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Title

A statistical investigation into the sharing of common genetic factors between blood pressure and obesity phenotypes in nuclear families from the Greater Bilbao (Spain).

Running title

Genetics of blood pressure and obesity

Author´s name

Aline Jelenkovic, Alaitz Poveda, Esther Rebato.

Department

Department of Genetics, Physical Anthropology and Animal Physiology, Faculty of Science and Technology, University of the Basque Country, Bilbao 48080, Spain.

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Corresponding autor.

Aline Jelenkovic. Department of Genetics, Physical Anthropology and Animal Physiology, Faculty of Science and Technology, University of the Basque Country, Apdo 644, Bilbao 48080, Spain. Tel: 34 94 6015405. Fax: 34 94 601 3145. Email: aline.jelenkovic@ehu.es

Co-authors´ email addresses

Poveda Alaitz alaitz.poveda@ehu.es; Rebato Esther esther.rebato@ehu.es

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Abstract

OBJECTIVES: Several obesity phenotypes (e.g. body mass and fat, fat distribution) have been suggested to be a risk for elevated blood pressure. This study was undertaken (1) to determine the heritability of four blood pressure phenotypes: SBP, DBP, PP and MAP and (2) to assess the strength of genetic and environmental correlations between these phenotypes and the different obesity related traits.

METHODS: The studied sample consisted of 429 nuclear families living in the Greater Bilbao (Spain) and included 1302 individuals aged 4-61 years. Univariate and bivariate quantitative genetic analyses were performed using a variance components procedure implemented in SOLAR software.

RESULTS: SBP, DBP, PP and MAP were significantly influenced by genetic factors with heritability estimates of 0.25, 0.28, 0.14 and 0.31 respectively, and presented high genetic and environmental correlations between them (except DBP-PP). On the other hand, whereas SBP, DBP and MAP showed common environmental factors with almost all body mass and fat related traits, pleiotropic effects were only detected for some pairs, especially for those phenotypes that included skinfolds. In contrast, PP did not exhibit common genetic or environmental factors with obesity phenotypes in the studied population

CONCLUSIONS: Blood pressure and obesity phenotypes do not share, in general, a substantial influence of common genetic and environmental effects. Finally, the results obtained revealed the importance of the amount of adipose tissue in the genetic correlations with SBP, DBP and MAP, at least, during the growth period.

Condensed Abstract

A sample of nuclear families from the Greater Bilbao (Spain) was analyzed to determine the pleiotropic factors between blood pressure and obesity related phenotypes. Low to moderate heritabilities were observed for SBP, DBP, PP and MAP. Blood pressure and obesity traits do not present, in general, a substantial influence of common genetic and environmental effects. Whereas SBP, DBP and MAP shared environmental factors with almost all obesity traits, pleiotropic effects were especially observed with skinfolds related phenotypes. These findings revealed the importance of the amount of adipose tissue in the genetic correlations with SBP, DBP and MAP during the growth period.

Keywords

Continuous blood pressure; obesity; adiposity; genetics; anthropometry; nuclear family.

Introduction

Worldwide, cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality, representing 30% of all global deaths [1]. Several lifestyle factors (i.e. diet, sedentariness, smoking, alcohol) and health related factors (i.e. hypertension, diabetes, abdominal obesity, psychosocial factors, abnormal lipids) have shown association with CVDs. The INTERHEART case-control study estimated that hypertension was associated with 22% and abdominal obesity with 63% of the population attributable risk for acute myocardial infarction in west Europe [2]. Over the past decade, the prevalence of obesity has doubled in Western and Westernizing countries. Nowadays, this health problem affects, independently of the age, an important proportion of the Spanish population [3]. In Spain three children out of every ten are overweight or obese, which places this European country in second place after the US in terms of child overweight [4].

The concomitance of chronic disorders such as obesity, hypertension, and CVDs has led to many authors to study the potential genetic and environmental correlations between blood pressure (BP) and obesity phenotypes, however, the majority of studies only analyzed systolic blood pressure (SBP) and diastolic blood pressure (DBP) as indicators of BP. But BP is also characterized by its pulsatile (PP) and steady (MAP) components. PP represents blood pressure variation and is affected by left ventricular ejection fraction, large-artery stiffness, early pulse wave reduction, and heart rate and MAP is a function of left ventricular contractility, heart rate, and vascular resistance and elasticity averaged over time [5, 6]. Both PP and MAP are associated with ischemic stroke in uncontrolled hypertensive individuals [6], being therefore of interest in the study of CVDs.

