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Heritability and genetic correlations of obesity indices with ambulatory and office beat-to-beat blood pressure in the Oman Family Study


Objective: To more precisely and comprehensively estimate the genetic and environmental correlations between various indices of obesity and BP.

Methods: We estimated heritability and genetic correlations of obesity indices with BP in the Oman family study (n = 1231). Ambulatory and office beat-to-beat BP was measured and mean values for SBP and DBP during daytime, sleep, 24-h and 10 min at rest were calculated. Different indices were used to quantify obesity and fat distribution: BMI, percentage of body fat (%BF), waist circumference and waist-to-height ratio (WHtR). SOLAR software was used to perform univariate and bivariate quantitative genetic analyses adjusting for age, age², sex, age-sex and age²-sex interactions.

Results: Heritabilities of BP ranged from 30.2 to 38.2% for ambulatory daytime, 16.8–21.4% for sleeping time, 32.1–40.4% for 24-h and 22–24.4% for office beat-to-beat measurements. Heritabilities for obesity indices were 67.8% for BMI, 52.2% for %BF, 37.3% for waist circumference and 37.9% for WHtR. All obesity measures had consistently positive phenotypic correlations with ambulatory and office beat-to-beat SBP and DBP (r-range: 0.14–0.32). Genetic correlations of obesity indices with SBP and DBP were higher than environmental correlations (r_G: 0.16–0.50; r_E: 0.01–0.31).

Conclusion: The considerable genetic overlap between a variety of obesity indices and both ambulatory and office beat-to-beat BP highlights the relevance of pleiotropic genes. Future GWAS analyses should discover the specific genes both influencing obesity indices and BP to help unravel their shared genetic background.

Keywords: ambulatory blood pressure, correlations, heritability, obesity indices, office beat-to-beat blood pressure

Abbreviations: %BF, percentage of body fat; BP, blood pressure; GWAS, genome-wide association studies; OFS, Oman family study; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio

INTRODUCTION

Obesity plays a major role in adversely affecting cardiovascular risk factors, including hypertension, dyslipidemia and diabetes mellitus, which are probably independent risk factors for atherosclerosis and cardiovascular events [1]. A recent review emphasized the intimate pathophysiological relationship between obesity and hypertension [2] and population-based studies showed that at least two-thirds of hypertension prevalence can be directly attributed to obesity [3]. The rise in BP with increases in BMI has been confirmed by various large-scale cross-sectional as well as longitudinal epidemiological studies [4–6]. In the longitudinal Coronary Artery Risk Development in Young Adults study, SBP and DBP did not change significantly in six examinations during 15 years among young people with steady BMI values (within 2 kg/m² of baseline), whereas in those with a BMI increase over 2 kg/m², SBP rose annually between 0.31 and 0.83 mmHg per year and DBP between 0.57 and 0.68 mmHg per year regardless of their baseline BMI [6]. Cross-sectional surveillance data of both National Health and Nutrition Examination Surveys (1988–1994 to 1999–2000) [5] in the United...
States and Chinese National Surveys on Students’ Constitution and Health (2005–2010) [4] examining trends in SBP/DBP among children and adolescents reported that BP increased over time but that this increase was reduced 12.0–40.5% after adjustment for BMI, indicating that the increase in BP was partially because of the rise in BMI. Meanwhile, a number of twin and family studies also showed familial aggregation of BMI and BP, which may be driven by shared genetic and/or environmental factors [7–9]. These twin and family studies estimated the genetic and environmental overlap between obesity and BP, but only used conventional office BP measurements and BMI as indicator of general obesity. Compared with office BP, ambulatory BP measurements have a number of advantages, such as providing a larger number of BP measurements, profiling BP behavior and capturing variations over 24-h. Most importantly, it is generally recognized to be more strongly associated with target organ damage and also a stronger predictor of cardiovascular morbidity and mortality [10]. Although BMI is the most commonly used surrogate marker of obesity, it lacks the capability of discriminating between body fat and lean mass [11]. A meta-analysis of 32 different studies on 31,968 individuals indicated that the BMI definition of obesity failed to identify nearly 50% of the population with excess percentage of body fat (%BF) [12]. The latter measure of %BF is recognized as a better predictor of cardiovascular risk factors than BMI [13]. In addition, more studies showed the importance of central or abdominal obesity measured by waist circumference and by fat distribution measured by waist-to-height ratio (WHR) in predicting cardiovascular risk [14].

