Predictors of an Increased Risk of Future Hypertension in Utah
A Screening Analysis

Steven C. Hunt, Susan H. Stephenson, Paul N. Hopkins, and Roger R. Williams

A prospective study on 1,482 adult members of 98 Utah pedigrees was carried out to determine which variables may be associated with an increased risk of hypertension incidence. After an average of 7 years of follow-up, 40 individuals had been placed on antihypertensive medications to lower blood pressure. Baseline study variables included anthropometries, clinical chemistry measurements of blood and urine, socioeconomic and lifestyle variables, and detailed erythrocyte ion transport and concentration measurements. Age (relative risk of 4.28 for a 2 SD difference, \( p < 0.0001 \)) and baseline systolic and diastolic blood pressures (relative risks of 3.55 and 3.52, respectively, both \( p < 0.0001 \)) had the strongest associations with hypertension incidence. Controlling for age and baseline blood pressure, the following age- and sex-adjusted variables were associated with an increased risk of future hypertension (relative risks for a 2 SD difference, all \( p < 0.10 \)): family history of hypertension (2.85); height (1.97); body mass index (2.31); abdominal girth (2.66); subscapular, suprailiac, and triceps skinfold thicknesses (2.79, 2.52, and 2.28, respectively); percent ideal body weight (2.63); log triglyceride concentration (2.02); plasma uric acid (2.16); inorganic phosphate (0.50); and passive erythrocyte sodium permeability (1.59). The final model, which included all of the age- and sex-adjusted variables (\( p < 0.10 \)) in a backward elimination logistic regression analysis, consisted of age (4.78), systolic blood pressure (2.91), subscapular skinfold thickness (2.21), height (1.92), uric acid (2.06), inorganic phosphate (0.50), and family history of hypertension (1.82). None of the ion transport or concentration measurements was associated with an increased risk of hypertension. We conclude that the risk factors of age, body fat and size, plasma uric acid, low plasma inorganic phosphate, and family history of hypertension, previously shown to be significant in cross-sectional studies, prospectively increase the risk of hypertension. If other variables have important predictive roles, then they may affect only a subset of this or other large study populations. (Hypertension 1991;17:969-976)

A growing number of variables are being identified in population cross-sectional studies or in laboratory studies that are related to mechanisms involved in blood pressure control. Although these studies increase our knowledge of the pathophysiology of blood pressure control, it is important to differentiate between factors that are altered before the actual blood pressure increase and factors that respond to the blood pressure changes. Prospective studies with varying lengths of follow-up have identified variables that seem to be altered in normotensive individuals whose blood pressures fit the clinical definition of "hypertension" during the follow-up period. Some of the variables shown to be associated with the development of hypertension include baseline systolic and diastolic blood pressure, \(^8\) age, measures of obesity including body mass index, various skinfold thicknesses and their ratios, weight and changes in these variables, \(^9\) pulse rates, \(^10\) pulmonary function, alcohol consumption, \(^11\) smoking, \(^12\) plasma uric acid, \(^13\) lipids, \(^14\) intracellular sodium, \(^15\) and family history of hypertension.

The present study investigates 46 socioeconomic, physical exam, and biochemical variables and their relation to the development of hypertension over a 7-year follow-up period. These variables include many of the cation transport rates and concentrations measured in erythrocytes that have been suggested as intermediate phenotypes closely related to an underlying defect causing high blood pressure.

**Methods**

The subjects of this study were screened in the Cardiovascular Genetics Clinic at the University of Utah.
were calculated for those who smoked. Height was
day x number of years smoked) of cigarette smoking
question for current consumption. Pack-years (packs/
Education level was the actual number of years of
income ranging from less than $5,000 to more than
level was a graded response to nine categories of
The information was then classified into five catego-
Family history was defined using a continuous variable
sounds (Infrasonde SR-2 Automatic Blood Pressure
Recorder, Sphygmetrics, Inc., Woodland Hills, Calif.).
Erythrocyte sodium–lithium countertransport was
measured as described by Canessa et al19 and
modified by Smith et al.20 Lithium–potassium
cotransport and the membrane passive leak rate
constants were measured as previously described,21
as were the number of ouabain binding sites and
ouabain-sensitive sodium efflux rate and
rate constant.24 Intracellular sodium and magne-
sium and plasma magnesium were measured by
atomic absorption spectroscopy25 and plasma renin
activity by radioimmunoassay kits measuring gener-
ated angiotensin I.

