Genetic, Environmental, and Phenotypic Links Between Body Mass Index and Blood Pressure Among Women

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Greater relative weight is associated with higher blood pressure, but the reasons are unknown. The inability of current technology to induce sustained weight loss among overweight persons precludes experimental tests of whether this association is causal. We evaluated the degree to which the covariation between body mass index (BMI; kg/m²) and blood pressure (BP) among women is due to pleiotropic genetic factors, environmental factors, or phenotypic causation. The sample included 75 monozygotic (MZ) and 39 dizygotic (DZ) pairs of adult female twins. "BP" was calculated as the unweighted mean of systolic and diastolic. Data were analyzed through structural equation modeling. A model was specified stipulating that additive genetic effects (A) and unique environmental effects (E) each contributed to the covariance between BMI and BP, thus allowing for both pleiotropic and unique environmental influences on the covariance between BMI and BP. Dropping the pleiotropic influences significantly worsened the model ($\chi^2 = 4.62, df = 1, P = .092$), suggesting significant pleiotropic effects. Dropping the environmental influences on the cross-phenotype covariance did not significantly worsen the model ($\chi^2 = 1.42, df = 1, P = .233$). This indicates no significant effect of the environment on the covariance between BMI and BP. Finally, a model of phenotypic causation in which BMI directly influenced BP was fitted. This model provided the best single parameter explanation of the BP-BMI covariation. These data suggest that, among women, regardless of the source of variation, changes in BMI should lead to long-standing changes in BP. © 1995 Wiley-Liss, Inc.

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INTRODUCTION

Obesity and hypertension are prevalent conditions in the United States and both are risk factors for cardiovascular disease and early mortality [Pi-Sunyer, 1991]. It is also known that greater fatness or obesity in the extreme is associated with greater blood pressure or hypertension in the extreme [Dustan, 1991a,b; Heyden et al., 1990; Staessen et al., 1988]. Although there is considerable speculation [Henry, 1988; Resnick et al., 1992; Brindley and Rolland, 1989], the exact reasons for this association are currently unknown [Dustan, 1991a,b].

Understanding the causal connections between blood pressure and relative weight is an important step in our ability to understand variations in each and potentially treat and prevent excesses of each. Conceptually, the easiest way to understand whether and to what extent relative weight influences BP is to randomly assign a large sample of overweight people to an experimental manipulation that induces sustained weight loss. Unfortunately, our current technology has proven incapable of accomplishing this task.

When randomized experiments are not feasible, quantitative genetic studies of related individuals can often help resolve issues of causation [Neale and Cardon, 1992; Falconer, 1989; Heath et al., 1993]. Broadly speaking, in a bivariate situation, five models of phenotypic covariation can be proposed. These five models are graphically presented in Figures 1 through 5. Although these models do not describe specific physiological mechanisms, they do distinguish between broad...
categories of causal linkage and therefore may be helpful in pointing the direction for more specific studies of mechanisms. Before proceeding further, we should point out that the figures contain no correlational paths between environmental causes across twins. This is because (as we show in the results section) univariate analyses showed these paths to be nonsignificant. The five alternative models are briefly described below.

**Model 1: Environmental Links**

Figure 1 depicts a model in which the covariation between body mass index (BMI; kg/m²) and BP is due solely to joint environmental factors, that is, the same environmental influences that affect BMI also have some influence on BP. An example of this might be living in an environment that promotes eating highly processed and fried foods. Such an environmental factor might lead one to consume a great deal of these foods which tend to be high in fat and calories, thereby causing weight gain. However, because these foods also tend to be high in sodium, this same environmental factor might also cause increases in BP (Henry, 1988). According to this hypothesis, weight loss would be unnecessary to reduce blood pressure among the obese. Rather, obese persons would only need to switch to eating high calorie foods that were low in sodium. Although there is some evidence against this particular sodium hypothesis (Staessen et al., 1985), numerous other joint environmental influences (e.g., psychological stress) could be proposed.