To more precisely and comprehensively estimate the genetic and environmental correlations between obesity and BP, we analyzed a number of obesity indices in relation to both ambulatory and office beat-to-beat BP measures using data from the Oman Family Study (OFS). The OFS is a population-based family study from an isolated population that is environmentally and genetically homogeneous and is expected to have better power to examine the genetic contributions to BP and obesity indices and their overlap than studies conducted in outbred, heterogeneous populations [15].

**METHODS**

**Study population**

Five large, extended and highly consanguineous families totaling 1231 individuals with 304, 142, 225, 279 and 281 volunteers, each living in a separate village within a perimeter of 20 km around the City of Nizwa. Interviewed people represented approximately 10–15% of the total number of individuals in these five pedigrees. They were 16–80 years old and all voluntarily took part in the study, appeared healthy, and had no clinical complaints as determined by their actual waking and sleeping time as recorded in their diaries and confirmed by changes in BP. The average BP levels during the total 24-h and during daytime and sleep periods were calculated [19].

For the office beat-to-beat BP measurement, after reporting to the field research center at 0700 h and removing the BP monitor, participants were made to rest in supine position for 10 min on a comfortable bed, in a quiet office with a temperature between 24 and 26°C. Measurements were acquired for the subsequent 10 min using the Task Force Monitor (CNS Systems, Graz, Austria). The beat-to-beat BP was recorded using the vascular unloading technique whereby finger cuff readings were recorded, automatically counterchecked and corrected every minute, by the oscillometric BP measurements recorded from the contralateral upper arm.

Participants taking antihypertensive medications (n = 189) were not asked to stop medication, but the measured BP results were corrected (+15 mmHg for SBP and +10 mmHg for DBP) prior to analysis as recommended by previous studies [20,21].

**Measurement of obesity indices**

Height and weight were measured using standard methods. Waist circumference was measured by a soft tape at the
largest circumference between the lowest rib and iliac crest. %BF was assessed using electrical impedance (Tanita, Tokyo, Japan) [22], which showed good consistency compared with dual-energy X-ray absorptiometry as the recognized gold standard for measuring %BF (difference controlled within 5%). BMI was calculated as weight/height², where the units of weight and height are kilogram (kg) and meter (m), respectively. WHR was calculated as waist circumference/height, where the units of waist circumference and height are both centimeters (cm).

Statistical analysis
Descriptive statistics were used to present the baseline characteristics of the study sample and Student’s t-tests were used to test for sex differences in the means. Prior to analysis, distributions of all variables were checked. To obtain better approximations of normal distributions, measurements of BMI and all BP variables were transformed by natural logarithm. No outliers (more than four standard deviations from the mean) were observed. SOLAR (v7.2.5) software [23] was used to perform univariate and bivariate quantitative genetic analyses. SOLAR uses a variance-component method to analyze family-based quantitative data by decomposing the phenotypic variance into genetic and environmental components using the observed covariance in the trait among family members (Equation 1).

\[
\sigma^2_p = 2\Phi\sigma^2_G + I\sigma^2_E, \tag{1}
\]

where \(\Phi\) is a \(n\times n\) matrix of kinship coefficients, \(\sigma^2_p\) is the phenotypic variance, \(\sigma^2_G\) is the variance because of the additive genetic effects, \(\sigma^2_E\) is the variance because of the environmental effects and \(I\) is the identity matrix of order \(n\). Each genetic and environmental variance component is accompanied by a structuring matrix that predicts the covariance among individuals associated to that component. The structuring matrix for \(\sigma^2_G\) is twice the kinship coefficient (2\(\Phi\)) and for unmeasured, nongenetic factors (i.e. \(\sigma^2_E\)), it is the identity matrix \(I\). SOLAR estimates the narrow sense heritability (\(b^2\)) by the proportion of the phenotypic variance that can be attributed to additive genetic effects, that is, \(b^2 = \sigma^2_G / \sigma^2_p\). The significance of \(b^2\) was determined by using a likelihood ratio test where the log-likelihood of the estimated model is compared with that of the nested model where \(\sigma^2_G\) is fixed to zero using a chi-square test with 1 degree of freedom [24].