Statistical Analysis
Relative risks and 95% confidence intervals were
calculated from logistic regression coefficients com-
paring 1 and 2 SD differences in means of the
continuous variables. All variables were sex-
and age-adjusted (cubic polynomial in age) with the
residuals used in the logistic regression analyses.
Triglyceride levels were log transformed.
Each variable listed in Table 1 was used in sepa-
rate logistic regression models controlling for age
(Table 2). Next, all variables that were significant
at $p<0.20$ were included in a regression model (one at a
time) along with age, systolic blood pressure, and
body mass index (Table 3). All variables that re-
mained significant at $p<0.20$ were entered in a
stepwise logistic regression. The final model con-
sisted of variables remaining significant at $p<0.10$
(Table 4).

Although the nonrespondents to the follow-up ques-
tionnaire were excluded from analysis in a previous
study,18 they were included as normotensive subjects in
the current study. There was a response bias for a
number of variables in this analysis (described later),
and exclusion of the large number of nonrespondents

Study Variables
Variables analyzed for their relation to hyperten-
sion are listed in Table 1. With subjects in a sitting
position, the means of four systolic and diastolic blood
pressures were obtained by an automated blood pres-
sure device that made a permanent tracing of the
sounds (Infrasonde SR-2 Automatic Blood Pressure
Recorder, Sphygmetrics, Inc., Woodland Hills, Calif.).
Family history was defined using a continuous variable
that compares the observed number of events in a
family to the expected number, based on the family
size, age and gender of each family member, and Utah
population-derived hypertension incidence rates.13
The information was then classified into five catego-
ries ( $-1.0$, $-1.0-0.49$, $0.5-0.99$, $1.0-1.99$, and
$\geq 2.0$), which represent a protective, an average,
a suggestive, a positive, and a very positive family history
of hypertension. At least two first-degree relatives
were required to have hypertension before an individ-
ual was assigned to categories 4 and 5. Annual income
level was a graded response to nine categories of
income ranging from less than $5,000 to more than
$50,000. The mean family income was about $20,000.
Education level was the actual number of years of
education. Alcohol use was determined by a yes/no
question for current consumption. Pack-years (packs/
day x number of years smoked) of cigarette smoking
were calculated for those who smoked. Height was
measured without shoes, using a stadiometer (Siber
Hegner Machinery, Ltd., Zürich), and body mass
index was calculated from the measured weight in
kilograms divided by the square of height in meters.
Abdominal girth was measured with a steel tape at the
level of the umbilicus. Skinfold thicknesses were mea-
sured by Harpenden calipers (Siber Hegner) to the
nearest millimeter; three measurements at each site
were averaged. Ideal body weight was determined from
the Metropolitan Life tables for a given age, sex,
and frame size determined by wrist circumference.
Clinical chemistries were measured on fasting
blood samples using an autoanalyzer (SMAC II
Analyzer, Technicon Instruments Corp., Tarrytown,
N.Y.). Plasma total cholesterol, triglycerides, and
high density lipoprotein (HDL) cholesterol were
obtained. Plasma ionized calcium was measured by a
calcium-specific electrode (Applied Medical Tech-
nologies, Palo Alto, Calif.) with adjustment to a pH
of 7.4, and digoxinlike factor was measured by a
digoxin radioimmunoassay kit (Rianen Digoxin RIA
Kit, New England Nuclear, North Billerica, Mass.).
Urinary sodium and potassium were obtained from a
timed 12-hour, overnight, fasting urine sample.
Patient characteristics, and study design
have been described in detail elsewhere.11

Questionnaire follow-up of hypertension onset was
attempted in 1989 for all pedigree members, with a
response rate of 67% by the end of the year. The
nonrespondent characteristics have been given pre-
viously12 and are discussed later. Average length of
follow-up was 7 years. New-onset hypertension,
which developed in 40 individuals, was defined as
current antihypertensive medication prescribed since
the time of the second visit to our clinic in 1983–1985.
Therefore, hypertension developed at least 2½ years
after the baseline measurements were obtained.
Hypertension at either baseline examination was de-
efined as currently taking antihypertensive medica-
tions, or having taken antihypertensive medications
in the past, and having a baseline diastolic blood
pressure above 90 mm Hg as measured in our clinic.
A rigorous description and justification of the base-
line and follow-up cohort composition have been
previously published.12 Informed consent was ob-
tained from all participants, and the study followed
guidelines approved by an institutional review board
at the University of Utah.

