Familial Factors of Blood Pressure and Adiposity Covariation

Gregory Livshits, Linda M. Gerber

Abstract—In the present study, we used the maximum likelihood approach as implemented by variance analysis and attempted to quantify genetic and environmental components of variance in systolic (SBP) and diastolic (DBP) blood pressure in 514 individuals who belonged to a total of 135 nuclear families of Chuvasha, Russia, ethnic origin. The extent to which these interindividual differences depend on age, gender, body mass index (BMI) and other anthropometric measurements was investigated. Major findings include the following. (1) The variation in both SBP and DBP was significantly affected by genetic factors ($h^2_{SBP}=0.51\pm0.13$, $h^2_{DBP}=0.20\pm0.09$), shared household environment, and age. These effects were stronger with respect to SBP, which also showed significant gender differences in baseline values and rate of SBP increase with age. (2) Genetic and common household factors, as well as undetected residual effects, were not completely independent. The respective 3 facets of correlation between SBP and DBP were significant: $0.66\pm0.10$, $0.76\pm0.11$, and $0.55\pm0.14$. (3) SBP and DBP each showed significant phenotypic correlations with BMI and anthropometric factors. These correlations had a substantial genetic component but were not equal for SBP and DBP. DBP showed the highest genetic correlation with arm circumference ($r_G=0.63$), whereas for DBP, this was found with hip skinfold ($r_G=0.88$). (4) Bivariate heritability estimates, as well as adjustment of BP measurements for BMI and selected anthropometrics, indicated that DBP likely does not have independent genetic heritability. The residual genetic variance of adjusted SBP remained significant, although substantially lower in comparison with the nonadjusted $h^2$. (*Hypertension*. 2001;37:928-935.)

Key Words: blood pressure ■ genetics ■ anthropometrics ■ body mass index

Extensive literature exists that documents the relationship between blood pressure (BP) and measures of body fat and fat distribution.1–4 Most studies report significant associations for men and women both within populations5,6 and between populations.7,8 Recent studies suggest this relationship has early beginnings, perhaps from birth or maybe prenatally.9–11

Measures of adiposity reported vary from study to study, as do their relationships to BP. The most commonly reported adiposity measures include weight, waist circumference, subscapular and triceps skinfold measures (as well as their sum), and indices such as body mass index (BMI), waist-to-hip (circumference) ratio (WHR), and various skinfold ratios. A recent review of studies that examined the associations of adiposity measures to BP found the vast majority reported significant relationships.6

The WHR has been found to be associated with BP in some studies12,13 but with diastolic BP (DBP) and not systolic BP (SBP) in other studies.14 In contrast, Gerber et al 6 found that of the 7 adiposity measures examined, all were significantly related to BP except the WHR. Subscapular skinfold thickness was the best adiposity predictor of BP, but BMI was also found to be a good predictor. Seidell et al8 concluded from a multicenter study of women that among anthropometric (AP) variables, BMI was the best overall predictor of both SBP and DBP. The significant positive association between BMI and both SBP and DBP has been reported in studies of African-Americans,15 Chinese,16,17 Africans, and Caribbeans.18 The studies conducted in China, Africa, and the Caribbean are especially noteworthy because significant relationships held even in these lean populations.

Despite the large body of publications that clearly suggest a consistent and substantial relationship between the BP measurements and AP characteristics, relatively few studies have addressed the extent and relative contributions of genetic and environmental effects on this covariation. The conclusions reached in these studies vary from the position of substantial genetic correlation between BP and AP,19–21 which could be so great that heritability of BP is almost wholly attributable to genetic factors that affect obesity,22 to conclusions that reject any genetic contributions to this correlation.23,24

In the present study, we assessed a large number of AP traits and BP in 514 individuals who belonged to a total of...
135 nuclear pedigrees. The genetic correlation between body composition measures and BP was analyzed in an attempt to quantify the contributions of heritability and environmental components to this association.