Bivariate quantitative genetic analyses were conducted to estimate the genetic and environmental correlations of obesity indices with BP using SOLAR. The model is an extension of that shown in Equation 1, where the phenotypic covariance between two individuals for two traits is given by a \(2\times2\) covariance matrix and can be calculated as in Equation 2:

\[
r_p = \left( \sqrt{b^2_{BP} \times r_G \times b^2_{Obesity}} \right) + \left( \sqrt{\sigma^2_{BP} \times r_E \times \sigma^2_{Obesity}} \right), \tag{2}
\]

where \(r_G\) is the additive genetic correlation and \(r_E\) the environmental correlation between obesity indices and BP, and \(\sigma^2\) is the environmental contribution to the overall phenotypic variance of the particular BP or obesity indices. With \(r_G\), the extent of common genetic effects on the two traits being analyzed is measured (i.e. pleiotropy). To test for the significance of shared genetic effects (\(|r_G| > 0\)), \(r_G\) was first estimated and subsequently fixed to zero in a nested sub-model allowing for a comparison of the two models using a likelihood ratio test. Similarly, to test for complete overlap of genetic effects (\(|r_G| = 1\)), \(r_G\) was fixed to one and compared with the more general model in which it was freely estimated. If \(r_G = 0\), it means that the two traits being analyzed are influenced by independent genetic factors. If \(|r_G| = 1\), the genetic factors are completely shared [24, 25].

RESULTS
A total of 1231 participants with a median age of 28 years (interquartile range: 21–45) were included in the analyses. Slightly more women participated in the study (54.9%). Men were taller and heavier, but no significant sex differences were found for age. In general, men had significantly higher BP. There were no significant sex differences for BMI and waist circumference, but men had lower %BF and WHR than women (Table 1).

Results of the univariate analyses showed that heritability estimates (\(b^2\)) ranged from 30.2 to 38.2% for daytime BP, 16.8–21.4% for sleeping BP, 32.1–40.4% for 24-h BP and 22–24.4% for office beat-to-beat BP. Heritability estimates were similar for ambulatory daytime and 24-h BP, but higher than ambulatory sleep and office beat-to-beat BP. Heritability estimates of BMI, %BF, waist circumference and WHR were 67.8, 52.2, 37.3 and 37.9%, respectively. Heritability estimates of all the traits were highly significantly different from 0 (Table 2).

The results of the bivariate quantitative genetic analyses showed consistently significant and positive phenotypic correlations between different obesity measurements and ambulatory daytime BP (\(r_G = 0.14–0.20\)), sleeping BP (\(r_G = 0.20–0.27\)), 24-h BP (\(r_G = 0.18–0.25\)) and office beat-to-beat BP (\(r_G = 0.14–0.32\)) (Table 3). The genetic correlations between BP and obesity indices were always larger than the environmental correlations, no matter whether BP was assessed during the daytime (\(r_G = 0.23–0.35\) vs. \(r_E = 0.01–0.12\)), at night (\(r_G = 0.34–0.49\) vs. \(r_E = 0.07–0.20\)), during 24-h (\(r_G = 0.26–0.39\) vs. \(r_E = 0.05–0.16\)) or as beat-to-beat measurement at the office (\(r_G = 0.16–0.50\) vs. \(r_E = 0.12–0.31\), except for BMI and office beat-to-beat DBP (\(r_G = 0.20\) vs. \(r_E = 0.22\)).

