyłość, Polska

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Introduction

Regular physical activity (ACT) is a recognized method of non-pharmacological prevention many chronic diseases, including cardiovascular diseases (CVD), which are the leading cause of death in Poland, especially in men 65 years of age and younger in Warmia and Masuria region in comparison to mean death rate in Poland (41.3 % vs. 27.6%) [1]. The proposed antihypertensive mechanisms of physical activity include neurohormonal regulation, vascular and structural adaptation, catecholamine and sympathetic nervous system activity extenuation, peripheral vascular resistance reduction, insulin sensitivity improvement, plasma renin activity reduction and increase in cerebral blood flow. Lack of physical activity and sedentary lifestyle is fourth independent risk factor for premature death directly responsible for 5.5% of deaths in the world (3.2 million people), followed by hypertension (12.8%), tobacco smoking (8.7%) and diabetes 5.8%) [2]. In highly developed

countries low physical activity level is responsible for 7.7% of deaths (0.6 million people), and independently responsible for 6% of coronary heart disease, 7% of type 2 diabetes, 10% of breast cancer and 10% of colon cancer [3]. Physically inactive persons have a 30% higher relative risk of death compared to those who are active. Worldwide, 23% of people are physically inactive [3]. It is estimated that reducing the prevalence of physical inactivity by 10% or 25% will prevent respectively 533,000 or 1 300 000 deaths worldwide [3]. The current World Health Organization guidelines for healthy adult on physical activity recommend 150 minutes of moderate-intensity aerobic physical activity throughout the week or at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity. Sedentary lifestyle and high-calorie, high-fat diets are the leading causes of generalized and abdominal overweight, which is the fifth risk factor for premature death. Waist circum-

ference measurement is one of the methods to assess abdominal obesity and visceral fat. It is probably superior to body mass index (BMI) in predicting CVD risk. This is based on findings that increased visceral adipose tissue is associated with many metabolic abnormalities, including low glucose tolerance, reduced insulin sensitivity and abnormal lipid profiles, which are risk factors for type 2 diabetes and CVD [4]. A value of waist circumference ≥ 94 cm for European men is one of the metabolic syndrome criteria. Between 1980 and 2014, the prevalence of overweight in the world doubled to reach 36.9% of adults (2.1 billion) of whom 13% were obese [5]. In European Union countries overweight was measured by 50.2% and obesity by 15.4% [6], in Poland 53.3% and 16.7% respectively [7]. It is independent risk factor for the development of a number of diseases including CVD, type 2 diabetes, musculoskeletal disorders, osteoarthritis and many cancers. Overweight has also economic influence which is estimated at up to 2.8% of gross domestic product. Among others it consists of costs of obesity and its complications treatment and limitation or loss of ability to work and premature death. According to estimates, treatment costs over obese patient are almost 50% higher than over patient with normal body weight [8] and in Europe involves 2–7% of healthcare budget. In Poland overweight may be responsible for 25% of hospital admissions [10]. From 1980's people consume much more energy than they expend, what is still not clearly explained [11]. Increasing physical activity can create energy deficit through increased energy expenditure and have potential to control appetite [12]. For this reason physical activity and exercise can be the solution for the ongoing obesity epidemic.

Goal

The aim of this study was to evaluate the prevalence of physical activity, blood pressure and abdominal obesity in 631 randomly selected men from Warmia and Masuria region in Poland based on data obtained in ProM project.

Material and methods

631 randomly selected men in age of 19–82 years (47.2 ± 13.7 years) were examined between December 2014 and December 2016. Each subject signed an informed consent to participate in the ProM Project. The study protocol was approved by the Ethics Committee of the Regional Medical Chamber of Warmia and Masuria in Poland. The study was conducted with respect to guidelines of Good

Clinical Practice. Study participants completed standardized questionnaire assessing their physical activity level. Waist circumference was measured by tape. Arterial blood pressure was 4 times measured by Omron M3/Japan, 2 times both on the left and right arm, after 10 minutes pause second measurements (on the left and right arm) were performed. Laboratory tests (serum glucose, triglycerides (TG), HDL-, LDL- and total cholesterol) were measured in a certified laboratory in 398 participants. The SPSS V.23 Software (IBM Corp./USA) was used for statistical analyses. Analyses were performed separately for three groups depending on time of physical activity in week:

— ACT+ (subjects with physical activity ≥ 150 min/week),

— ACT+/- (between 150 and 30 min/week),

— ACT- (physical activity < 30 min/week or never).