Because obesity is a heterogeneous phenotype, it turns out necessary to investigate the relationship between BP phenotypes and the different indicators of body mass, body fat and fat distribution. The most commonly reported adiposity measures in relation to BP phenotypes include weight, waist circumference, skinfolds thickness, and indices such as body mass index (BMI), and waist-to hip ratio (WHR) [7-14]. Factors extracted from a factor analysis (FA) could represent features that contain a higher degree of genetic variance than the original variables separately [15]. This methodology is widely used in the study of correlated measures as circumferences or skinfold thickness [16-18]. Finally, Heath-Carter somatotype [19], provides a more generalized approach to body types and summarizes body shape in three basic components: endomorphy, mesomorphy and ectomorphy (fatness and leanness, musculoskeletal development for the individual´s height and linearity related component, respectively).

Obesity is the most common identifiable cause of hypertension in children [20]. However, pleiotropic effects between BP and adiposity in children have not been studied thoroughly. Differences in genetic determination of BP have been found between children and adults [21-23]. Although corroboration is often observed, heritabilities and therefore genetic and environmental correlations are not necessarily transferable from adults to children because genetic expression and environmental influences may vary with age [24]. However, the early relationship, perhaps from birth or maybe prenatally between weight and body size and blood pressure [25, 26] makes this approach of substantial interest.

Accordingly, the aims of the present study were (1) to determine the heritability of four BP phenotypes (SBP, DBP, PP and MAP), (2) to examine the contribution of genetic and environmental effects on the covariation among these phenotypes, and also between blood pressure and a large set of obesity related measures in nuclear families of the Greater Bilbao, and (3) to compare these results with those from other populations.

Materials and methods

Sample

The present research was conducted on 429 nuclear families, composed of 602 males (mean age 10.57 and 45.34, ranging from 4 to 19 and 29 to 61 for the offspring and parental generation, respectively) and 700 females (mean age 10.56 and 42.78, ranging from 4 to 18 and 27 to 57). The great majority of nuclear families includes one or two son/daughters (59.7% and 36.4%, respectively), followed by three (3.3%) and four siblings (0.7%), with a mean number of children per family of 1.45. This is a randomly ascertained cohort in that participating families were not selected for any specific feature or trait. The data collection was carried out in 22 education centres of the Greater Bilbao (Spain) during two academic years (2006-2007 and 2007-2008). Both primary and secondary schools were public character education centres, with the exception of two of them, which were private centres. Permission was asked from the Basque Government (only for public centres), and also from the direction of each centre. The project was approved by the ethics committee of the University of the Basque Country and written informed consent was obtained from all study participants.

This sample forms part of an urban population of medium socioeconomic level. Greater Bilbao is a comarca of Biscay (Basque Country) and includes the City of Bilbao and

other 21 municipalities situated along the Nervión river. Today, Greater Bilbao is considered to be the main economic area of the Basque Country and one of the most important of Spain. Due to the sample recruitment methodology and the increasing percentage of immigration in the studied area, individuals with different origins and genetic background were measured. However, in order to avoid possible mixture of different genetic backgrounds, only Caucasian individuals who presented a European origin were definitively included in the study. The original sample included a greater number of individuals, but in the present study, only those who presented blood pressure data were analyzed.

Phenotypic data

Blood pressure measurements were taken on the left arm of each participant following a 10-min rest period. The measurements were taken twice at 5-min intervals using the Omron M6 (HEM-7001-E) digital device, validated according to The International Protocol of the European Society of Hypertension [27]. For subjects receiving antihypertensive treatments, the recorded blood pressures were adjusted by adding 10 mm Hg and 5 mmHg to SBP and DBP, respectively [28]. Next, new derived variables were obtained from the two primary measures; pulse pressure [PP = SBP - DBP) and mean arterial pressure [MAP = 1/3 SBP + 2/3 DBP].

Anthropometric measures included, height, weight, the two biepicondylar breadths (humerus and femur), five circumferences (upper arm relaxed and contracted, waist, hip and medial calf) and six skinfold thicknesses (biceps, triceps, subescapular, suprailiac, abdominal and medial calf). All measurements were obtained by the same investigator (A.J.) for the whole sample following standard anthropometric techniques [29].

Skinfolds were measured using a Lange caliper (Cambridge Scientific Industries, Cambridge**,** MD), circumferences were taken to the nearest mm by using a Harpenden anthropometric tape (Holtain Ltd) and the other measurements with a Siber-Hegner anthropometer (GPM, Zurich, Switzerland) accurate to 1mm. A digital balance to the nearest 0.1 kg was used to measure body weight. From these anthropometric measures four indices of body mass, body fat, and fat distribution were derived: Body mass index [BMI = weight (kg)/height (m^2)], the sum of all 6 skinfolds (SF6), the waist to hip ratio [WHR = waist circumference / hip circumference] and the trunk to extremity skinfold ratio [TER = (suprailiac + subscapular + abdominal)/(medial calf + biceps + triceps)]. Finally, the three components of the Heath-Carter´s anthropometric somatotype were calculated according to formulas described in [19].