**Methods**

**Sample and Measurements**

Pedigree data from Chuvasha (Russia) were gathered randomly from individuals who previously volunteered to participate in other studies not related to the present one. Further details on sample selection and data collection procedures were reported by Livshits et al.25

The present sample contained 135 nuclear pedigrees composed of 527 observed individuals. The vast majority of pedigrees included 2 parents with 1 to 3 offspring each. The age of the individuals ranged from 18 to 91 years for men and from 18 to 86 years for women. The present data were collected in 1994 from individuals living in 40 villages near the city of Cheboksary as part of an epidemiological study on bone aging. The pedigree ascertainment was random with regard to health status and other assessed outcome variables.

Ethnically, Chuvasha consists of a mixed white population who intermarried with the local Finno-Ugor tribes.26 The climate of Chuvasha where the present population lives is moderately continental with average temperatures of −12°C in January and 19°C in July and a mean annual precipitation of ~450 mm.27

Consecutive BP measurements were taken on the left arm of each participant while in a seated position after a 10-minute rest. With a standard mercury sphygmomanometer and stethoscope, the measurements were taken twice at 5-minute intervals by the same nurse (see Livshits et al for further details). The average of the 2 blood pressure measurements was used as the estimate of SBP and DBP in the present analysis. AP measures taken from each individual included 8 skinfold measures from the body trunk and extremities: (1) chest (Che.sk), (2) abdomen (Abd.sk), (3) subscapular (Sub.sk), (4) hip (Hip.sk), (5) upper arm medial (Med.sk), (6) upper arm dorsal (Dor.sk), (7) lower arm (Low.sk), and (8) calf (Clf.sk); 9 circumference measures, including the chest and various levels of upper and lower extremities; (1) mesosternal chest minimal (Mmi.cr), (2) waist (Wai.cr), (3) hip (Hip.cr), (4) upper arm (Upp.cr), (5) lower arm (Low.cr), (6) wrist (Wri.cr), (7) thigh (Thi.cr), (8) calf (Clf.cr), and (9) ankle (Ank.cr); and the 2 indices of WHR and BMI. All measurements were obtained with standard AP techniques.28

**Statistical Analysis**

Pairwise correlation coefficients were calculated for all AP variables with each other and with SBP and DBP measures. Correlations between BP variables and adiposity measures were also tested as stratified by generation and gender (ie, father, mother, son, and daughter) with control for age. Two-tailed probability levels for statistical significance are reported.

**Statistical/Genetic Analysis**

To examine genetic and environmental effects on the variation of each of the selected traits in the study, variance component analysis was performed using the FISHER statistical package,29 with minor modifications. The program finds the best-fitting and most parsimonious model of the trait variability and produces maximum likelihood estimates of genetic and various common family environment components and corresponding standard errors on the basis of

### Table 1. Characteristics of the Chuvasha Study Sample by Generation/Gender Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Father</th>
<th>Mother</th>
<th>Son</th>
<th>Daughter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.6±6.1 (115)</td>
<td>62.9±5.9 (122)</td>
<td>34.4±9.9 (178)</td>
<td>36.6±10.4 (112)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>139.4±20.6 (109)</td>
<td>139.8±23.6 (115)</td>
<td>124.1±13.9 (176)</td>
<td>120.4±15.3 (112)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>82.1±12.8 (109)</td>
<td>82.0±12.8 (115)</td>
<td>74.3±11.2 (176)</td>
<td>73.5±11.0 (112)</td>
</tr>
</tbody>
</table>