Two groups were performed depending on the blood pressure measurement:

— AHT+ (subjects with elevated values of systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg or antihypertensive therapy),

— AHT- (subjects with blood pressure values $< 140/90$ mmHg and no hypertensive therapy).

Results

631 men completed the study, for whom 398 laboratory test were performed. The characteristics of the study group are shown in the Table I. Figure 1 shows that ACT-, ACT+/- and ACT+ accounted respectively for 53% ($n = 334$), 24% ($n = 152$) and 23% ($n = 145$) of all respondents. AHT+ accounted for 55.6% ($n = 353$) of respondents (Fig. 2). Men with waist circumference ≥ 94 cm accounted for 63.9% ($n = 403$) of studied population. In ACT- increased arterial blood pressure was measured more frequently in comparison with ACT+ (57.5% vs. 50%, $p = 0.008$) (Fig. 3). In ACT+ waist circumference, diastolic blood pressure and heart rate were significantly lower in comparison to ACT-, respectively: waist circumference — 96.5 cm vs. 99.7 cm, $p = 0.009$, DBP — 85.4 mmHg vs. 87.7 mmHg, $p = 0.008$, HR — 70 bpm vs. 71 bpm, $p < 0.001$ and pulse pressure was significantly higher, 50.4 mmHg vs. 47.5 mmHg, $p = 0.016$. (Fig. 4–6). Table II shows that there were no significant differences in these parameters between ACT- and ACT+/-, also laboratory tests did not differ between all three groups of respondents. Figure 7–10 and 11 present in all patients statistically significant positive correlation between

Table 1. Clinical characteristics of the study population

Parameter	N	Mean ± SD	Minimum	Maximum
Age (years)	631	47.22 ± 13.7	19	92
Waist circumference [cm]		98.1 ± 12.2	56	138
SBP [mmHg]		135.9 ± 16.5	93	212
DBP [mmHg]		87.6 ± 10.8	61	130
Pulse pressure [mmHg]		48.3 ± 10.9	23	104
Heart rate [bpm]		72.7 ± 10.9	43	116
Age (years)	398	48.22 ± 12.53	19	82
Waist circumference [cm]		98.0 ± 12.1	56	134
SBP [mmHg]		137.3 ± 17.1	93	213
DBP [mmHg]		88.9 ± 10.9	61	130
Heart rate [bpm]		72.6 ± 10.7	43	105
Pulse pressure [mmHg]		48.3 ± 11.06	22	105
Triglycerides [mmHg]		141.2 ± 93.8	36	752
HDL [mmHg]		52.1 ± 14.0	19	100
Glucose [mmHg]		100.5 ± 23.6	61	301

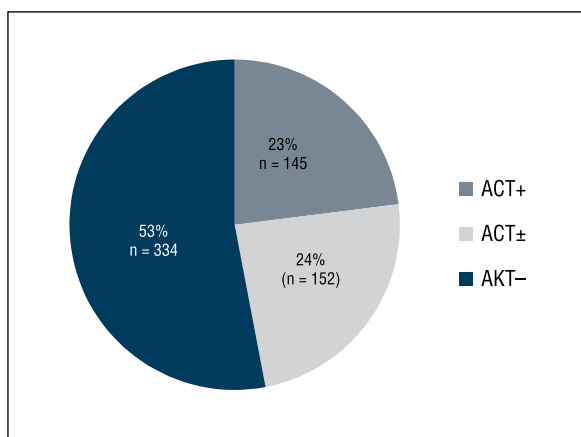


Figure 1. Prevalence of physical activity level in studied population

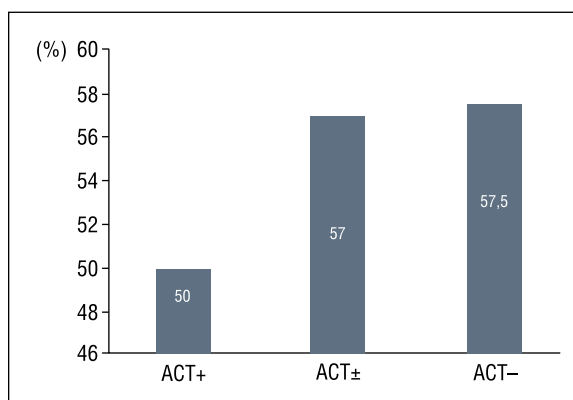


Figure 3. Proportion of men with increased blood pressure measures in physical activity level groups