**Model 2: Pleiotropic Genetic Links**

It is clear at this point that both relative weight (i.e., weight for height) and blood pressure (BP) are highly heritable. Recent work has demonstrated the strong role of genes in determining variations in human fatness [Stunkard et al., 1986a,b, 1990; MacDonald and Stunkard, 1990]. Approximately 70% of the variance in relative weight is a function of genetic variation [Stunkard et al., 1986a,b, 1990; MacDonald and Stunkard, 1990]. Similarly, twin, family, and adoption research has shown that anywhere from 25 to 65% of the variance in both systolic and diastolic BP is genetic in origin [Corey et al., 1986; Feinlab et al., 1977; Williams, 1991].

Pleiotropy is a term which means that a single gene or set of genes causes multiple phenotypes in the same individual. The common confluence of obesity, hypertension, diabetes, and hyperlipidemia is so well documented that some have suggested that these “Big Four” may represent a single “syndrome” with a common and perhaps genetic origin [Schwartz, 1991], in other words, pleiotropy. If the connection between BMI and BP was solely and directly pleiotropic, weight loss...
could not result in long-term reductions in BP because weight loss does not change one’s genotype. It is important to distinguish here between two conceptions of leiotropy. In a very broad sense, anytime the genotype influences any phenotype that in turn influences a second phenotype, pleiotropy can be said to occur. This is referred to as relational pleiotropy [Rieger et al., 1991]. However, here we use the term more narrowly to imply a situation in which the genotype influences two or more phenotypes independently of the phenotypes influencing each other. In other words, even if variation in one phenotype were held constant, variation in the relevant portions of the genotype would still be associated with variations in the second phenotype. This is referred to as mosaic pleiotropy [Rieger et al., 1991].

Researchers have only recently begun to explore possible pleiotropic links among CVD risk factors. For example, Groop et al. [1993] reported that an allele of the glycogen synthase gene is associated not only with IDDM but also with hypertension. Hanis et al. [1983] found no evidence of significant pleiotropy in bivariate analyses of weight (BMI was not used) and BP.

In contrast, Schork et al. [1994] analyzed data, including blood pressure, BMI, selected serum lipid levels, fasting glucose, and several other putative mediators of blood pressure in 5376 individuals from 2184 households in Gubbio, Italy. Data for each variable were analyzed with bivariate models where the second variable was blood pressure. Results indicated statistically significant bivariate pleiotropic effects, the sum total of which accounted for approximately 6% of the variance in BP. Similarly, Allison et al. [1993] used meanling and found some support for pleiotropic effects of a major gene on both BMI and BP among children. Unfortunately, the above studies did offer strong tests of whether the associations were purely pleiotropic, whether the pleiotropic action occurred “through” phenotypic causation, and, finally, whether the environment also played a role in the BMI association.

Two studies have addressed the issue of whether the connection between relative weight and BP is purely anetnic. Newman et al. [1990] examined 250 pairs of mongolitic (M) white male twins. Twins’ weight and height served as “independent variables” and systolic P, diastolic BP, and other CVD risk factors served as “dependent variables.” For each pair of twins, the twin with the higher BMI was categorized as the heavier twin and the twin with the lower BMI was categorized as the lighter twin. Heavier twins were then compared to the lighter twins on the dependent variables using dependent samples t tests. This design allows one to determine the extent to which greater relative weight is associated with other risk factors in genetically matched pairs. Therefore, any difference observed must be environmental in origin [Nance, 1984]. Newman et al. [1990] observed that both diastolic and systolic BP were significantly greater among the heavier twins (P < .05). Thus, the association between BP and BMI cannot be due to pleiotropy alone. Grim et al. [1990] performed similar measurements and analyses with 12 MZ male and 5 MZ female black twin pairs from Barbados. This sample size provided very little statistical power and resulted in the conclusion “there was no evidence that the heaviest twin had the highest blood pressure” [Grim et al., 1990, p. 807]. Given the sample size and the results of Newman et al. [1990], it is likely that this conclusion represents a Type II error. There was a significant correlation between intrapair difference in triceps skinfold and systolic BP offering some support for an independent environmental association between fatness and BP among blacks.