After excluding all individuals with hypertension or a
stroke at the first or second visit (221 individuals),
1,482 normotensive adults belonging to 98 multigen-
erational pedigrees were included in the study. These
pedigrees were chosen because of the occurrence of
coronary death, stroke death, or hypertension inci-
dence in the probands. The pedigree ascertainment
criteria, patient characteristics, and study design
were described in detail elsewhere.11

were 97% and 99% for the first and second
visits, respectively. With subjects in a sitting
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<table>
<thead>
<tr>
<th>Variables</th>
<th>Normotensive Mean</th>
<th>Normotensive SD</th>
<th>Hypertensive Mean</th>
<th>Hypertensive SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (%)</td>
<td>49.4</td>
<td>50.0</td>
<td>55.0</td>
<td>49.7</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>34.42</td>
<td>13.41</td>
<td>47.25</td>
<td>11.09</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>110.9</td>
<td>10.91</td>
<td>121.5</td>
<td>11.34</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>65.5</td>
<td>9.13</td>
<td>71.6</td>
<td>8.81</td>
</tr>
<tr>
<td>Family history of HBP</td>
<td>2.5</td>
<td>1.17</td>
<td>2.9</td>
<td>1.20</td>
</tr>
<tr>
<td>Income*</td>
<td>5.93</td>
<td>1.91</td>
<td>5.77</td>
<td>1.76</td>
</tr>
<tr>
<td>Education (yr)</td>
<td>13.3</td>
<td>2.04</td>
<td>12.9</td>
<td>2.07</td>
</tr>
<tr>
<td>Alcohol (%) yes</td>
<td>23.0</td>
<td>42.1</td>
<td>15.8</td>
<td>36.5</td>
</tr>
<tr>
<td>Cigarettes (pack-yr)</td>
<td>0.26</td>
<td>2.26</td>
<td>0.79</td>
<td>3.96</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.1</td>
<td>6.27</td>
<td>172.3</td>
<td>5.94</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.8</td>
<td>4.3</td>
<td>27.2</td>
<td>5.0</td>
</tr>
<tr>
<td>Abdominal girth (cm)</td>
<td>85.26</td>
<td>10.88</td>
<td>92.16</td>
<td>12.16</td>
</tr>
<tr>
<td>Subscapular SF (mm)</td>
<td>18.07</td>
<td>8.58</td>
<td>23.20</td>
<td>11.08</td>
</tr>
<tr>
<td>Suprailiac SF (mm)</td>
<td>20.56</td>
<td>9.69</td>
<td>24.97</td>
<td>11.67</td>
</tr>
<tr>
<td>Triceps SF (mm)</td>
<td>17.99</td>
<td>7.06</td>
<td>21.16</td>
<td>8.32</td>
</tr>
<tr>
<td>Ideal weight (%)</td>
<td>115.3</td>
<td>17.98</td>
<td>126.5</td>
<td>20.31</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>193.5</td>
<td>40.41</td>
<td>193.5</td>
<td>30.01</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>107.7</td>
<td>1.65</td>
<td>131.2</td>
<td>1.63</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>48.0</td>
<td>11.00</td>
<td>46.0</td>
<td>13.53</td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
<td>140.2</td>
<td>2.04</td>
<td>140.2</td>
<td>2.45</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>4.43</td>
<td>0.36</td>
<td>4.47</td>
<td>0.35</td>
</tr>
<tr>
<td>Chloride (mmol/l)</td>
<td>106.0</td>
<td>2.49</td>
<td>106.4</td>
<td>3.30</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>12.78</td>
<td>3.08</td>
<td>13.11</td>
<td>4.74</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>98.2</td>
<td>19.3</td>
<td>101.5</td>
<td>18.2</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.97</td>
<td>0.14</td>
<td>0.99</td>
<td>0.21</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.50</td>
<td>1.16</td>
<td>6.01</td>
<td>1.29</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.52</td>
<td>0.39</td>
<td>9.46</td>
<td>0.37</td>
</tr>
<tr>
<td>Free calcium (mg/dl)</td>
<td>4.69</td>
<td>0.20</td>
<td>4.70</td>
<td>0.22</td>
</tr>
<tr>
<td>Phosphate (mg/dl)</td>
<td>3.17</td>
<td>0.49</td>
<td>3.00</td>
<td>0.48</td>
</tr>
<tr>
<td>Protein (g/dl)</td>
<td>7.09</td>
<td>0.41</td>
<td>7.15</td>
<td>0.42</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>4.41</td>
<td>0.27</td>
<td>4.43</td>
<td>0.26</td>
</tr>
<tr>
<td>Urinary sodium (mg/12 hr)</td>
<td>1,682.0</td>
<td>725.2</td>
<td>1,847.9</td>
<td>581.0</td>
</tr>
<tr>
<td>Urinary potassium (mg/12 hr)</td>
<td>922.0</td>
<td>513.5</td>
<td>951.8</td>
<td>267.4</td>
</tr>
</tbody>
</table>

SD, standard deviation; BP, blood pressure; HBP, high blood pressure; SF, skinfold; HDL-C, high density lipoprotein cholesterol; RBC, red blood cells; k_LNa, cotransport rate constant of L–Na cotransport; k_Leak, rate constant of passive Li leak; k_KNa, pump, rate constant of ouabain-sensitive Na–K exchange.