Statistical analysis

All statistical computations were carried out using SPSS package version 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Firstly, two FA with the principal components extraction method were computed, regardless of sex and age, for the two categories of adiposity related traits (i.e. circumferences and skinfolds). FA is a useful multivariate methodology that offers the possibility to reduce a large set of correlated measures into a smaller number of uncorrelated domains or factors that capture much of the underlying covariance structure among the multiple dimensions [17]. The first analysis included five body circumferences (upper arm relaxed and contracted, waist, hip and medial calf) and the second analysis was carried out for the six skinfolds (biceps, triceps, subescapular, suprailiac, abdominal and medial calf). The eigenvalue of 1 criterion was implemented to retain the factors. To asses whether or not the two set of variables were appropriate for FA, Kaiser- Meyer-Olkin (KMO) and Bartlett's Test of

Sphericity were applied. KMO test has been 0.857 for the circumferences factor and 0.829 for the skinfolds factor, being both “meritorious” according to Kaiser Criteria [30]. As expected, the null hypothesis of variable independence for the five and six items (circumferences and skinfolds, respectively) was rejected at a level of significance of 0.000. Thus, both tests suggested that all measures used were appropriate for the analysis. Finally, factor scores for each individual on the first factor were used in further analysis.

Next, a stepwise regression analysis was used to remove the effects of age (age, age^2 and age^3), within each generation and sex for all the studied blood pressure and anthropometric traits. Phenotypes were then generated for each individual by retaining the residual regression score and then standardizing to a mean of 0 and a variance of 1 within each group. As none of the phenotypes showed a kurtosis > 2.0 (after adjustment for age and sex), no transformation was applied to the data [31].

Quantitative genetic analysis

In the first stage of genetic analysis, we used the program package MAN-6 forWindows [32] to calculate the familial correlations of all adjusted traits. Narrow sense or additive heritabilities (h^2) for both BP and anthropometric phenotypes were calculated using the variance-components method implemented in Sequential Oligogenic Linkage Analysis Routines (SOLAR 4.2.7 available online at: http://www. sfbr.org/solar/; [33]). This method distinguishes between the additive genetic (V_G) and environmental (V_E) components that form the total variation of the trait (V_P): $V_P = V_G + V_E$. The portion of the total phenotypic variance accounted for by the additive genetic variance is denoted by narrow sense heritability (h^2): $h^2 = V_G / V_P$. The environmental component includes

environmental factors, the non-additive genetic component, and measurement errors. Parameters estimation was performed by restricted maximum likelihood methods. In the process, the null hypothesis, in which the additive genetic variance (V_G) equals zero, was tested against an alternative hypothesis in which the additive genetic variance was estimated. Minus two times the difference in the log likelihood between the two models is distributed as a ½ chi-square statistic with 1 degree of freedom.

Bivariate genetic analysis (also implemented in SOLAR) is the extension from univariate genetic analysis and was conducted to partition the total phenotypic relations (ρ_P) between the pairs of traits into genetic (ρ_G) and environmental correlations (ρ_E): $\rho_P = \rho_G \sqrt{(h^2_1 h^2_2)} + \rho_E \sqrt{((1 - h^2_1)(1 - h^2_2))}$. In this equation, h^2_1 and h^2_2 are the heritabilities of trait 1 and trait 2, respectively. The bivariate phenotype is modeled as a linear function of the individual's phenotypic values, the population means, the additive genetic values, and environmental effects. The significance of ρ_P, ρ_G and ρ_E was calculated by comparison of the log-likelihood of a more restricted model in which the same parameter is set to zero. To test if covariation between traits was entirely due to shared genes (i.e., complete pleiotropy), the significance of ρ_G differing from 1 was also evaluated.

Results

Preliminary statistical analysis

Table 1 presents the basic descriptive statistics for all studied traits separated by generation and sex. BP phenotypes showed greater values for males in both generations, except for DBP in the offspring generation. In line with this, mean values for the majority of anthropometric traits were higher for fathers than for mothers, with the exception of some body fat related variables (skinfolds of the extremities, SF6,

endomorphy) and ectomorphy. In the filial generation, all skinfold thicknesses, SF6 and endomorphy have shown to be greater for females.