Skinfold measurement, mm

<table>
<thead>
<tr>
<th>Che.sk</th>
<th>10.2±5.5 (112)</th>
<th>16.4±7.6 (118)</th>
<th>10.6±5.0 (176)</th>
<th>17.1±6.3 (112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abd.sk</td>
<td>13.2±7.1 (112)</td>
<td>21.1±10.0 (117)</td>
<td>13.9±7.1 (177)</td>
<td>19.9±7.5 (112)</td>
</tr>
<tr>
<td>Sub.sk</td>
<td>9.7±4.6 (113)</td>
<td>15.4±7.2 (119)</td>
<td>10.3±4.3 (177)</td>
<td>15.4±6.3 (112)</td>
</tr>
<tr>
<td>Hip.sk</td>
<td>7.9±3.4 (113)</td>
<td>13.6±5.7 (119)</td>
<td>8.2±3.7 (177)</td>
<td>14.9±5.8 (112)</td>
</tr>
<tr>
<td>Med.sk</td>
<td>3.0±1.2 (114)</td>
<td>5.5±2.9 (119)</td>
<td>3.2±1.1 (177)</td>
<td>6.2±3.2 (112)</td>
</tr>
<tr>
<td>Dor.sk</td>
<td>7.0±2.8 (114)</td>
<td>14.0±5.7 (119)</td>
<td>7.4±2.9 (177)</td>
<td>15.1±4.8 (112)</td>
</tr>
<tr>
<td>Low.sk</td>
<td>3.7±1.4 (114)</td>
<td>5.4±2.6 (119)</td>
<td>3.7±1.4 (177)</td>
<td>6.3±3.1 (112)</td>
</tr>
<tr>
<td>Clf.sk</td>
<td>6.0±2.5 (113)</td>
<td>10.4±4.5 (119)</td>
<td>6.6±2.7 (176)</td>
<td>11.4±4.0 (112)</td>
</tr>
</tbody>
</table>

Circumference measurement, mm

<table>
<thead>
<tr>
<th>Mmi.cr</th>
<th>908.2±71.0 (114)</th>
<th>872.2±82.7 (119)</th>
<th>914.5±60.5 (177)</th>
<th>862.4±65.1 (112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wai.cr</td>
<td>827.4±106.2 (114)</td>
<td>806.7±116.4 (119)</td>
<td>807.6±71.4 (177)</td>
<td>766.3±100.6 (112)</td>
</tr>
<tr>
<td>Hip.cr</td>
<td>895.0±68.6 (113)</td>
<td>952.3±97.7 (119)</td>
<td>917.1±50.8 (177)</td>
<td>965.1±75.0 (112)</td>
</tr>
<tr>
<td>Upp.cr</td>
<td>259.5±31.6 (114)</td>
<td>267.4±39.8 (119)</td>
<td>283.2±24.1 (177)</td>
<td>281.2±36.6 (112)</td>
</tr>
<tr>
<td>Low.cr</td>
<td>248.8±21.6 (114)</td>
<td>230.7±20.0 (119)</td>
<td>266.2±18.1 (177)</td>
<td>241.5±18.7 (112)</td>
</tr>
<tr>
<td>Wri.cr</td>
<td>171.8±12.2 (113)</td>
<td>161.4±12.6 (119)</td>
<td>176.3±9.7 (177)</td>
<td>162.9±10.9 (112)</td>
</tr>
<tr>
<td>Thi.cr</td>
<td>471.5±44.8 (112)</td>
<td>497.1±56.3 (119)</td>
<td>513.4±41.0 (177)</td>
<td>540.8±43.4 (112)</td>
</tr>
<tr>
<td>C1f.cr</td>
<td>317.4±27.3 (113)</td>
<td>319.7±26.3 (119)</td>
<td>341.1±27.6 (176)</td>
<td>342.0±25.4 (112)</td>
</tr>
<tr>
<td>Ank.cr</td>
<td>209.3±17.3 (114)</td>
<td>211.3±14.9 (118)</td>
<td>220.9±15.7 (177)</td>
<td>219.7±13.0 (112)</td>
</tr>
<tr>
<td>WHR</td>
<td>0.92±0.07 (113)</td>
<td>0.84±0.06 (119)</td>
<td>0.88±0.05 (177)</td>
<td>0.79±0.06 (112)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.8±3.6 (113)</td>
<td>24.6±4.7 (119)</td>
<td>23.4±2.7 (177)</td>
<td>24.5±3.9 (112)</td>
</tr>
</tbody>
</table>

Values are mean±SD (n).
pedigree data. The method allows one to partition the total phenotypic variation of the study trait (V\textsubscript{PH}) into a number of components, according to contributing factors: (1) V\textsubscript{AD} is additive genetic component, (2) V\textsubscript{SP} is shared spouse environment component, (3) V\textsubscript{HS} is common household environment component, (4) V\textsubscript{EK} is individual specific residual component. The general univariate model can be constructed by sequential restriction of the parameters to the expected values: for example, no genetic determination of trait, V\textsubscript{AD} = 0.