*Cut point of categories 5 and 6 is $20,000 of family income.
### Table 2. Relative Risks of Future Hypertension for One and Two Standard Deviation Differences in Means of Each Age- and Sex-Adjusted Study Variable, Controlling for Age

<table>
<thead>
<tr>
<th>Variables</th>
<th>1 SD difference</th>
<th>2 SD difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood pressure and demographic variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>2.07 (1.60,2.68)</td>
<td>4.28 (2.56,7.17)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex (women vs men)</td>
<td>0.83 (0.44,2.45)</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.88 (1.45,2.44)</td>
<td>3.55 (2.11,5.96)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>1.88 (1.37,2.57)</td>
<td>3.52 (1.87,6.62)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Family history HBP</td>
<td>1.53 (1.10,2.13)</td>
<td>2.35 (1.22,4.53)</td>
<td>0.01</td>
</tr>
<tr>
<td>Income</td>
<td>0.93 (0.69,1.24)</td>
<td>0.86 (0.48,1.53)</td>
<td>0.61</td>
</tr>
<tr>
<td>Education level</td>
<td>0.83 (0.61,1.14)</td>
<td>0.70 (0.37,1.29)</td>
<td>0.25</td>
</tr>
<tr>
<td>Alcohol (yes vs. no)</td>
<td>0.69 (0.30,1.58)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Cigarettes</td>
<td>1.10 (0.93,1.30)</td>
<td>1.21 (0.87,1.69)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Anthropometrics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>1.40 (1.03,1.92)</td>
<td>1.97 (1.05,3.76)</td>
<td>0.03</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.52 (1.20,1.93)</td>
<td>2.31 (1.43,3.74)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Abdominal girth</td>
<td>1.63 (1.26,2.12)</td>
<td>2.66 (1.58,4.48)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Subscapular skinfold</td>
<td>1.67 (1.26,2.21)</td>
<td>2.79 (1.60,4.88)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Suprailiac skinfold</td>
<td>1.59 (1.16,2.17)</td>
<td>2.52 (1.34,4.71)</td>
<td>0.004</td>
</tr>
<tr>
<td>Triceps skinfold</td>
<td>1.51 (1.13,2.02)</td>
<td>2.28 (1.28,4.07)</td>
<td>0.005</td>
</tr>
<tr>
<td>Percent ideal weight</td>
<td>1.62 (1.26,2.09)</td>
<td>2.63 (1.59,4.35)</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>Blood and urine variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>1.00 (0.73,1.37)</td>
<td>1.00 (0.53,1.86)</td>
<td>0.99</td>
</tr>
<tr>
<td>Log triglycerides</td>
<td>1.42 (1.06,1.89)</td>
<td>2.02 (1.13,3.59)</td>
<td>0.02</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.82 (0.59,1.15)</td>
<td>0.68 (0.35,1.32)</td>
<td>0.25</td>
</tr>
<tr>
<td>Sodium</td>
<td>1.03 (0.76,1.40)</td>
<td>1.07 (0.58,1.95)</td>
<td>0.83</td>
</tr>
<tr>
<td>Potassium</td>
<td>1.12 (0.83,1.52)</td>
<td>1.26 (0.68,2.51)</td>
<td>0.46</td>
</tr>
<tr>
<td>Chloride</td>
<td>1.18 (0.86,1.61)</td>
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<td>Blood urea nitrogen</td>
<td>1.10 (0.82,1.46)</td>
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<td>Glucose</td>
<td>1.09 (0.90,1.32)</td>
<td>1.19 (0.81,1.75)</td>
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</tr>
<tr>
<td>Creatinine</td>
<td>1.08 (0.81,1.45)</td>
<td>1.17 (0.65,2.09)</td>
<td>0.60</td>
</tr>
<tr>
<td>Uric acid</td>
<td>1.47 (1.10,1.96)</td>
<td>2.16 (1.22,3.83)</td>
<td>0.008</td>
</tr>
<tr>
<td>Total calcium</td>
<td>0.84 (0.61,1.15)</td>
<td>0.71 (0.38,1.33)</td>
<td>0.28</td>
</tr>
<tr>
<td>Free calcium</td>
<td>1.05 (0.72,1.52)</td>
<td>1.10 (0.52,2.31)</td>
<td>0.81</td>
</tr>
<tr>
<td>Phosphate</td>
<td>0.71 (0.52,0.97)</td>
<td>0.50 (0.27,0.94)</td>
<td>0.03</td>
</tr>
<tr>
<td>Total protein</td>
<td>1.15 (0.85,1.57)</td>
<td>1.33 (0.72,2.46)</td>
<td>0.37</td>
</tr>
<tr>
<td>Albumin</td>
<td>1.09 (0.79,1.51)</td>
<td>1.20 (0.63,2.28)</td>
<td>0.59</td>
</tr>
<tr>
<td>Urinary sodium</td>
<td>1.27 (0.94,1.71)</td>
<td>1.61 (0.89,2.92)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Ion transport and related variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na–Li countertransport</td>
<td>1.02 (0.75,1.40)</td>
<td>1.05 (0.56,1.96)</td>
<td>0.88</td>
</tr>
<tr>
<td>k_LK cotransport</td>
<td>0.89 (0.60,1.30)</td>
<td>0.79 (0.36,1.69)</td>
<td>0.54</td>
</tr>
<tr>
<td>k_Lr</td>
<td>1.26 (1.00,1.59)</td>
<td>1.59 (1.00,2.52)</td>
<td>0.05</td>
</tr>
<tr>
<td>Ouabain binding sites</td>
<td>1.05 (0.78,1.41)</td>
<td>1.10 (0.62,1.98)</td>
<td>0.74</td>
</tr>
<tr>
<td>Ouabain affinity</td>
<td>0.92 (0.64,1.32)</td>
<td>0.84 (0.40,1.74)</td>
<td>0.64</td>
</tr>
<tr>
<td>Na–K pump</td>
<td>1.05 (0.73,1.51)</td>
<td>1.10 (0.53,2.27)</td>
<td>0.80</td>
</tr>
<tr>
<td>Na–K pump rate</td>
<td>0.83 (0.55,1.25)</td>
<td>0.69 (0.30,1.57)</td>
<td>0.37</td>
</tr>
<tr>
<td>Intracellular sodium</td>
<td>1.15 (0.83,1.58)</td>
<td>1.32 (0.70,2.48)</td>
<td>0.40</td>
</tr>
<tr>
<td>Intracellular magnesium</td>
<td>0.93 (0.66,1.32)</td>
<td>0.87 (0.43,1.74)</td>
<td>0.69</td>
</tr>
<tr>
<td>Plasma magnesium</td>
<td>0.94 (0.60,1.48)</td>
<td>0.89 (0.36,2.20)</td>
<td>0.81</td>
</tr>
<tr>
<td>Plasma rennin activity</td>
<td>0.82 (0.51,1.31)</td>
<td>0.67 (0.26,1.72)</td>
<td>0.41</td>
</tr>
<tr>
<td>Digoxin level</td>
<td>0.99 (0.81,1.20)</td>
<td>0.97 (0.66,1.45)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