Factor loading patterns of the two factors are shown in Table 2 together with the eigenvalue and percentage of variance explained by each factor. As can be observed, a single factor was retained for each set of measures. These circumferences (CRsF) and skinfolds factors (SKsF) explained about 92.7 and 72.3% of the total variation in both sets of traits, respectively. The high values obtained suggested that CRsF can be interpreted as a general indicator of overall body mass and SKsF as a measure of amount of fat. Both synthetic traits were used as summary variables in the quantitative genetic analysis.

Univariate genetic analysis

Familial correlations and the estimates of the univariate variance component analysis (h^2) for the studied traits are shown in Table 3. All significant correlations were of positive magnitude and both BP and anthropometric traits have shown to be significantly heritable in the Greater Bilbao population. Concerning blood pressure phenotypes, whereas parent-offspring correlations were statistically significant for all the traits, none of the correlations was significant in spousal pairs and only DBP and MAP showed to be correlated between siblings. Low to moderate heritabilities were estimated for these phenotypes (0.25, 0.28, 0.14 and 0.31 for SBP, DBP, PP and MAP respectively). When these four traits were adjusted for BMI, variance components were similar to those observed without adjustment (data not shown). Regarding anthropometric traits, whereas spouses only correlated for weight, waist circumference, BMI, WHR and ectomorphy, parent-offspring and siblings correlations were significant for all the studied anthropometric traits. As expected, the magnitude of the correlations

between spouses was substantially lower than between parents and offspring or sib pairs, which demonstrated a similar trend of correlations. Moderate heritability estimates were observed for the adiposity related traits (0.29-0.50). Overall body phenotypes (weight, CRsF and BMI) were the most influenced by additive genetic effects, whereas those traits including only the abdominal area (waist circumference and WHR) were the less determined by these genetic effects. Concerning the anthropometric somatotype, the lowest heritability was found for the fatness component (0.40) followed by the linearity (0.48) and the musculoskeletal component (0.60).

Bivariate genetic analysis

Phenotypic (ρ_P), genetic (ρ_G) and environmental (ρ_E) correlations were calculated between pairs of BP phenotypes (Table 4) and also between BP and anthropometric traits (Table 5). Although SBP and DBP showed a high genetic correlation (0.88), phenotypic and environmental correlations, although still high, were lower than those for SBP-MAP and DBP-MAP (Table 4). The difference in the magnitude between phenotypic, genetic and environmental correlations was also observed for PP-MAP, whereas SBP-PP, SBP-MAP and DBP-MAP presented very similar values for these three correlations. Despite the substantially high correlations observed between SBP and PP, none of the three correlations was significant between PP and DBP.

Phenotypic correlations between BP and anthropometric traits were all significant (with the exception of PP-WHR) and mostly weak to moderate (Table 5). Concerning genetic and environmental relationships, correlations between PP and the obesity phenotypes were not significantly different from zero. For the rest of phenotypes, whereas common environmental factors affected almost all of the analyzed pairs (31 out of 33) with values ranging from 0.15 to 0.31, only 11 genetic correlations were significant between

BP phenotypes and the anthropometric traits. SF6 and SKsF were the only two traits that exhibited significant genetic correlations with SBP, DBP and MAP. Apart from these two obesity related traits, CRsF, weight and endomorphy also presented pleiotropic effects with some BP phenotypes. Among the significant genetic correlations, the greater value was found for SBP-SF6 and SBP-SKsF (0.32) and the lowest for MAP-weight (0.23). All traits considered, only the ectomorphy showed negative correlations (environmental) with BP phenotypes, indicating that environmental factors acting to increase the value of one trait decrease the trait value of the other.

Discussion

Our investigation of nuclear families confirms the relationship between BP and obesity phenotypes not only in the adulthood, but also during the growth period. Once the phenotypic correlation is partitioned into genetic and environmental factors, the influence of these two components varies between the particular pairs of risk factors. Although the results showed that BP and obesity traits do not seem to share major common genetic or environmental backgrounds, we found shared environmental effects for almost all the studied pairs (except for PP). Pleiotropic effects were observed between a smaller number of pairs and were, in general, more important in determining the phenotypic covariation of those traits composed principally of adipose tissue, than of other obesity traits. To the best of our knowledge, this represents the first attempt to use quantitative genetic methods to estimate the heritability of BP phenotypes and their covariation with obesity traits in Spanish nuclear families.