The genetic correlations of the different obesity indices (BMI, %BF, waist circumference and WHR) with ambulatory BP seemed to be higher in sleeping BP (\(r_G = 0.34–0.49\)) compared with daytime BP (\(r_G = 0.23–0.35\)) and 24-h BP (\(r_G = 0.26–0.39\)). Table 3 shows that all these \(r_G\)s were significantly greater than 0 except for the one between WHR and daytime SBP (\(r_G = 0.23, P = 0.051\)). However, as expected, the genetic factors were not completely shared as all \(r_G\)s were significantly less than 1. No large differences were found between the genetic correlations of SBP (\(r_G = 0.23–0.50\)) and DBP (\(r_G = 0.16–0.49\)) with the different obesity measures.

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The aim of our study was to estimate the heritability of ambulatory BP and obesity indices among siblings, the heritability estimates for ambulatory SBP and DBP were 0.37 and 0.24, respectively for daytime and 0.34 and 0.22 for night-time measurements (\(r_{c2}\); 0.12–0.31; \(P < 0.05\)) and usually larger than those between ambulatory BP and obesity indices (\(r_{c2}\); 0.01–0.20).

## DISCUSSION

The aim of our study was to estimate the heritability of ambulatory and office beat-to-beat BP and various indices of obesity and to explore to what extent they shared genetic and/or environmental factors. Our study echoed previous findings on the heritability estimates and the positive phenotypic, genetic and environmental correlations between office BP and BMI. Here we confirmed substantial genetic correlations between ambulatory BP and other indices of general obesity (%BF), abdominal obesity (waist circumference) and fat distribution (WHtR). Shared genetic factors contributed more to the phenotypic correlations than environmental factors. The genetic correlations seemed to vary under different conditions as they were higher during sleep than for daytime SBP and DBP.

Our study found moderate heritability for ambulatory and office beat-to-beat SBP and DBP, which varied for different measurement conditions. It was higher for daytime compared with sleep BP and the heritabilities of office beat-to-beat BP were lower compared with those for ambulatory daytime and 24-h BP measurements. These results were in line with the univariate BP heritability estimates we published previously [19] and similar to other family studies of ambulatory BP conducted in different populations (SBP: ranging from 0.25 to 0.39; DBP: ranging from 0.20 to 0.41) [29–31]. For example, Fava et al. [26] reported that in 118 Swedish families with 260 siblings (without antihypertensive treatment), heritabilities were significant for ambulatory night-time SBP (37%), DBP (32%), ambulatory daytime SBP (33%), 24-h SBP (30%) and DBP (29%) (\(P < 0.05\) for all). Another family study conducted in 1009 individuals from 271 nuclear Swiss families also reported significant heritability for ambulatory daytime SBP (39%), night-time SBP (25%), 24-h SBP (37%) and ambulatory daytime DBP (28%), night-time DBP (20%), 24-h DBP (26%), respectively [29]. In a study of African families consisting of 314 individuals (147 men and 167 women) and with at least two hypertensive siblings, the heritability estimates for ambulatory SBP and DBP were 0.37 and 0.24, respectively for daytime and 0.34 and 0.37 for night-time measurements (\(P < 0.05\) for all estimates) [27]. A study of 520 white European nuclear families including 2020 individuals reported heritabilities of 0.33 for mean 24-h SBP and 0.41 for mean 24-h DBP [28].