SD, standard deviation; HBP, high blood pressure; HDL-C, high density lipoprotein cholesterol; k_LK cotransport, rate constant of Li–K cotransport; k_Lr, rate constant of passive Li leak.
TABLE 3. Relative Risks of Future Hypertension for One and Two Standard Deviation Differences in Means of Each Age- and Sex-Adjusted Study Variable, Controlling for Age, Body Mass Index, and Sitting Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Variables</th>
<th>1 SD difference</th>
<th>2 SD difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic blood pressure</td>
<td>1.28 (0.88,1.88)</td>
<td>1.65 (0.77,3.55)</td>
<td>0.20</td>
</tr>
<tr>
<td>Family history of HBP</td>
<td>1.41 (1.00,1.99)</td>
<td>1.99 (1.00,3.94)</td>
<td>0.05</td>
</tr>
<tr>
<td>Height</td>
<td>1.40 (1.01,1.94)</td>
<td>1.95 (1.02,3.75)</td>
<td>0.04</td>
</tr>
<tr>
<td>Abdominal girth</td>
<td>1.33 (0.76,2.33)</td>
<td>1.77 (0.58,5.41)</td>
<td>0.32</td>
</tr>
<tr>
<td>Subscapular skinfold</td>
<td>1.45 (0.95,2.22)</td>
<td>2.10 (0.90,9.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Suprailiac skinfold</td>
<td>1.25 (0.84,1.85)</td>
<td>1.55 (0.70,3.44)</td>
<td>0.28</td>
</tr>
<tr>
<td>Triceps skinfold</td>
<td>1.21 (0.83,1.75)</td>
<td>1.46 (0.69,3.07)</td>
<td>0.32</td>
</tr>
<tr>
<td>Percent ideal weight</td>
<td>2.48 (0.83,7.38)</td>
<td>6.13 (0.69,54.42)</td>
<td>0.10</td>
</tr>
<tr>
<td>Log triglycerides</td>
<td>1.27 (0.92,1.74)</td>
<td>1.61 (0.85,3.04)</td>
<td>0.15</td>
</tr>
<tr>
<td>Urn acid</td>
<td>1.27 (0.92,1.75)</td>
<td>1.62 (0.85,3.07)</td>
<td>0.14</td>
</tr>
<tr>
<td>Phosphate</td>
<td>0.78 (0.56,1.08)</td>
<td>0.61 (0.32,1.17)</td>
<td>0.14</td>
</tr>
<tr>
<td>Urinary sodium</td>
<td>1.08 (0.77,1.51)</td>
<td>1.16 (0.59,2.29)</td>
<td>0.66</td>
</tr>
<tr>
<td>k_Li</td>
<td>1.20 (0.92,1.57)</td>
<td>1.45 (0.85,2.48)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