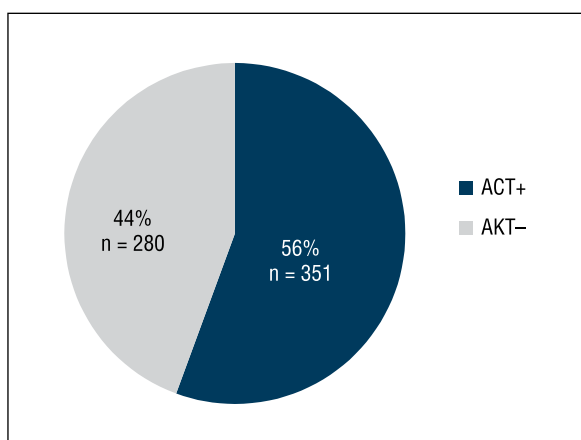


Figure 2. Prevalence of arterial hypertension in studied population

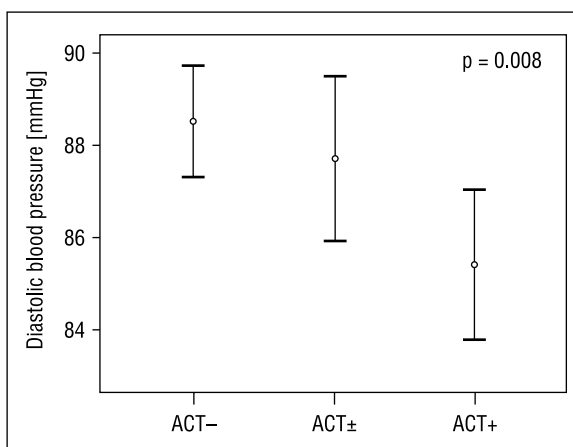


Figure 4. Comparison of diastolic blood pressure depending on physical activity level

waist circumference and systolic blood pressure ($r = 0.316$, $p < 0.001$), diastolic blood pressure ($r = 0.318$, $p < 0.001$), mean arterial pressure ($r = 0.340$, $p < 0.001$), pulse pressure ($r = 0.153$, $p < 0.001$) and heart rate ($r = 0.172$, $p < 0.001$). It was observed that group of participants with waist circumference < 94

cm had significant lower values of blood pressure parameters in comparison to participants with waist circumference ≥ 94 cm (SBP — 128.4 mmHg vs. 140.2 mmHg, $p < 0.001$, DBP — 82.7 mmHg vs.