### Table 2. Heritability estimates of blood pressure and obesity measurements

<table>
<thead>
<tr>
<th>Traits</th>
<th>(N)</th>
<th>(h^2)</th>
<th>SE</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime SBP</td>
<td>1178</td>
<td>0.302</td>
<td>0.048</td>
<td>4.27 \times 10^{-23}</td>
</tr>
<tr>
<td>Daytime DBP</td>
<td>1178</td>
<td>0.382</td>
<td>0.052</td>
<td>2.15 \times 10^{-30}</td>
</tr>
<tr>
<td>Sleep SBP</td>
<td>1138</td>
<td>0.214</td>
<td>0.049</td>
<td>4.32 \times 10^{-10}</td>
</tr>
<tr>
<td>Sleep DBP</td>
<td>1138</td>
<td>0.168</td>
<td>0.047</td>
<td>8.0 \times 10^{-6}</td>
</tr>
<tr>
<td>Total 24-h SBP</td>
<td>1155</td>
<td>0.321</td>
<td>0.051</td>
<td>8.27 \times 10^{-23}</td>
</tr>
<tr>
<td>Total 24-h DBP</td>
<td>1155</td>
<td>0.404</td>
<td>0.054</td>
<td>3.59 \times 10^{-30}</td>
</tr>
<tr>
<td>Office beat-to-beat SBP</td>
<td>1123</td>
<td>0.244</td>
<td>0.053</td>
<td>5.1 \times 10^{-10}</td>
</tr>
<tr>
<td>Office beat-to-beat DBP</td>
<td>1123</td>
<td>0.220</td>
<td>0.052</td>
<td>1.19 \times 10^{-6}</td>
</tr>
<tr>
<td>Obesity index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>1231</td>
<td>0.678</td>
<td>0.050</td>
<td>7.70 \times 10^{-57}</td>
</tr>
<tr>
<td>Body fat</td>
<td>1214</td>
<td>0.522</td>
<td>0.056</td>
<td>2.35 \times 10^{-35}</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>1204</td>
<td>0.373</td>
<td>0.053</td>
<td>3.70 \times 10^{-21}</td>
</tr>
<tr>
<td>Waist-to-height ratio</td>
<td>1204</td>
<td>0.379</td>
<td>0.053</td>
<td>3.23 \times 10^{-22}</td>
</tr>
</tbody>
</table>

Models were adjusted for age, sex, age\(^2\), age \times sex and age\(^2\) \times sex. BP, blood pressure.
Some of this variation in BP heritability estimates may be because of different genes contributing to BP regulation under different measurement conditions, such as daytime vs. night-time or office vs. real life, which was also shown in previous twin studies [30,31]. For daytime vs. night-time we confirmed this in our own data by performing bivariate analyses of ambulatory BP during daytime and sleep. The genetic correlation between daytime and sleep was 0.83 for SBP and 0.69 for DBP. Both correlations were significantly different from 1 (P < 0.001) indicating partly different genes influencing BP during these measurement conditions. These results are further supported by findings from mouse model studies showing rhythmic gene expression in normal heart and aorta under light–dark conditions with two major peaks: one in the light and one in the dark [32,33].

Earlier heritability estimates of obesity indices varied among different populations (BMI: ranging from 0.16 to 0.85; %BF: ranging from 0.35 to 0.43; waist circumference: ranging from 0.37 to 0.81) [34–36]. Taking abdominal obesity as an example, Davey et al. [37] reported that the heritability was over 90% for abdominal obesity in an Indian population, whereas a family study in an Old Order Amish community showed a heritability of 57% for waist circumference and 13% for waist-to-hip ratio, respectively [38]. Compared with above studies, our study reported moderate (37.3–67.8%) heritability estimates for the obesity indices.

Our study found consistently significant and positive phenotypic correlations between BP and obesity indices. This pattern was consistent with results from large-scale epidemiological studies [39]. Virgina et al. [39] reported that significant associations (adjusted odds ratio ranged from 2.6 to 7.4) were found between overweight, obesity, or high waist circumference with high BP after adjusting for age and sex among Lithuanian adolescents. Some animal studies have suggested that the association between obesity and BP was mediated by leptin [40], but human studies do not support this [41]. In our own data, %BF showed the largest correlation with leptin (r = 0.764; P < 0.01), followed by the other three obesity indices (r ranging from 0.472 to 0.621; all P values < 0.01). Compared with the four obesity indices, we found much lower correlations (r ranging from −0.035 to 0.144) of leptin with the different BP measurements in our study. The pattern of correlations between leptin and BP measures closely mimicked the results for %BF, but were much more modest and often nonsignificant (Supplementary Table 2, http://link.s.lww.com/HJH/B305). Obesity is the well-recognized risk factor for hypertension and genetic factors may play an important role in this association. Howe et al. [42] reported that a genetic risk score composed of 32 BMI loci identified in genome-wide association studies (GWAS) was strongly associated with SBP both at age 6 and 17 years and in a meta-analysis [43] on 57 464 hypertensive cases and 41 256 controls, it was found that the first GWAS-identified obesity gene (FTO), also known as FTO alpha-ketoglutarate-dependent dioxygenase and located on chromosome 16. It was the first gene identified in a genome-wide association study of BMI as an index of general obesity [44] and was significantly associated with hypertension.