SD, standard deviation; HBP, high blood pressure; k_Li, rate constant of passive Li leak.

would bias the results for these variables. While some of the nonresponding individuals likely will be misclassified as being normotensive, the number is small compared with the total number of normotensive subjects and will have no effect on the normotensive group variable distributions. Most importantly, there were no differences in baseline blood pressures between the respondents and nonrespondents. All models were analyzed twice based on the following criteria: 1) it was assumed that nonrespondents to the follow-up questionnaire were normotensive, and 2) the nonrespondents were excluded.

Because the individuals who participated in this study were related, the observations were not independent. A logistic regression method, which controls for the intraclass correlation between related family members while estimating the independent variable standard errors, was used to prevent a "too small" estimate of the standard error of the parameters from increasing a variable's significance level. Since the blood pressure correlation between relatives more distant than first-degree is small, we controlled only for the dependence within sibships rather than entire pedigrees. All results reported in the tables are from the standard logistic regression model without correction for the sample dependence. Because this may result in a possibly "too small" estimate of a variable's standard error, Rosner's method was used on the variables included in the final model.

Using the harmonic mean of the numbers of hypertensive and normotensive subjects (n=78) and assuming a sibship intraclass correlation of 0.1 (yielding an effective sample size of 65) and a significance level of p=0.10, this study had powers of 80% and 99% to detect differences between group means of 0.5 and 0.8 SDs, respectively.

Results

The means and standard deviations of the baseline variables are presented in Table 1. The average age at baseline was almost 13 years older for those who became hypertensive (p<0.0001). Baseline systolic and diastolic blood pressures were 11 mm Hg and 6 mm Hg higher, respectively (both p<0.0001), in the hypertensive individuals than in those who remained normotensive. Those who became hypertensive had a stronger family history of hypertension but did not differ in educational or income level. Alcohol and cigarette use did not differ between groups.

TABLE 4. Relative Risks of Future Hypertension for One and Two Standard Deviation Differences in Means of Each Age- and Sex-Adjusted Study Variable With All Variables in One Multivariate Model

<table>
<thead>
<tr>
<th>Variables</th>
<th>1 SD difference</th>
<th>2 SD difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>2.19 (1.61,2.97)</td>
<td>4.78 (2.59,8.83)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.70 (1.29,2.25)</td>
<td>2.91 (1.67,5.07)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Subscapular skinfold</td>
<td>1.49 (1.07,2.05)</td>
<td>2.21 (1.16,4.21)</td>
<td>0.017</td>
</tr>
<tr>
<td>Urc acid</td>
<td>1.44 (1.03,2.01)</td>
<td>2.06 (1.05,4.05)</td>
<td>0.035</td>
</tr>
<tr>
<td>Inorganic phosphate</td>
<td>0.70 (0.49,1.00)</td>
<td>0.50 (0.24,1.01)</td>
<td>0.051</td>
</tr>
<tr>
<td>Height</td>
<td>1.38 (0.98,1.95)</td>
<td>1.92 (0.96,3.81)</td>
<td>0.064</td>
</tr>
<tr>
<td>Family history of HBP</td>
<td>1.35 (0.95,1.91)</td>
<td>1.82 (0.91,3.64)</td>
<td>0.090</td>
</tr>
</tbody>
</table>