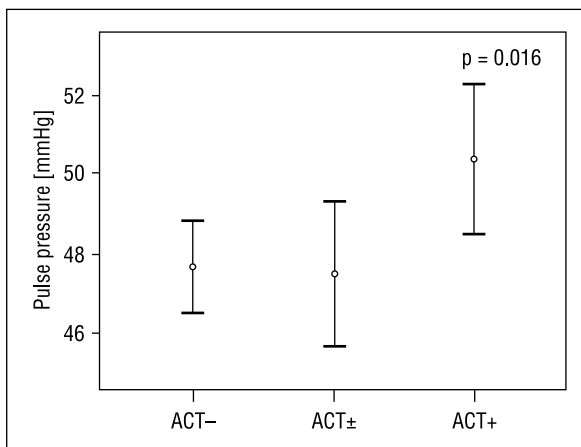


Figure 5. Comparison of pulse pressure depending on physical activity level

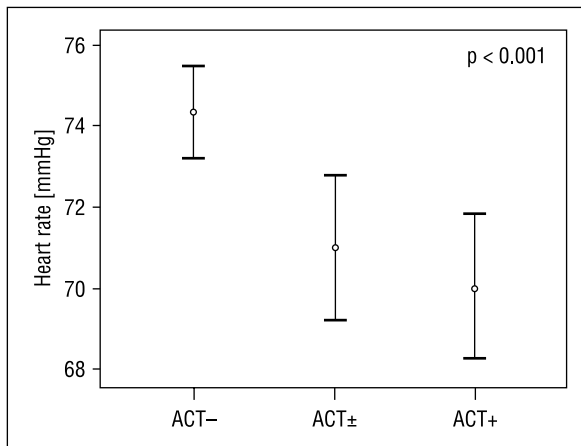


Figure 6. Comparison of heart rate depending on physical activity level

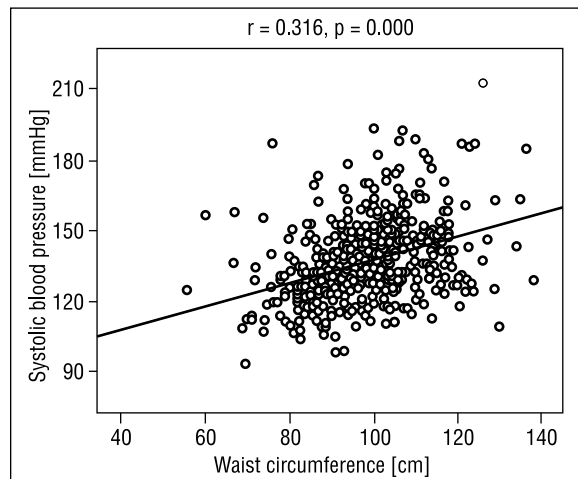


Figure 7. Correlation between waist circumference and systolic blood pressure

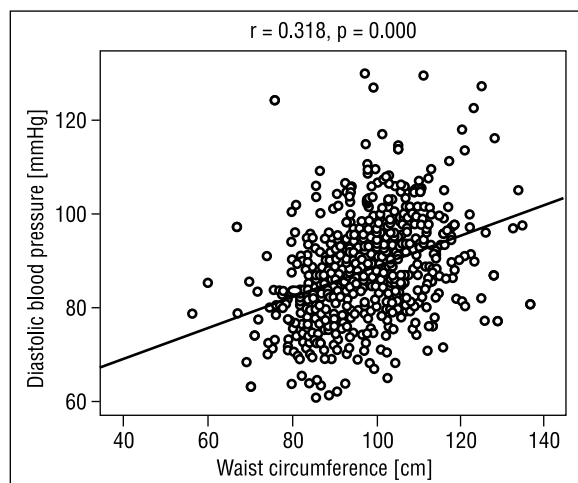


Figure 8. Correlation between waist circumference and diastolic blood pressure

Table II. Comparison of waist circumference, systolic blood pressure and laboratory test values depending on physical activity

Parameter	ACT-	ACT+/-	p	ACT+	p ACT-	p ACT+/-
Waist circumference [cm]	99.7	96.5	0.009	95.8	0.001	0.714
SBP [mmHg]	136.2	135.2	0.766	135.8	0.898	0.684
TG [mg/dl]	142.6	142.6	0.622	134.5	0.851	0.801
Cholesterol [mg/dl]	205.9	211.7	0.410	207.9	0.832	0.551
HDL [mg/dl]	51.0	54.3	0.238	52.7	0.675	0.567
LDL [mg/dl]	125.1	126.1	0.558	126.9	0.655	0.891
Glucose [mg/dl]	100.3	100.8	0.712	97.8	0.781	0.948