The Newman et al. [1990] and Grim et al. [1990] studies do not provide estimates of the proportion of covariation between BMI and BP that is environmental in origin. Moreover, they provide no information on possible pleiotropic origins of this covariation. A second limitation is that these data provide very little information about women. Thus, none of the studies reviewed above “tells the whole story.”

Model 3: Phenotypic Causation—BMI Influences BP

This model probably characterizes the prevailing opinion in the field, that is, that weight gain causes increases in BP and weight loss causes decreases in BP. The strongest evidence in favor of this hypothesis is the fact that weight reduction does lead to BP reductions [Staessen et al., 1986]. However, there are problems with these data, the greatest being that these studies have been short-term. Therefore, it is difficult to separate the effects of a acute caloric restriction from weight loss. In a recent study of obese persons, Peterson et al. [1993] showed that BP dropped with weight loss. However, even among patients who maintained their weight loss, BP began to rise back toward baseline values. Unfortunately, to date, investigators have been unable to demonstrate the long-term benefits of weight loss due to the extreme difficulty in getting people to lose weight and consistently keep it off for an extended period of time.

Model 4: Phenotypic Causation—BP Influences BMI

We include this and the next model primarily for completeness and not because we think that they are particularly plausible. However, it is possible that, for
example, as a person's BP goes up physical activity becomes more aversive, is therefore performed less, and weight gain results. We know of no data to support such an interpretation.

Model 5: Reciprocal Causation—BP and BMI Influence Each Other

To the extent that Models 3 and 4 are possible, reciprocal causation is possible. That is, BP and BMI each may influence the other. This should be distinguished from BP and BMI simply being correlated due to a shared influence from some other variable [Heath et al., 1993] (hence our use of two single headed arrows rather than a one double arrow). The reciprocal causation model fit is described extensively by Neale and Cardon [1992; chapter 13 and references therein]. The purpose of this study is to test the five competing models described above using a sample of female twins.

METHODS

Subjects

The sample consisted of a total of 75 MZ and 39 DZ pairs of female twins from the Greater Boston Twin Registry, a volunteer twin registry constructed in 1981 of adults from suburban areas surrounding Boston, Massachusetts. Zygosity was determined by a computerized decision tree algorithm based on the questionnaire of Sarna et al. [1978] and validated in a subgroup of twins by serological comparisons. Further details of this sample can be found in Redline et al. [1987]. The twins were examined in their homes by trained interviewers who administered the questionnaires and obtained the anthropometric measurements and measures of blood pressure in a standardized manner. Descriptive statistics for age, body mass index, and systolic and diastolic blood pressure can be found in Table I. All twins were white.

Measures

Two measures were used in the main analyses: body mass index (BMI) and blood pressure (BP). BMI, or Quetelet's index, is defined as kg/m². The BMI has the desirable properties of being minimally correlated with height, highly correlated with weight and more directly measures of body fat, and is a standard in epidemiological research [Garro and Webster, 1985].

Systolic and diastolic BP were measured three times each in a sitting position with a random-zero mercury sphygmomanometer and the three readings averaged to ensure a high degree of reliability. "BP" was calculated as the mean of systolic and diastolic after they were converted to z-scores (i.e., standardized to have a mean of 0 and a variance of 1). This was done for three purposes. First, the aggregated measure is likely to be more reliable than either measure alone. Second, having one rather than two blood pressure variables maintains a better subjects to variables ratio. Finally, this allows our results to be more easily compared to those of Schork et al. [1994], who also used a combined BP measure. However, it should be noted that in preliminary analyses, we analyzed diastolic and systolic BP separately and obtained largely divergent results.

Data Analysis

Preparation of the data. A total of 119 pairs of twins was available initially. One pair was dropped as an outlier because the Mahalanobis' D calculated from both twins’ BMIs and BPs was 31.98 (this can be interpreted as $X^2 = 4, P < .0001$) [Tabachnick and Fidell, 1989]. Four cases were dropped due to missing data. Thus, 114 pairs of twins remained.