Our study also identified significant genetic contributions to the phenotypic correlation of different obesity indices with ambulatory and office beat-to-beat BP. This pattern was generally in line with twin and family studies of conventionally measured BP and BMI [7–9]. For example,
Schieken, et al. [7] found a significant phenotypic correlation between SBP and BMI in a twin study of children ($r=0.29$) and showed that the percentage of variance of SBP explained by genetic factors common between SBP and BMI was 8%. Similar findings were reported in an adult study of Chinese twins, which showed that the genetic and unique environmental correlations were 0.38 and 0.17, respectively, between BMI and SBP and 0.48 and 0.12 between BMI and DBP. The genetic factors influencing both BMI and BP accounted for 6 and 7% of the total variance in SBP and DBP, respectively [8]. In a large family study of 2912 individuals from 767 adult nuclear families, the phenotypic correlation between SBP and BMI was 0.36 and the genetic correlation was 0.30 [9]. Our study did not find significant environmental correlations between ambulatory BP and obesity indices, except for sleep SBP with BMI, waist circumference and WHR and for 24-h BP with waist circumference and WHR. Thus, shared genetic factors had a larger contribution to the phenotypic correlations between ambulatory BP and obesity than environmental factors. However, it was found that all environmental correlations of obesity indices with office beat-to-beat BP were significantly different from 0 and were higher than with ambulatory BP. In addition, in the current study, genetic correlations with obesity indices seemed to be lower for daytime BP than for sleeping BP but no differences were found between SBP and DBP. This might possibly be because of partly different genes regulating daytime and night-time BP [30,45].

A strength of this family study is that it was conducted in a homogeneous Arab population, in which the individuals had a very similar genetic background (tradition of encouraging consanguineous marriage) and shared environmental effects (living in a relatively isolated region). Consequently, it was expected to have somewhat better power to examine the genetic contributions to BP and obesity indices than studies conducted in outbred, heterogeneous populations [15]. Another strength is that BP values were measured using 24-h ambulatory monitoring, which is believed to better predict target organ damage than conventional BP methods [46]; and various indices, including %BF as a more accurate measure of general obesity than BMI, waist circumference representing abdominal obesity and WHR representing fat distribution, were used to capture different aspects of obesity. Furthermore, the effects of hypertension medication were corrected to optimally preserve genetic variability as recommended by previous studies [20,21] to ensure data quality. However, there are also some limitations of this study. Firstly, although our study contained data on more than 1200 participants, the sample size may still not be large enough to clearly discriminate between genetic and/or environmental correlations among different obesity indices and/or BP conditions. Secondly, waist-to-hip ratio (WHR) would also be a good index to represent central obesity, but unfortunately hip circumference was only measured in part of the sample. Instead, we decided to use WHR, on which we had complete data and showed a strong phenotypic correlation ($r_p=0.62$, $P<0.01$) with WHR for the part of the sample of which WHR was available. Furthermore, previous studies also reported that WHR and WHR had comparable correlations with SBP ($r$: 0.41 vs. 0.36) or DBP ($r$: 0.35 vs. 0.31) [47].

In conclusion, our study quantified the considerable genetic overlap between a variety of obesity indices and both ambulatory and office beat-to-beat BP and highlights the relevance and potential of identification of pleiotropic genes. More advanced analyses, for example, GWAS could and should be undertaken to discover the specific genes both influencing obesity indices and BP, and thus help unravel the shared genetic background of these two clinically relevant traits.

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Author contributions statement: T.M. analyzed the data and drafted the manuscript; Z.A., D., J., M.O.H., S.A.Y., R.B., A.G.C. and S. A. collected data; M. L. M. and A.M.R. helped to explain the results; H.R., I.M.N., J.F. and H.S. revised the manuscript critically; all authors reviewed the manuscript.

Conflicts of interest

There are no conflicts of interest.

REFERENCES


Genetic associations of obesity indices with BP