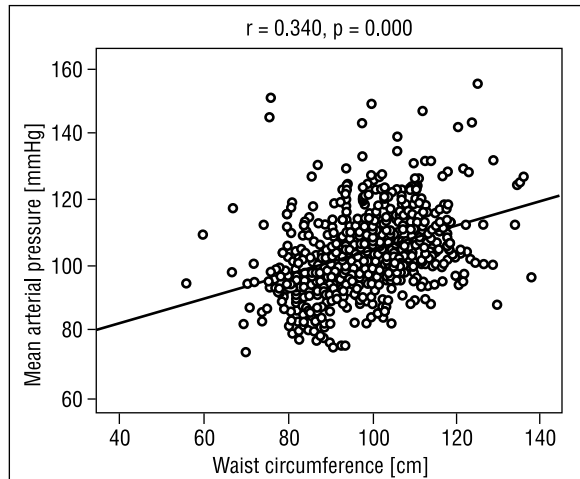


Figure 9. Correlation between waist circumference and mean arterial pressure

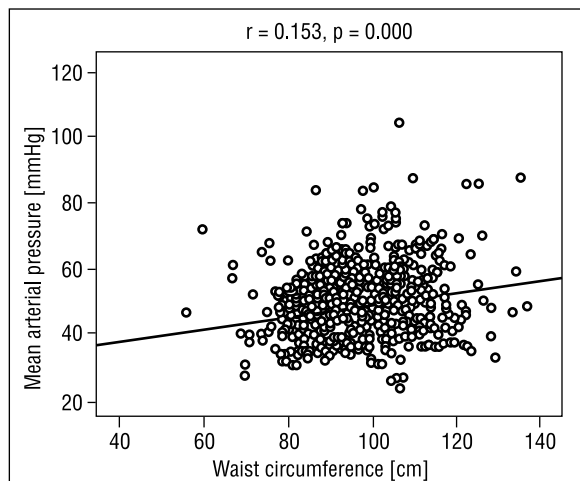


Figure 10. Correlation between waist circumference and pulse pressure

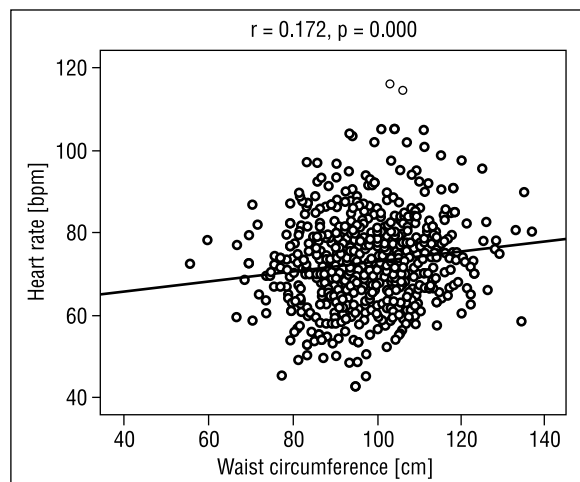


Figure 11. Correlation between waist circumference and heart rate

90.4 mmHg, $p < 0.001$, MAP — 97.6 mmHg vs. 107.0 mmHg, $p < 0.00$ and PP — 45.7 mmHg vs. 49.7 mmHg, $p < 0.001$) what is presented in Figure 12 and Table III.

Discussion

The prevalence of physical inactivity in men in Warmia and Masuria was found higher than in Poland (53% vs. 18.7%) [13] and Europe (53% vs. 28.6%) [14]. However, the percentage of respondents who meet WHO physical activity recommendations was lower in Warmia and Masuria comparing to Poland (23% vs. 48.2%) [15] and Europe (23% vs. 64.5%) [16]. Prevalence of increased blood pressure measured in our study was 55.6% and was higher than mean in Poland (55.6% vs. 32%) [17] and Europe (55.6% vs. 44%) [18]. Lack of physical activity was associated with increased values of waist circumference, diastolic blood pressure and heart rate. We observed that the individual higher waist circumference had measured higher systolic and diastolic blood pressure, mean arterial pressure, pulse pressure, and heart rate. We also observed the significant differences in men with waist circumference ≥ 94 cm comparing to men with waist circumference < 94 cm for all of the blood pressure parameters. These findings show that lack of physical activity and abdominal obesity is linked with higher risk of arterial hypertension and, by the way, with cardiovascular diseases (CVD) development, especially in men from the Warmia and Masuria region with increased prevalence of arterial hypertension and physical inactivity. It can explain increased mortality from cardiovascular diseases in men < 65 years comparing to other regions in Poland. The rising prevalence of overweight and obesity in a number of countries has been described as a global pandemic [19] and no change in this trend has been reported in the past 33 years among most of countries. Global mean BMI in men increased from 21.7 kg/m^2 in 1975 to 24.2 kg/m^2 in 2014 [20] and the proportion of men with a BMI of 25 kg/m^2 or greater increased between 1980 and 2013 from 28.8% to 36.9% [21]. In Poland mean BMI in men increased from 24.4 kg/m^2 (22.9 ± 25.8) in 1995 to 26.9 kg/m^2 (26.3 ± 27.7) in 2014 [22]. Also prevalence of men in Poland with BMI ≥ 25 kg/m^2 increased from 43.6% to 65.2% in these years [22]. Further investigation has to be concerned. These findings also support development of strategies to combat the entire spectrum of excess adiposity and sedentary lifestyle in this population.

