AJH 2004; 17:936–940

# Families and the Natural History of Blood Pressure

## A 27-Year Follow-Up Study

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**Background:** Previous studies on familial aggregation of blood pressure (BP) have reported data on family history of hypertension. Data on actual parental BP levels and the subsequent natural history of BP in their offspring are scarce.

**Methods:** In a population-based study with 596 children aged 5 to 19 years, cardiovascular risk factors were measured annually from 1975 through 2002. Parental data were obtained at baseline. Repeated BP measurements were studied as a function of tertiles of age-adjusted BP measured in their parents at baseline.

**Results:** Systolic BP during follow-up was higher in offspring whose parents were both in the highest tertile compared with children whose parents were not in the highest tertile (difference 2.7 mm Hg, 95% confidence interval 0.2 to 5.2). Having both parents in the highest tertile of diastolic BP resulted in a substantially higher diastolic BP ranging from 1.9 mm Hg at age 15 years to 8.5 mm Hg at age 45 years. These differences were adjusted for age, sex, body mass index, total serum cholesterol, smoking habits, and alcohol consumption.

**Conclusions:** The results of this study indicate that actual parental BP is an important predictor of BP development from childhood into young adulthood. This is important when constituting cardiovascular risk profiles for children and young adults. Am J Hypertens 2004;17: 936–940 © 2004 American Journal of Hypertension, Ltd.

**Key Words:** Blood pressure, children, adolescence, familial aggregation, natural history.

Prospective studies have shown that cardiovascular disease aggregates in families.[1,2] This is probably due in part to familial aggregation of important cardiovascular risk factors such as blood pressure (BP) and plasma cholesterol.[3,4] It has long been recognized that primary hypertension has its roots early in life.[5,6] Familial aggregation of BP levels is well established in cross-sectional studies in various societies[7–10] and has been shown to be detectable in children at a very young age.[11]

In longitudinal studies, children with a family history of hypertension were shown to have persistently higher BP levels than children without such a history over follow-up periods of up to 10 years.[12–14] Still, the usefulness of recording a positive family history in the prediction of hypertension in the individual is considered to be limited.[15,16] No data are available on young parents" actual BP levels in relation to the subsequent natural history of BP in their children. It is of particular interest to know whether parental BP levels are predictors of their offspring"s subsequent BP development into young adulthood, and whether this holds for the whole distribution of parental BP. In young adulthood, environments are shared less than in childhood, and the more stable BP levels are claimed to be predictive of future hypertension and its cardiovascular sequelae.[17] In our 27-year follow-up study, we assessed the relationship between BP levels measured in young parents and the subsequent course of BP levels in their offspring, measured annually from childhood to young adulthood.

## Methods

### Study Population

Families with children 5 to 19 years of age who were living in two districts in the Dutch town of Zoetermeer

Received May 6, 2004. First decision May 24, 2004. Accepted June 4, 2004.

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This work was supported by Dutch Heart Foundation grant 96.179.

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0895-7061/04/$30.00
doi:10.1016/j.amjhyper.2004.06.010

were invited to participate in a cross-sectional population-based study on risk-indicators for chronic disease, name ly, the Epidemiological Preventive Study Zoetermeer (EPOZ). All participants were included between 1975 and 1978.[18] Zoetermeer is a suburban residential community (at that time, with about 55,000 inhabitants) that is near The Hague in the Netherlands. Of all persons living in 2 districts of Zoetermeer, 4649 (82%) took part in the study. From this group, a random sample of 596 children was selected for annual follow-up in a study on the natural history of cardiovascular risk factors and their determinants. Between 1975 and 1993, subjects visited the research center annually in the same month of the year, preferably at the same time of the day. In 2002, all subjects were invited for an examination that included measurements of both BP and measurements of atherosclerosis. The median number of visits was 15 (range 2 to 19). The median follow-up time for the present analyses is 23 years. The present study is based on 452 subjects with data available on BP in both the mother and father. Response gradually declined to 83% in 1993. In 2002 the response was 61%. The Medical Ethics Committee of the Erasmus Medical Center approved the study, and all participants gave informed consent.

### Measurements

Blood pressure was measured using a Hawksley random-zero sphygmomanometer (Lancing, Sussex, UK) according to a standardized protocol[19] on the left brachial artery of a sitting subject after a resting period of 15 minutes. A cuff of 23 cm by 10 or 14 was used, depending on the arm circumference. The largest cuff was usually used in a child $>$10 years of age. Diastolic BP was taken at the fifth Korotkoff phase, and the mean of two consecutive measurements was used in the analyses. Between 1975 and 1993 the same research assistant performed all of the BP measurements, and in 2002 three research assistants performed the measurements. Body height and weight were measured, and body mass index (BMI) was calculated as weight (kg)/height$^2$ (m$^2$). At each visit, nonfasting blood samples were taken. In the period 1975 to 1993, serum total cholesterol was determined by an enzymatic procedure using Boehringer Mannheim CHOD/PAP High Performance (Mannheim, Germany). The latest serum total cholesterol measurements were determined by an automated enzymatic procedure using Roche CHOD-PAP reagent kit (Roche Diagnostics, Basel, Switzerland). Information on smoking habits and alcohol use, medical history, and medication use was obtained through questionnaires. In addition, women were asked about, menstrual cycle, and pregnancies, and use of oral contraceptives. Parental data of the subjects were obtained at baseline. In parents, BP was measured similarly using a Hawksley random-zero sphygmomanometer (Lancing, Sussex, UK) according to a standardized protocol.[19] Total cholesterol was determined by an enzymatic procedure using Boehringer Mannheim CHOD/PAP High Performance. Parental information on smoking habits, alcohol consumption, medical history, and use of antihypertensive medication was obtained through questionnaires.