SD, standard deviation; HBP, high blood pressure.
All of the baseline anthropometric measurements were significantly higher in the hypertensive group. Plasma triglyceride levels were also higher but not HDL cholesterol or total cholesterol. Out of all of the plasma clinical chemistry measurements, uric acid ($p=0.006$) and inorganic phosphate ($p=0.034$) were significant. Plasma ionized calcium, plasma renin activity, and digoxinlike factor were not significantly different. Urinary sodium and potassium excretion did not differ between groups. Although most of the erythrocyte ion transport rates and concentrations have been associated with hypertension in cross-sectional studies, none showed any baseline difference between groups in this prospective study.

Table 2 shows the relative risks for a 1 and 2 SD difference in means between the hypertensive and normotensive groups after controlling for baseline age. The standard deviation used was the pooled standard deviation of the two groups from Table 1. Table 3 controls for body mass index and sitting systolic blood pressure, in addition to age, in every model. Systolic blood pressure was used because it had a slightly stronger association than diastolic blood pressure. With systolic blood pressure in the model, diastolic blood pressure was only significant at $p=0.20$. Even with body mass index in the model, subscapular skinfold thickness was independently significant ($p=0.09$). The other anthropometric variables, except height, were no longer significant.

Table 4 shows the results when all of the variables significant at $p<0.20$ in Table 3 are initially included in the same stepwise multivariate logistic regression model. Age and systolic blood pressure were the strongest predictors of increased risk of hypertension. Body mass index, which was not significant when either subscapular skinfold thickness or uric acid was in the model, was removed. Height and family history of hypertension were borderline significant. Plasma uric acid and inorganic phosphate each had independent, significant associations with hypertension after adjusting for the other variables. Individuals with high uric acid had twice the risk of becoming hypertensive after 7 years compared with those who had uric acid levels 2 SDs lower. Lower phosphate levels were associated with twice the risk of hypertension. After adjusting for the nonindependence of the cohort observations, the variables listed in Table 4 remained significant at $p<0.10$ level. Age, blood pressure, and family history became slightly more significant and uric acid became slightly less significant, with the other variables remaining the same.

To check for response bias, $t$ tests between the respondents and nonrespondents for each variable were run. The nonrespondents were less educated ($p=0.03$), had lower incomes ($p=0.05$), drank alcohol ($p=0.0004$), smoked more ($p=0.02$), had higher phosphate levels ($p=0.007$), and had more ouabain binding sites ($p=0.003$) than did the respondents. When the final results were reanalyzed excluding the nonrespondents, only subtle changes were seen in the results. If triglyceride level were not allowed to enter the model, then the results were identical to those including the nonrespondents in the analysis. Exclusion of the nonrespondents alters the interaction of triglycerides and uric acid with the other significant variables (primarily family history of hypertension) so that at the step where uric acid had entered the model with the nonrespondents included, triglycerides were just barely more significant than uric acid and entered the model. Because of the correlation between triglycerides and uric acid ($r=0.28$), uric acid did not subsequently enter the model. Since the nonrespondents had higher phosphate levels than the responding normotensive individuals, excluding them made the normotensive mean more similar to the hypertensive mean, and the significant result for plasma phosphate was no longer significant at $p<0.10$ ($p=0.11$). The final model with the nonrespondents removed has log triglycerides instead of uric acid and plasma phosphate. However, if an interaction term for family history and uric acid is included in the stepwise model, the interaction term remains in the final model replacing triglycerides ($p=0.14$). No other two-variable interaction terms were significant. The nonsignificant results did not change after replacing alcohol use (yes/no) with the number of drinks (12 oz beer, 4 oz wine, or one shot of liquor) per week ($p=0.42$).