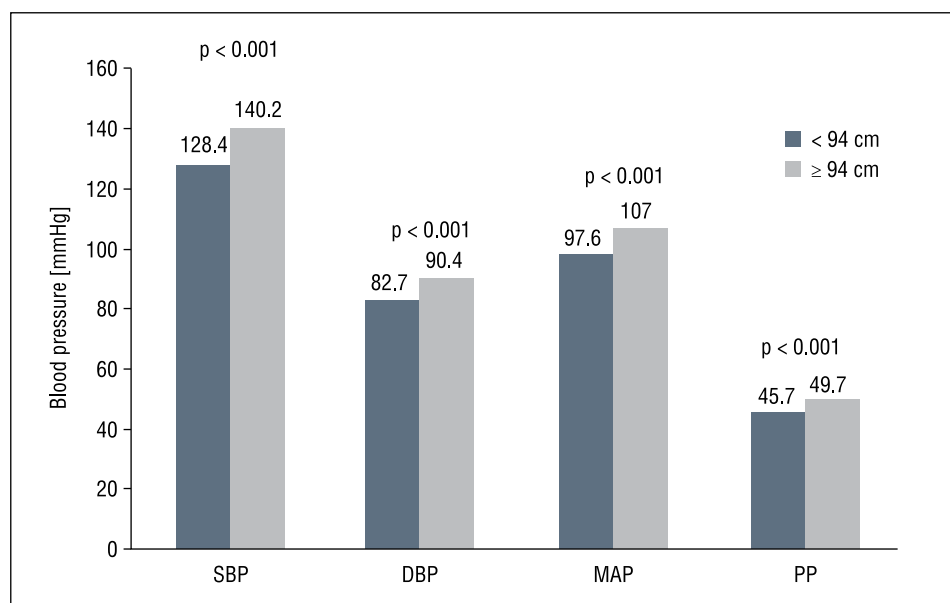


Figure 12. Comparison of systolic and diastolic blood pressure mean arterial pressure and pulse pressure depending on waist circumference

Table III. Age adjusted correlation between waist circumference < 94cm or ≥ 94cm and systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse pressure and heart rate

Age adjusted parameters	Correlation						P U test Mann Whitney Age adjusted between < 94 cm and ≥ 94 waist circumference
	Waist circumference [cm]						
	< 94 cm (n = 228)			≥ 94 cm (n = 403)			
	Mean ± SD	r	p	Mean ± SD	r	p	
SBP [mmHg]	128.4 ± 14.0	0.099	0.14	140.2 ± 16.3	0.198	< 0.001	< 0.001
DBP [mmHg]	82.7 ± 9.8	0.121	0,073	90.4 ± 10.4	0.173	0.001	< 0.001
MAP [mmHg]	97.6 ± 10.4	0.121	0,073	107.0 ± 11.5	0.200	< 0.001	< 0.001
PP [mmHg]	45.7 ± 9.6	0.021	0.76	49.7 ± 11.4	0.124	0.013	< 0.001
HR [bpm]	71.1 ± 10.5	0.040	0.55	73.6 ± 11.0	0.105	0.037	0.012

Conclusions

Only 1 out of 4 men in Warmia and Masuria region in Poland meets the WHO physical activity recommendations, 64% of them have abdominal obesity and more than a half had measured increased values of arterial blood pressure. These findings reveal probably the increased risk of premature mortality among men in Warmia and Masuria region comparing to population of Poland and Europe.