### Statistical Analysis

Parental BP level was examined as a determinant of offspring BP levels over time. Tertiles of age-adjusted BP distributions were made separately for fathers and mothers using linear regression. The highest tertile included parents using antihypertensive medication. A categorical variable indicating for each child the number of parents (none, one, or both) in the highest tertile of BP was used as the determinant in the subsequent analysis. Repeatedly measured BP levels in offspring were studied as outcome. Because repeated BP measurements within children are nonindependent observations, we used unbalanced repeated measurement analysis. The relationship between BP and age was modeled using fractional polynomials.[20] Intercept and age were used as random effects. The same modeling was used to obtain mean BP in offspring by parental BP adjusted for offspring sex, age, height, BMI, total cholesterol, smoking habits, and alcohol consumption. The interaction term age offspring*parental blood pressure was added to evaluate whether the relationship between parental BP and offspring BP changed with increasing age of offspring. The model included repeated BP measurements in offspring as the dependent variable and an indicator for parental BP tertile as well as the above-mentioned factors as independent variables. To evaluate the impact of paternal and maternal BP separately, offspring BP level was analyzed according to continuous BP levels in, respectively, fathers and mothers. The interaction terms gender*paternal systolic blood pressure, gender*maternal systolic blood pressure, gender*paternal diastolic blood pressure, and gender*maternal diastolic blood pressure were added to assess the paternal and maternal effects on sons and daughters separately. All statistical analyses were performed by using the Statistical Analysis System (SAS Institute, Cary, NC), with the Proc Mixed module for unbalanced repeated measures analysis.

## Results

The mean age, median years of follow-up, and the levels of risk factors at baseline of both parents and offspring are shown in Table 1. The mean baseline systolic BP of 362 subjects seen in 2002 and of 183 subjects not seen in 2002 was, respectively, 113.3 mm Hg and 114.8 mm Hg ($P$ = .26). The final model included age and age$^{-½}$. Figure 1 reflects the association between parental systolic BP and systolic BP of the offspring. Offspring with both parents in the highest BP tertile at baseline had persistently higher systolic BP levels throughout the 27-year follow-up as compared with offspring with only one parent or no parents in the highest tertile. Differences between the highest and the lowest parental tertiles were statistically significant. The difference for systolic BP was estimated at 2.72

**Table 1.** Characteristics of parents and offspring at first visit

| Variable | Mother *n* = 452 | Father *n* = 452 | Female Offspring *n* = 219 | Male Offspring *n* = 233 |
|---|---|---|---|---|
| Age (y) | 41.9 (7.4) | 44.8 (7.9) | 12.9 (4.1) | 13.3 (4.2) |
| Height (cm) | 164.5 (6.0) | 176.1 (6.8) | 152.1 (17.6) | 157.9 (22.2) |
| Weight (kg) | 65.9 (10.2) | 76.4 (10.1) | 44.4 (15.3) | 47.3 (18.0) |
| Total cholesterol (mmol/L) | 5.7 (1.1) | 5.9 (1.1) | 4.8 (0.7) | 4.6 (0.8) |
| Systolic blood pressure (mm Hg) | 125.7 (16.6) | 128.6 (15.3) | 112.9 (13.2) | 115.5 (16.5) |
| Diastolic blood pressure (mm Hg) | 79.3 (11.7) | 79.4 (11.3) | 67.2 (10.4) | 67.7 (10.1) |
| Body mass index (kg/m$^2$) | 24.3 (3.6) | 24.6 (2.8) | 18.5 (3.2) | 18.1 (2.7) |
| % Hypertensive* | 22.8 | 26.8 | | |
| Antihypertensive drugs (%) | 2.6 | 2.0 | | |
| Median follow-up (y) | | | 23.2 | 23.3 |

Values are mean (SD) unless otherwise indicated.
* Using antihypertensive medication or having systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg.

mm Hg (95% confidence interval 95% CI 0.21 to 5.24). The coefficient for the interaction term age offspring*parental systolic blood pressure was not statistically significant ($P = .67$), indicating that parentally determined systolic BP differences in offspring did not vary with increasing age of offspring. Figure 2 shows the positive association between parental diastolic BP and diastolic BP of offspring. The coefficient of the interaction term age offspring *parental diastolic blood pressure was highly statistically significant ($P = .006$). Having both parents in the highest tertile of diastolic BP resulted in a substantially higher diastolic BP in the offspring, from 1.94 mm Hg at age 15 years to 8.47 mm Hg at age 45 years and 11.74 mm Hg at age 60 years.