Significant familial correlations were observed for the four BP traits between parents and offspring and for DBP and MAP in the sibling generation. In agreement with other authors [34], the lack of correlation between spouses, who share many environmental factors with each other and with their offspring, suggests that the observed correlations between siblings and between parent-offspring did not result entirely from shared environmental influences. A genetic basis for the biological mechanics affecting BP has been widely reported in the literature [8-11, 24, 35, 36], with narrow sense heritability estimates ranging from 20% to 50%. Our observations confirm this low to moderate influence of additive genetic effects on the interindividual variation of BP phenotypes and explained some 25%, 28%, 14% and 31% of the total residual variance (for SBP, DBP, PP and MAP, respectively). As can be seen, the highest heritability was found for MAP and the lowest value for PP, which consistent with at least one other study [35]. The genetic determination of BP is supported by two recent investigations, in which multiple loci with evidence of association with levels of SBP, DBP and hypertension have been identified. Each association explained a small proportion of the total variation in SBP or BDP, however, the variants identified present an aggregate effect on BP, acting throughout the whole range of values [37, 38].

Although familial correlations for all obesity related traits were significant between parent-offspring and siblings, spouses only correlated for some of these traits. Significant correlations between spouses could be reflecting the effects of cohabitation since marriage (shared environment) and/or the effects of “assortative mating” (correlated for the trait at the time of their marriage). Although the present data are not suitable to distinguish between these two effects, it is of interest to remark on the significant correlations obtained, as if assortative mating exits, the genetic component of

variance will be slightly increased [39, 40]. According to the investigations carried out in other populations [8, 9, 14, 24], obesity related phenotypes showed a moderate heritability (29-50%) in the Greater Bilbao nuclear families. Concerning anthropometric somatotype, the lowest genetic determination observed for the fatness component (endomorphy) was in the range of the previously mentioned obesity phenotypes. The lack of congruence between the published studies in defining which somatotype component is more heritable, results on different patterns of heritability among the populations [19, 41-43].

According to other published works [10, 11, 14], the high phenotypic covariation observed between SBP and DBP corresponds at least in part to the high influence of pleiotropic factors affecting both traits, suggesting that genes that determine variation in both SBP and DBP explain more variance of the respective trait than the genes that determine SBP or DBP separately. As well as for the Danish twins [11] and for the Indian population [14], important contributions of common environmental factors were also encountered in variation of SBP-DBP. Concerning the relationships among the other BP phenotypes, our results are consistent with those reported from an investigation carried out in rats [44], in which no phenotypic correlation was found for DBP-PP. This lack of correlations is also supported by some genetic studies [45, 46], which showed that some loci influencing PP are different from the ones linked to either DBP or SBP.

In the studied sample all BP and anthropometric traits were phenotypically correlated (with the exception of PP-WHR) and presented similar values to those found in twins [11] and slightly lower than those of more extended pedigrees [10, 14]. Findings to date

clearly indicate that both BP and adiposity are complex multifactorial traits that develop during the close interaction of social, economic, behavioural, physiological, and other factors [9]. According to this, different interrelationships were observed for the pairs of traits when examining separately for genetic and environmental factors. In our population PP represents a special case, in which none of its genetic and environmental correlations with the anthropometric traits was significant. This lack of genetic correlation could be due, at least in part, to the low genetic determination observed for this trait. For this reason, the following part of the discussion will be based only on SBP, DBP and MAP. Concerning these three BP phenotypes, environmental correlations were significant for almost all the pairs formed with the anthropometric traits, however only three or four significant genetic correlations were observed with each BP trait. The comparison of the values between the different BP phenotypes and adiposity traits with others studies leads us to the conclusion that there is not an established pattern of phenotypic, genetic or environmental correlations between them. For example, our results are consistent with those of [11, 18] in determining slightly higher phenotypic correlations for SBP than for DBP, however, other studies [10, 14] found higher values for DBP. In the same way, genetic correlations were somewhat higher with SBP than with DBP, being in agreement with [8] but not with [11]. Finally, according to [8, 11] no appreciable differences in the environmental correlations between SBP and DBP were observed. On other hand, remarkable is the absence of genetic correlation between BP phenotypes and some adiposity related traits (e.g. BMI, waist circumference and WHR) that showed pleiotropic effects in other populations. The accepted measure of obesity in populations and in clinical practice (BMI) has shown to be genetically correlated with BP in several studies [8-11] as well as WHR [11, 12] and waist circumference [11]. Waist circumference has been found to be a good