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References

1. Demographic Yearbook of Poland 2016. Central Statistical Office, Warsaw 2016: 306–360.
2. Global health risks: mortality and burden of disease attributable to selected major risks. World Health Organization, Geneva, Switzerland 2010.
3. Lee IM, Shiroma EJ, Lobelo F, et al. Lancet Physical Activity Series Working Group. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012; 380(9838): 219–229, doi: 10.1016/S0140-6736(12)61031-9, indexed in Pubmed: 22818936.
4. Waist Circumference and Waist–Hip Ratio: Report of a WHO Expert Consultation Geneva, p.12, 8–11 Geneva, December 2008.
5. The GBD. 2013 Obesity Collaboration, Global, regional and national prevalence of overweight and obesity in children and adults 1980–2013: A systematic analysis, Lancet. 2014 Aug 30. ; 384(9945): 766–781, doi: 10.1016/S0140-6736(14)60460-8.
6. Eurostat. <http://ec.europa.eu/eurostat/web/health/health-status-determinants/data/database> (9 Feb 2016).
7. Central Statistical Office, Health status of population in Poland in 2014 Warsaw, 2016.

8. Sturm R, Ringel JS, Andreyeva T. Increasing Obesity Rates And Disability Trends. *Health Affairs*. 2004; 23(2): 199–205, doi: 10.1377/hlthaff.23.2.199.
9. Jarosz M, Rychlik E, et al. Otyłość wyzwaniem zdrowotnym i cywilizacyjnym. *Postępy Nauk Medycznych*. 2011(9): 712–717.
10. Levitsky DA, Pacanowski CR. Free will and the obesity epidemic. *Public Health Nutr*. 2012; 15(1): 126–141, doi: 10.1017/S1368980011002187, indexed in Pubmed: 21923977.
11. Shook RP, Hand GA, Drenowatz C, et al. Low levels of physical activity are associated with dysregulation of energy intake and fat mass gain over 1 year. *Am J Clin Nutr*. 2015; 102(6): 1332–1338, doi: 10.3945/ajcn.115.115360, indexed in Pubmed: 26561620.
12. Supplement to: Sallis JF, Bull F, Guthold R, et al. Progress in physical activity over the Olympic quadrennium. [http://dx.doi.org/10.1016/S0140-6736\(16\)30581-5](http://dx.doi.org/10.1016/S0140-6736(16)30581-5) (2016).
13. Gerovasili V, Agaku IT, Vardavas CI, et al. Levels of physical activity among adults 18–64 years old in 28 European countries. *Preventive Medicine*. 2015; 81: 87–91, doi: 10.1016/j.ypmed.2015.08.005, indexed in Pubmed: 26299619.
14. Drygas W, Saklak W, Kwaśniewska M, et al. Epidemiology of physical activity in adult Polish population in the second decade of the 21st century. Results of the NATPOL 2011 study. *Int J Occup Med Environ Health*. 2013; 26(6): 846–855, doi: 10.2478/s13382-013-0160-9, indexed in Pubmed: 24464564.
15. Marques A, Martins J, Peralta M, et al. European adults' physical activity socio-demographic correlates: a cross-sectional study from the European Social Survey. *PeerJ*. 2016; 4: e2066, doi: 10.7717/peerj.2066, indexed in Pubmed: 27280072.
16. Zdrojewski T, Bandosz T, Rutkowski M, et al. Rozpowszechnienie, wykrywanie i skuteczność leczenia nadciśnienia tętniczego w Polsce: wyniki badania NATPOL 2011. *Nadciś Tętn*. 2014; 18: 116–117.
17. Alwan A, Armstrong T, Bettcher D et al. Global status report on noncommunicable diseases 2010, Geneva, World Health Organization Geneva, 2011.
18. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. *The Lancet*. 2011; 378(9793): 804–814, doi: 10.1016/S0140-6736(11)60813-1, indexed in Pubmed: 21872749.
19. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014; 384(9945): 766–781, doi: 10.1016/S0140-6736(14)60460-8, indexed in Pubmed: 24880830.
20. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet*. 2016; 387(10026): 1377–1396, doi: 10.1016/s0140-6736(16)30054-x.
21. NCD Risk Factor Collaboration. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet*. 2016; 387(10026): 1377–1396, doi: 10.1016/s0140-6736(16)30054-x.