Since members of a twin pair necessarily share the same age, it is important to control for this prior to analysis, otherwise shared common environmental effects will be overestimated. Therefore, both BMI and BP were residualized for the effects of age, age², and age³ through ordinary least-squares multiple regression. Finally, since both BMI and BP residuals were positively skewed, a Box-Cox transformation [Box and Cox, 1964] was applied to each to transform them to approximate normality. After the addition of constants to ensure that all values were positive, BMI residuals were raised to the power of .34 and BP residuals were raised to the power of .73. This eliminated all skewness and markedly reduced kurtosis.

Model Testing

Data were analyzed through structural equation modeling as described by Neale and Cardon [1992; see especially chapters 12 and 13] using the MX software [Neale, 1991]. Briefly, structural equation modeling works in the following manner. The models in Figures 1 through 5 can be translated into a set of simultaneous equations. The values of the path coefficients (these are equivalent to partial regression coefficients in multiple regression) are the unknowns in these sets of simultaneous equations. For each set of simultaneous equations, a computer program finds the values for the unknowns that make the model best fit the observed data.
The use of structural equation modeling is described in general by Bentler and Stein [1992] and Neale and Cardon [1992] provide an extensive exposition on their use in genetic studies. All models were fitted to variance–covariance matrices.

We began by finding the optimal genetic models for BMI and BP separately. After finding these univariate models, the data were combined and competing models of the covariance between BMI and BP were tested. All models were fit to variance–covariance matrices which are given in Table II.

Some of the models tested can be considered to be nested within other models, that is, reduced or simplified versions of other models tested. Nested models can be tested for significance via likelihood ratio tests. Specifically, −2ln(L/L₀) is asymptotically distributed as χ², where L₀ is the likelihood of obtaining the observed data if the reduced model were true and L is the likelihood of obtaining the observed data if the full model were true, and with degrees of freedom equal to the difference between the number of parameters estimated in the two models. Nonnested models cannot be formally tested against another using the likelihood ratio statistic because no closed form for the null distribution of this statistic is known. Without resorting to simulating the distribution of the test statistic, nonnested models can be compared via goodness of fit indicators that take into account both the overall fit of the model and its number of parameters (i.e., its parsimony) [Browne and Cudeck, 1993]. The goodness of fit index used was the Akaike information criteria [AIC; Akaike, 1987]. The AIC is scaled such that lower numbers indicate better relative fit.

RESULTS

Univariate Results

For both BMI and BP, the optimal univariate model was one that included additive genetic influences (A) and unique environmental influences (E). The addition of shared common environmental effects (C) or nonadditive genetic effects (D) did not significantly improve the models for either BP or BMI (P > .05). Of course, C and D were not tested simultaneously because a model including both C and D with ordinary twin data is not identified [Neale and Cardon, 1992].

For BP, the A–E model fit the data well as judged by the χ² of 5.52 (df = 4, P = .239) and an AIC of −2.48. For BMI, an A–E model also fit the data best with a χ² of 6.95 (df = 4, P = .13) and an AIC of −1.05.

Multivariate Results

Following the univariate analyses, all data were combined and the five competing models previously described and depicted in Figures 1 to 5 were tested and compared against one another. We began by fitting what might be considered a “null” model (model 0) in which no parameters were introduced to allow BMI and BP to covary. This model was rejected as it provided a significantly poor fit to the data (P = .02).

The null model with 16 df is nested within each of models 1 through 4 (each has 15 df). Thus one can test whether models 1 through 4 are significantly better than the null model through a χ² test with 1 df. Each of models 1 through 4 was significantly better than the null model (P < .05). In turn, models 3 and 4 are nested within the 14 df reciprocal causation model (model 5) also allowing a χ² test with 1 df. Model 5 did not fit the data significantly better than either model 3 or 4. Thus, there is sufficient evidence to reject the null model of no covariation between BMI and BP and no evidence to warrant adoption of the complex reciprocal causation model.