indicator of abdominal fat and some authors have suggested that this trait could be even a more appropriate obesity indicator and a best predictor of cardiovascular diseases than BMI in adults [47] , adolescents [48] and in children [49]. The discrepancy between the results may be caused, at least in part, by the wide range of ages that makes up our sample. Well known is that body morphology and composition is not totally defined in childhood and adolescence. This lack of correlation could be due to changes in the expression of genes during the growth process, affecting therefore, covariation with BP phenotypes. However, our results are consistent with those observed in other adult populations as the Mexican and Indian [7, 14] where no shared genetic effects were found between BP and these obesity traits. In summary, the reasons for the divergent results remain unclear and the absence of genetic correlations for some pairs of factors could be explained by the effect of age, or by different genetic backgrounds among populations, or by the sum of both. Concerning traits that presented significant genetic correlations, our findings agree with those of [8] in determining pleiotropic effects between weight and SBP. SF6 and SKsF showed the highest genetic correlations with BP phenotypes in our population, however, no published study provides information about shared additive genetic effects using these two variables. Only phenotypic correlations (separated for men and women) were assessed in an investigation carried out in the Chuvashian population, where similar correlations coefficients were found for BP with SKsF and CRsF [18]. Again, no study refers to the pleiotropic effects between BP and somatotype components. In agreement with various studies [50-52], positive phenotypic association has been found for BP with endomorphy and mesomorphy, whereas negative correlations were observed with ectomorphy. According to the results obtained for body mass and fat related traits, fatness component (endomorphy) showed

pleiotropy with DBP and MAP, whereas non-significant genetic correlation were found for the musculoskeletal and linearity component.

Our most noteworthy finding was the stronger pleiotropic effects detected between BP phenotypes and those traits defining the amount of adipose tissue, that is, SF6 and SKsF, suggesting that fat tissue is the component most related to high values of BP. We are aware that the obtained results could be influenced by the inclusion of a wide range of ages in the offspring generation, but at the same time, this fact may be indicating the relevance of the amount of body fat in BP levels during childhood and adolescence. These findings could have some relevance in clinical prevention, where apart from the widely accepted measures of overweight in children (weight and BMI), measures of body fat should be taken into account in the surveillance programs.

Finally, the major limitation of the present study is the relatively small sample used for the family-based analysis, especially considering the wide range of ages analyzed. For this reason, larger samples with more individuals in each range of ages will be an interesting aim for the future in order to compare the mode in which the heritability and, genetic and environmental correlations changes through the growth period.

In conclusion, the present results indicate a moderate influence of the additive genetic effects on BP and obesity phenotypes in the Greater Bilbao population. Correlations between both groups of traits suggest that there are no major common genetic or environmental backgrounds affecting BP and obesity covariation. Whereas common environmental factors were relevant for almost all the analyzed pairs, pleiotropic effects were especially observed for those traits determining the adipose tissue, suggesting the

importance of the amount of body fat in the genetic relationships with SBP, DBP and MAP, at least, during the growth period.

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Table 1. Descriptive statistics of blood pressure phenotypes and anthropometric traits by generation and sex.

Phenotype	Fathers (n = 272)	Mothers (n = 408)	Sons (n = 330)	Daughters (n = 292)
SBP (mmHg)	131.20(13.97)	115.43(13.01)	110.70(12.98)	107.46(10.43)
DBP (mmHg)	79.43(9.69)	72.57(8.65)	61.45(7.84)	62.11(7.92)
PP (mmHg)	51.77(8.83)	42.77(7.83)	49.25(10.50)	45.35(8.43)
MAP (mmHg)	96.69(10.50)	86.82(9.56)	77.86(8.52)	77.22(7.89)
Height (cm)	174.94(6.59)	160.83(5.67)	143.62(18.41)	141.43(16.35)
Weight (kg)	80.94(11.13)	61.07(8.27)	39.99(15.63)	38.28(13.53)
Humerus breadth (cm)	6.85(0.32)	5.90(0.29)	5.67(0.69)	5.35(0.52)
Femur breadth (cm)	9.83(0.46)	8.85(0.41)	8.53(0.83)	7.97(0.70)
Upper arm circ. rel. (cm)	31.08(2.59)	27.88(2.64)	22.29(3.72)	22.22(3.40)
Upper arm circ. cont. (cm)	32.97(2.64)	28.99(2.73)	23.38(3.89)	23.01(3.37)
Waist circumference (cm)	92.28(8.86)	75.67(7.48)	64.06(8.03)	61.49(7.22)
Hip circumference (cm)	100.36(6.01)	98.42(6.49)	77.11(11.49)	78.76(12.64)
Medial calf circumference (cm)	38.48(2.56)	35.89(2.43)	30.49(4.50)	30.16(4.26)
Biceps skinfold (mm)	10.32(4.46)	14.91(6.01)	10.07(5.38)	12.12(5.45)
Triceps skinfold (mm)	13.23(5.02)	23.21(7.04)	15.06(6.07)	17.57(6.37)
Subescapular skinfold (mm)	24.61(8.12)	21.47(8.36)	10.34(5.83)	12.02(6.72)
Suprailiac skinfold (mm)	19.92(7.92)	17.33(8.98)	10.48(7.68)	12.95(8.44)
Abdominal skinfold (mm)	34.42(9.52)	26.16(9.07)	15.20(9.80)	17.48(9.46)
Medial calf skinfold (mm)	14.58(6.46)	22.42(7.18)	16.61(6.55)	19.02(6.66)
BMI (kg/m^2)	26.41(3.03)	23.61(3.07)	18.60(2.86)	18.47(2.90)
SF6(mm)	117.08(34.29)	125.88(40.62)	77.84(38.57)	91.24(40.39)
WHR	0.92(0.06)	0.77(0.05)	0.84(0.04)	0.79(0.06)
TER	2.18(0.55)	1.08(0.30)	0.82(0.27)	0.83(0.24)
Endomorphy	5.40(1.44)	6.08(1.68)	4.10(1.72)	4.84(1.74)
Mesomorphy	5.28(1.02)	4.24(1.01)	4.44(0.83)	3.90(0.88)