The effects of age and gender on each studied variable were estimated simultaneously with the variance components, using the linear regression function estimated simultaneously with the variance components, using the classic formula:

\[ V_{PH} = V_{AD} + V_{SP} + V_{HS} + V_{EK} \]

To determine the possible extent of genetic and environmental covariation between all possible pairs of traits, covariance decomposition analysis (bivariate analysis) was undertaken with the same FISHER package. In this analysis, both genetic and environmental covariation (all r\textsubscript{P}≤0.01) with SBP, with BMI and upper arm circumference demonstrating significant associations in all 4 groups. The bivariate heritability estimate was calculated using the classic formula:

\[ h^2_{adj}(XY) = \frac{2COV_{adj}(XY)}{V_{adj}(XY)/V_{adj}(XX)COV_{adj}(YY)/V_{adj}(YY)} \]

To avoid bias due to multiple testing, principal components analysis was also conducted. The results of both the univariate and bivariate analyses yielded very similar estimates to our variance decomposition approach and corroborated our findings for the effects of genetic factors, shared marital environment, and residual effects on single AP variables. Due to the greater ease in interpretation, only the latter results are presented.

**Results**

Basic descriptive statistics for all study variables by generation and gender cohort are given in Table 1. The mean ages of the parent generation are 64 and 63 years, respectively, for fathers and mothers, and the mean age is 34 years for sons and 37 years for daughters. As expected, mean skinfold thicknesses were higher among women than among men, whereas the gender pattern in circumferences varied by adiposity measure.

Correlation coefficients between AP characteristics and BP, with control for age, are shown in Table 2. At least 5 AP measures in each group show significant (all r\textsubscript{P}≤0.01) associations between AP variables and BMI, with significance (P<0.05) achieved in 8 relationships among the sons and in 13 among the daughters.
Variance Analysis

Table 3 provides parameter estimates for each of the 5 components examined, as obtained in the univariate analyses. Each estimate of the most parsimonious model was found a number of times. The optimization began with different randomly selected initial values but converged finally to the same parameter estimates. With respect to BP measurements, variance analysis with simultaneous estimates for gender and age effects showed (1) for SBP, 51% of the total variation was attributable to genetic factors and almost 30% was accounted for by shared household environment, and (2) for DBP, both parameter estimates were lower, ~20% and ~22%, respectively. In all instances, likelihood ratio tests indicated, with P<0.01, that neither V 0.001. The strength of the correlation ranged from moderate and marginally significant (0.409 ± 0.203) between DBP and BMI to a quite high and significant estimate between DBP and Hip.sk (0.88 ± 0.17). As seen in Table 4, genetic correlations of SBP with both BMI and Upp.cr were of substantial magnitude and statistical significance. The analyses demonstrated significant bivariate heritability estimates for each pair of study traits as shown in Table 4. Approximately 50% of the SBP variation attributable to genetic factors is shared with those that determine adiposity variation. In particular, between 24% and 27% of SBP variation adjusted for gender and age effects was accounted for by genetic factors shared with Upp.cr and BMI, respectively. For DBP, the situation is different. The effects of genetic factors on the interindividual variation in Hip.sk and DBP simultaneously were of the higher magnitude as DBP-specific genetic effects. These are probably the same genes (h 2 = 0.20 versus h 2 = 0.26), and numerical differences can likely be explained by the relatively large standard error associated with the h 2 estimate for DBP (Table 3). Bivariate h 2 values for DBP and BMI, however, are considerably lower and only marginally significant (P = 0.07).

To examine the extent of SBP (and DBP) genetic variation independent of genetic sources that govern adiposity variation, our univariate model was slightly modified. The matrix of the observable covariates now included not only age, T, but also BMI and Upp.cr for SBP and BMI and Hip.sk for DBP, respectively. As seen in Tables 5 and 6, the obtained results are easily interpreted. First, concerning the covariates, age and gender effects, although they changed substantially quantitatively, they qualitatively showed the same trend as before. Correlation (regression) between SBP and Upp.cr was also strong and highly significant but gender independent (β = 0.151 ± 0.024 for both genders). The independent effect of BMI on SBP was not observed. Finally, the contribution of the genetic factors on SBP variation dropped to 37.3% (from 51.4% in the previous analysis), whereas V HS did not change.