Models 1 through 4 cannot be tested against one another because they are not nested models. However, one can compare their relative fit. The AIC was lowest for model 3 (AIC = −9.60) indicating the best relative fit and the nonsignificant χ² indicates that the overall fit is good.

The inferential statistics for the 5 bivariate models fitted are displayed in Table III. The parameter estimates of the optimal model (i.e., model 3; phenotypic causation from BMI to BP) are given in Table IV. As can be seen, 72% of the variance in BMI was genetic in origin. This is quite consistent with other research [Stunkard et al., 1986a,b, 1990; MacDonald and Stunkard, 1990]. Also consistent with past research [Williams, 1991], genetic factors accounted for 59% of the variance in BP. Thirty-six of this 59% genetic influence was direct while 23% (i.e., 72% of 33%) see Table IV) operated indirectly through BMI.

DISCUSSION

Taken together, these analyses suggest that the association between BMI and BP is likely the result of phenotypic causation in which BMI directly influences BP. This has clear implications for obesity treatment and preventive medicine. It suggests that, all other things being equal, maintaining or achieving a modest BMI is likely to result in long-term mainte-
nance of a modest blood pressure. Thus, when weight loss studies observe a reduction in BP, this reduction is unlikely to be solely the result of caloric restriction and will therefore not be solely transitory.

Several methodological issues should be considered. First, this sample included few markedly obese or hypertensive individuals. It is possible that disparate results would be obtained in the extreme upper range of BMI and BP. Second, this sample included white women only. It is possible that alternative results would have been obtained if men or other ethnic groups were studied and we are currently conducting research to address this question. Third, the sample size was modest, which suggests that our power to discriminate between models of phenotypic causation versus phenotypic causation plus pleiotropy was also quite modest. This issue was also raised by Hanis et al. [1983]. Finally, there is always some possibility that part of the way BMI exerts its influence on BP is artifactual, that is, through the introduction of measurement bias with sphygmomanometry.

Future research might also extend this line of inquiry to other risk factors that are associated with BMI such as dyslipidemias and glucose intolerance. Finally, we hope to conduct future analyses that incorporate measurements of putative mediating variables (mechanisms) of the BMI–BP relationship so that these causal hypotheses can be evaluated and refined.

ACKNOWLEDGMENTS

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REFERENCES


TABLE III. Inferential Statistics for the Five Competing Bivariate Models

<table>
<thead>
<tr>
<th>Model</th>
<th>( x^2 )</th>
<th>df</th>
<th>P</th>
<th>AIC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0. Null model: No covariation between BMI and BP</td>
<td>29.70</td>
<td>16</td>
<td>.020</td>
<td>-2.31</td>
</tr>
<tr>
<td>1. Environmental association but no pleiotropy</td>
<td>24.91</td>
<td>15</td>
<td>.051</td>
<td>-6.09</td>
</tr>
<tr>
<td>2. Pleiotropy but no environmental association</td>
<td>21.72</td>
<td>15</td>
<td>.115</td>
<td>-8.28</td>
</tr>
<tr>
<td>5. Reciprocal causation: BP and BMI influence each other</td>
<td>20.41</td>
<td>14</td>
<td>.118</td>
<td>-7.60</td>
</tr>
</tbody>
</table>

* AIC = Akaike's information criterion = \( x^2 - 2df \).

TABLE IV. Squared and Standardized Parameter Estimates* for Optimal Model—Phenotypic Causation: BMI Influences BP

<table>
<thead>
<tr>
<th></th>
<th>( A^2 )</th>
<th>( E^2 )</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>.355</td>
<td>.318</td>
<td>.327</td>
</tr>
<tr>
<td>BMI</td>
<td>.717</td>
<td>.283</td>
<td></td>
</tr>
</tbody>
</table>

*The entries in this table can be interpreted as the percent of variance of the row variable explained by the column factor (e.g., additive genetic factors) (A) account for 71.7% of the variance in BMI.