Ectomorphy	1.34(0.93)	1.61(0.98)	2.68(1.17)	2.60(1.15)

n- Number of subjects, SBP- Systolic blood pressure, DBP- Diastolic blood pressure, PP- Pulse pressure, MAP- Mean arterial pressure, BMI- Body mass index, SF6- Sum of 6 skinfolds, WHR- Waist to hip ratio, TER- Trunk to extremity skinfold ratio.

Mean (Standard deviation)

Table 2. Factor analysis of circumference and skinfold variables.

Circumferences	Factor loadings	Skinfolds	Factor loadings
Upper arm (rel.)	0.981	Biceps	0.898
Upper arm (cont.)	0.984	Triceps	0.839
Waist	0.936	Subescapular	0.828
Hip	0.957	Suprailiac	0.904
Medial calf	0.955	Abdominal	0.847
		Medial calf	0.781
Eigenvalue	4.634		4.339
Percent of total variance (%)	92.685		72.312

Table 3. Familial correlations and narrow sense heritability estimates (h^2) for the studied blood pressure and anthropometric phenotypes.

Traits	Correlations[a]			Heritability ± S.E. [b]
	Spouses	Parent-offspring	Siblings	
Blood pressure				
SBP	-0.00	**0.13**	0.12	0.25±0.06
DBP	0.04	**0.12**	**0.27**	0.28±0.06
PP	-0.01	**0.09**	-0.01	0.14±0.06
MAP	0.02	**0.14**	**0.27**	0.31±0.06
Anthropometric				
Weight	**0.16**	**0.28**	**0.27**	0.50±0.05
Waist circumference	**0.18**	**0.23**	**0.17**	0.39±0.06
BMI	**0.15**	**0.26**	**0.24**	0.46±0.05
SF6	0.12	**0.24**	**0.21**	0.43±0.06
WHR	**0.20**	**0.13**	**0.35**	0.29±0.06
TER	0.03	**0.20**	**0.31**	0.42±0.06
CRsF	0.12	**0.27**	**0.25**	0.48±0.05
SKsF	0.12	**0.25**	**0.23**	0.43±0.06
Endomorphy	0.10	**0.23**	**0.22**	0.40±0.06
Mesomorphy	0.06	**0.33**	**0.30**	0.60±0.05
Ectomorphy	**0.16**	**0.27**	**0.27**	0.48±0.05

SBP- Systolic blood pressure, DBP- Diastolic blood pressure, PP- Pulse pressure, MAP- Mean arterial pressure, BMI- Body mass index, SF6- Sum of 6 skinfolds, WHR- Waist to hip ratio, TER- Trunk to extremity skinfold ratio, CRsF- Circumferences factor, SKsF- Skinfolds factor.

[a] p-values <0.05 are marked in bold (for correlations).

[b] All estimates were significant at level p<0.0001, with the exception of PP (p=0.007)

Table 4. Phenotypic (ρ_P), additive genetic (ρ_G) and environmental (ρ_E) correlations between blood pressure phenotypes.

		SBP	DBP	PP
DBP	ρ_P	**0.66**		
	ρ_G	**0.88(0.07)**		
	ρ_E	**0.58(0.04)**		
PP	ρ_P	**0.73**	0.00	
	ρ_G	**0.73(0.11)**	0.32(0.22)	
	ρ_E	**0.74(0.03)**	-0.09(0.06)	
MAP	ρ_P	**0.88**	**0.94**	**0.33**
	ρ_G	**0.89(0.02)**	**0.98(0.01)**	**0.50(0.17)**
	ρ_E	**0.82(0.02)**	**0.92(0.01)**	**0.29(0.05)**

SBP- Systolic blood pressure, DBP- Diastolic blood pressure, PP- Pulse pressure, MAP- Mean arterial pressure.

p-values <0.05 are marked in bold.