A similar outcome to SBP was demonstrated for DBP (Table 6). In addition to previously detected gender and age effects, Hip.sk and BMI were retained in the model. Both effects were different in men and women. However, although the effect of Hip.sk was much higher in men than in women,
as measured by regression coefficient β (0.829 versus 0.321), the effect of BMI was negligible in men. In accordance with the above reported bivariate h^2 estimates (Table 4), Table 6 demonstrates that almost no independent genetic effects on DBP were detected in the last model, V_{Ap}=14.8±11.8.

**Discussion**

A vast amount of evidence suggests a strong and consistent relationship between BP levels and various measures of adiposity. Findings to date clearly indicate that both BP and AP are complex multifactorial traits that develop during the close interaction of social, economic, behavioral, physiological, and other factors. The large number of twin, adoption, and family studies also points out that genetic heritability accounts for a substantial portion of interindividual variation in each of these domains of the human phenotype.

In the present study, we used the maximum likelihood approach as implemented by variance decomposition analysis to quantify genetic and environmental components of variance in SBP and DBP among families living in Chuvasha, Russia. We also investigated the extent to which these interindividual differences are dependent on age, gender, BMI, and some selected AP measurements. Our major findings can be summarized as follows: (1) The variation of both SBP and DBP was significantly affected by genetic factors, shared household environment, and age (Table 3). These effects were stronger with respect to SBP, which also showed significant gender differences in baseline values and rate of SBP increase with age. (2) Genetic and common household factors, as well as undetected residual effects, were not completely independent. The respective 3 facets of correlation between SBP and DBP were significant: 0.66±0.10, 0.76±0.11, and 0.55±0.14. (3) SBP and DBP each showed significant phenotypic correlations with BMI and many other AP measures (Table 2). These correlations had a substantial genetic component but were not equal for SBP and DBP. SBP showed the highest genetic correlation with Upp.cr (rG=0.63), whereas for DBP, this was found with Hip.sk (rG=0.88). (4) Bivariate heritability estimates, as well as adjustment of BP measurements for BMI and selected AP factors, indicated that DBP likely does not have independent genetic heritability (Table 6). The residual genetic variance of adjusted SBP remained significant, although substantially lower in comparison with the nonadjusted h^2 (Table 5).

The strong genetic effect noted in this study is particularly noteworthy given the overall leanness of the sample. We can posit that if levels of adiposity were greater, there would be more variability seen in the adiposity measures with even greater genetic effects, with different effects on different measures. Another difference between this sample and most others is that high BP, for the most part, was not treated. This may help to explain the greater variability of BPs reported, especially in the parent generation.

There is a growing body of literature that suggests environmental factors that operate during fetal and early life may have profound effects on disease susceptibility in later life.
Barker and colleagues\textsuperscript{9,36,37} suggested that maternal undernutrition during pregnancy leads to retarded intrauterine growth and increased risk of hypertension and cardiovascular disease. Another theory\textsuperscript{38,39} hypothesizes that nephron numbers are programmable in utero such that deficiencies in nephron endowment at birth result in hypertension in later life. An alternative to the direct effect of the intrauterine influence on BP is that accelerated growth sometimes observed in low birth weight babies during early infancy may be linked to an accelerated rate of increase in BP levels that persist over time.\textsuperscript{4,40}

Circumstances operating in utero, and in early life, may affect the total interindividual variation of BP. It is unlikely that the induced variation would somehow simulate the genetic variation, which was assessed in our model through covariation between biological relatives. It could contribute to common family environment, which would be captured in our model under the category of the shared sibs environment, or through inequality of mother/offspring versus father/offspring covariation. The latter assumption is tested when the additive genetic component is estimated. Because none of these expectations were confirmed in our analysis, we believe that any environmental contribution to these components of variation was rather negligible.

Significant genetic effects on BP have been well established in numerous studies published during the past 3 decades (for reviews, see Ward\textsuperscript{32} and Livshits et al\textsuperscript{34}).