Discussion

The variables found significant in this study have been suggested as predictors of hypertension in other prospective studies. Our results are consistent with others in that age and baseline systolic blood pressure are the strongest determinants of hypertension incidence. Although all of the obesity measures were related to hypertension, subscapular skinfold thickness, representing central obesity, seems to have the strongest relation with hypertension independent of overall obesity as measured by body mass index. Other studies have suggested that uric acid is associated with increased blood pressure, with a univariate relative risk of 1.8 ($>4.4$ versus $<4.4$ mg/dl) in one study and a relative risk of 2.2 comparing the highest to lowest quintiles of uric acid, while controlling for other significant variables. Our relative risk of 2.1 for a 2 SD difference is comparable with these two studies. Selby et al did not measure triglyceride levels, which are correlated with uric acid. Our study shows that both variables have similar univariate associations but that they are not independently related to hypertension incidence. Whether uric acid or triglycerides entered the final model depended on the slight statistical variations that occurred with the inclusion or exclusion of the nonresponding subset of the initial cohort. Both variables may represent an abnormal metabolism, which seems to relate hypertension, lipid abnormalities, and coronary heart disease.

Although lower plasma ionized calcium has been extensively studied and related to hypertension, it is
interesting to note that in the original paper, there was a decrease of about 16% in plasma phosphate levels between hypertensive and normotensive patients compared with a 5% decrease in plasma ionized calcium. Although the two variables are physiologically related, our data show little statistical correlation. Maschio et al showed an 11% decrease in phosphate in hypertensive patients, while Cervellin et al showed a significant 5% decrease in male hypertensive patients and a nonsignificant 1% decrease in female hypertensive patients. Garrison et al published a relative risk of 0.81 for men and 0.61 for women, but these became nonsignificant after adjustment for other variables. Therefore, although there is suggestive evidence that phosphate is involved in the pathogenesis of hypertension, its weak relation may indicate that it is a reflection of some other more direct abnormality. This abnormality does not seem to be reflected by either total or ionized plasma calcium.

Ion transport and intracellular concentrations in various cell types have been of intensive interest as intermediate phenotypes in the pathway leading to hypertension. At present, they have not been as discriminating as had been hoped but still may provide important leads to the mechanism of blood pressure increase. The present study did not show that deviations in any of the ion measurements preceded the development of hypertension. The significant univariate association of the passive Na⁺ leak disappeared after adjusting for other variables. The present study had sufficient power to detect any physiologically meaningful difference in these variables. Also, since the previously known determinants of future hypertension were detected, problems with the study validity would not seem to be an explanation. A detailed discussion of the problems arising from a low response rate and misclassification of follow-up blood pressure status is given elsewhere.

The results of the present study may be applied to individuals belonging to extended families in which two or more members have early coronary heart disease, strokes, or hypertension. Although many unaffected branches of each large pedigree are at normal population risk, others are at increased risk of these diseases. In spite of the ascertainment criteria, the results found in this study are very similar to other studies that are more representative of the general population.

There may be three explanations for the lack of significant associations of these ion measurements with hypertension. First, the alterations in ion transport or concentration may be compensatory responses to a blood pressure increase due to an unrelated primary cause. Second, the length of follow-up in this study may not have been long enough because individuals with abnormal levels may not have reached the arbitrary blood pressure cutoff level for hypertension. An equally likely correlate is that the baseline measurements were not made at a young enough age, and an initial difference in blood pressure levels at a younger age disappeared later as possible age-related secondary influences masked the difference between groups. Third, these ion measurements may represent risk in only a subset of hypertensive individuals, and the risk cannot be detected in a large heterogeneous cohort.

While obesity may influence the expression of hypertension because of its large metabolic and resistance effects, even in those in whom it is not a primary cause, an ion defect may not have any influence on those who are not susceptible to that defect and can compensate by other mechanisms. Recently, we reported evidence that there may be subsets of individuals who are susceptible to abnormal sodium–lithium countertransport rates and have an increased risk of hypertension. In the entire cohort there was no evidence that high countertransport levels preceded hypertension. However, in those individuals who could be statistically classified as having the high genotype, there was four to five times the incidence of hypertension as among the other two genotypes. A prospective association between intracellular sodium and blood pressure was found in a subgroup of borderline hypertensive patients after a 5-year follow-up. We have also provided some evidence that intracellular sodium is genetically controlled. However, in this study we could find no indication of a prospective relation to hypertension.

One would not expect a large proportion of hypertension to be explained by any one genetic defect since most of the other common diseases have multiple defects, each explaining a small proportion of the disease. Longer follow-up of this cohort and more detailed segregation and linkage studies of the most promising ion transport and concentration measurements are required to determine which of the three previously mentioned alternatives may explain the negative results found for the ion transport and concentration measurements in this prospective study.

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References

7. Selby JV, Friedman GD, Quesenberry CP Jr. Precursors of essential hypertension: Pulmonary function, heart rate, uric
acid, serum cholesterol, and other serum chemistries. Am J Epidemiol 1990;131:1017–1027

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