( )- Standard error

Table 5 Phenotypic (ρ_P), additive genetic (ρ_G) and environmental (ρ_E) correlations between blood pressure phenotypes and anthropometric traits.

		SBP	DBP	PP	MAP
Weight	ρ_P	**0.28**	**0.22**	**0.17**	**0.27**
	ρ_G	**0.28(0.12)**	0.19(0.11)	0.30(0.16)	**0.23(0.11)**
	ρ_E	**0.30(0.06)**	**0.25(0.06)**	0.13(0.06)	**0.31(0.06)**
Waist circumference	ρ_P	**0.25**	**0.22**	**0.14**	**0.25**
	ρ_G	0.22(0.13)	0.10(0.13)	0.33(0.18)	0.144(0.123)
	ρ_E	**0.27(0.06)**	**0.28(0.06)**	0.08(0.06)	**0.31(0.06)**
BMI	ρ_P	**0.25**	**0.23**	**0.12**	**0.25**
	ρ_G	0.25(0.12)	0.20(0.12)	0.22(0.17)	0.22(0.11)
	ρ_E	**0.26(0.06)**	**0.25(0.06)**	0.10(0.06)	**0.29(0.06)**
SF6	ρ_P	**0.22**	**0.23**	**0.07**	**0.24**
	ρ_G	**0.32(0.13)**	**0.30(0.12)**	0.22(0.18)	**0.30(0.11)**
	ρ_E	**0.17(0.06)**	**0.20(0.06)**	0.03(0.06)	**0.21(0.06)**
WHR	ρ_P	**0.07**	**0.06**	0.04	**0.06**
	ρ_G	-0.15(0.17)	-0.21(0.16)	-0.02(0.21)	-0.20(0.16)
	ρ_E	**0.15(0.06)**	**0.17(0.06)**	0.06(0.06)	**0.18(0.06)**
TER	ρ_P	**0.12**	**0.11**	**0.07**	**0.13**
	ρ_G	0.05(0.14)	0.12(0.13)	0.03(0.18)	0.19(0.12)
	ρ_E	**0.16(0.06)**	0.11(0.06)	0.09(0.06)	**0.15(0.06)**
CRsF	ρ_P	**0.27**	**0.22**	**0.15**	**0.26**
	ρ_G	**0.29(0.12)**	0.18(0.12)	0.33(0.17)	0.22(0.11)
	ρ_E	**0.27(0.06)**	**0.26(0.06)**	0.10(0.06)	**0.30(0.06)**
SKsF	ρ_P	**0.21**	**0.23**	**0.07**	**0.24**
	ρ_G	**0.32(0.13)**	**0.28(0.12)**	0.23(0.17)	**0.29(0.11)**
	ρ_E	**0.17(0.06)**	**0.20(0.06)**	0.02(0.06)	**0.21(0.06)**
Endomorphy	ρ_P	**0.19**	**0.22**	**0.06**	**0.22**

	ρ_G	0.25(0.13)	**0.29(0.12)**	0.12(0.18)	**0.26(0.12)**
	ρ_E	**0.17(0.06)**	**0.18(0.06)**	0.05(0.06)	**0.20(0.06)**
Mesomorphy	ρ_P	**0.14**	**0.10**	**0.09**	**0.13**
	ρ_G	0.09(0.12)	0.11(0.11)	0.05(0.15)	0.10(0.10)
	ρ_E	**0.19(0.07)**	0.11(0.07)	0.13(0.07)	**0.16(0.07)**
Ectomorphy	ρ_P	**-0.19**	**-0.17**	**-0.09**	**-0.19**
	ρ_G	-0.21(0.12)	-0.23(0.12)	-0.07(0.17)	-0.21(0.11)
	ρ_E	**-0.19(0.06)**	**-0.15(0.06)**	-0.10(0.06)	**-0.18(0.06)**

SBP- Systolic blood pressure, DBP- Diastolic blood pressure, PP- Pulse pressure, MAP- Mean arterial pressure, BMI- Body mass index, SF6- Sum of 6 skinfolds, WHR- Waist to hip ratio, TER- Trunk to extremity skinfold ratio, CRsF- Circumferences factor, SKsF- Skinfolds factor.

p-values <0.05 are marked in bold.

( )- Standard error