### TABLE 4. Bivariate Genetic Analysis of Blood Pressure and AP Variables in Chuvasha Pedigrees

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SBP/BMI</th>
<th>SBP/Upp.cr</th>
<th>DBP/BMI</th>
<th>DBP/Hip.sk</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r_0^*$</td>
<td>0.561±0.153</td>
<td>0.628±0.156</td>
<td>0.409±0.203</td>
<td>0.877±0.172</td>
</tr>
<tr>
<td>$r_1^*$</td>
<td>0.024±0.200</td>
<td>0.627±0.177</td>
<td>0.162±0.128</td>
<td>0.085±0.144</td>
</tr>
<tr>
<td>$h^2$</td>
<td>0.268†</td>
<td>0.241†</td>
<td>0.126‡</td>
<td>0.262†</td>
</tr>
</tbody>
</table>

$r_0$ and $r_1$ indicate maximum likelihood estimates of the bivariate genetic and environmental correlations; $h^2$, corresponding bivariate heritability estimate.

*Values are mean±SEM.

†$P<0.01$.

‡NS.
BMI and body weight. Significant genetic correlations were found in these analyses, which are in accord with the present results.

The contribution of pleiotropy to BP and AP was found in studies by Majumder et al22 and Vinck et al,23 whereas in An et al,24 no genetic correlation was detected between the BP and AP. These 3 studies are useful to compare. All 3 used path analysis. Vinck’s team studied covariation in a twin design study, whereas the 2 other groups used mostly nuclear pedigrees. Vinck et al’s43 maximum likelihood estimates showed significant \( r_g \) between both SBP and DBP and BMI, yet the residual \( h^2 \) for both SBP and DBP remained significant, too. Majumder et al22 tested various hypotheses of BP transmission adjusted for AP variables and showed that there was no residual genetic heritability of adjusted SBP or DBP levels.

The discrepancy in the pleiotropic effects noted in these studies, including the present one, may be attributed to the following. (1) The basic familial resemblance (correlations) for BP measures was low (or lower) in the studies where residual \( h^2 \) was not significant. For example, in Majumder et al,22 maximum likelihood estimates of some familial correlations were significant, but some were not. Further analysis implementing path models showed that observed familial resemblance of BP levels is primarily due to cultural rather than to genetic inheritance. In our study, age- and gender-specific regression coefficient for Hip.sk. For other abbreviations, see Tables 3 and 5.

The results of bivariate analyses were also along the lines of the present study. The results of both of these studies are qualitatively in good agreement. For example, Schork et al’s variance components showed a significant additive genetic effect for both SBP and DBP. Our recalculations of data presented in Schork et al’s Table 3 indicated that additive genetic factors account for \( \approx 30\% \) and \( \approx 18\% \) of SBP and DBP variation adjusted for gender, age, and other concomitant variables. Interestingly, \( \approx 13\% \) and \( \approx 6\% \) of the adjusted variance were attributable to common household effects for SBP and DBP, respectively. Their results of bivariate analyses were also along the lines of the present study. Schork et al42 found high and significant genetic (0.90) and shared environment (0.70) correlations between SBP and DBP. Bivariate analyses between BP and AP measures in Schork et al’s study involved mean BP versus BMI and body weight. Significant genetic correlations were present in the present study and numerous other publications,4 many different AP traits correlate with BP. There are significant phenotypic and genetic correlations between various AP measures,44,45 but the magnitude of their covariation is different, as it is different between BP and selected AP traits (see Tables 2 and 4). The selection of the particular AP measure in the specific population may lead to different results. This heterogeneity can in turn be due to a number of factors, of which the main should likely include differences in measurement error, contribution of the genetic factors, and physiological pathways for different AP traits. Obviously, further studies, in particular those involving molecular/genetic technique, are needed to clarify the extent and which specific genes influence the BP/AP relationship.

Acknowledgment

This study was supported by a grant to Gregory Livshits from the Israeli Ministry of Health (agreement 4240).

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Hypertension. 2001;37:928-935
doi: 10.1161/01.HYP.37.3.928

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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