Systolic BP in the offspring rose 0.09 mm Hg (CI 0.04 to 0.13) per mm Hg increase in maternal systolic BP and diastolic BP rose 0.04 mm Hg (95% CI 0.01 to 0.08) per mm Hg increase in maternal diastolic BP. No difference in effect of maternal BP was seen in sons and daughters (for the interaction terms gender*maternal systolic BP and gender*maternal diastolic blood pressure, $P = .38$ and $P = .50$, respectively). For paternal systolic BP the interaction term with gender was borderline significant ($P = .07$), being an increase of 0.14 mm Hg per mm Hg increase in systolic BP in sons (CI 0.07 to 0.22) and an increase of 0.02 mm Hg per mm Hg in daughters (CI −0.05 to 0.09). The effect of paternal diastolic BP was significantly different for sons and daughters (for the interaction term gender*paternal diastolic blood pressure, $P = .02$), being an increase of 0.16 mm Hg per mm Hg for sons (CI 0.10 to 0.23) and an increase of 0.08 mm Hg per mm Hg for daughters (CI 0.01 to 0.14).

## Discussion

In this longitudinal study, we found that actual parental BP is a strong determinant of the natural history of BP in their offspring from childhood into young adulthood. The association was found for the highest tertile of BP levels of the parents and not only for parental hypertension.

Before we discuss our findings, some methodologic issues need to be considered. The group selected for follow-up was a random sample from the youngsters who

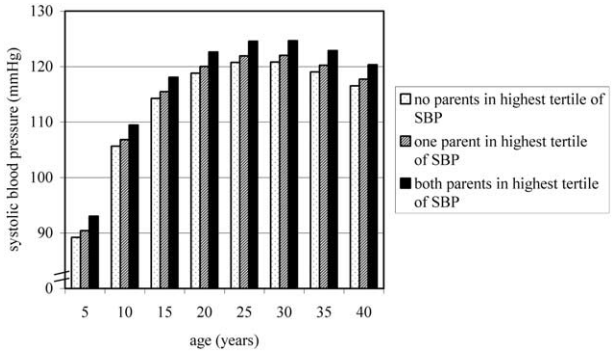


**FIG. 1.** Systolic blood pressure (SBP) development in offspring according to systolic blood pressure of parent(s). Values based on a repeated measurement regression model adjusted for offspring age, sex, standardized height, body mass index, total cholesterol, smoking habits, and alcohol consumption.

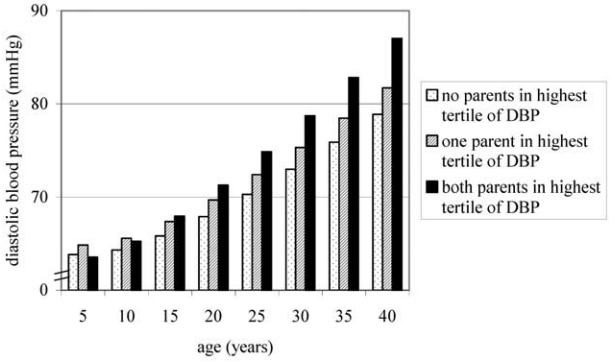


**FIG. 2.** Diastolic blood pressure (DBP) development in offspring according to diastolic blood pressure in parent(s). Values based on repeated measures regression model adjusted for offspring age, sex, standardized height, body mass index, total cholesterol, smoking habits, alcohol consumption, and the interaction term age*parental diastolic blood pressure.

participated in the baseline study. Blood pressure values among those lost to follow-up and those not lost to follow-up were similar. Therefore, we do not think that loss to follow-up has affected our results. Moreover, only small numbers of children were lost to follow-up in a strict sense; most only had some missing values. Measurements of BP include within-subject variability and measurement error. The large number of measurements of BP that were performed in each individual contributes to a more accurate estimation of the subject's true underlying BP levels at every age.

Cardiovascular risk factors including high BP are known to aggregate in families,[9,11–14] with studies showing variation in BP to be determined by both genetic and environmental influences.[14,21–25] A relationship between a positive family history of hypertension and BP in offspring from childhood to young adulthood has been shown,[12,13] including data in previous reports of the EPOZ study in children.[19,26] A genetic basis for the differences found in our study is supported by the fact that familial differences are not only present at a young age when environments are shared, but persist into young adulthood when environments become more different. Familial aggregation is also found for other important cardiovascular risk factors such as total serum cholesterol and low-density lipoprotein cholesterol,[27] smoking habits,[28] diabetes mellitus,[29] and obesity.[30] The association that we observed remained after controlling for these factors, suggesting that the findings in this study are independent of the familial aggregation of those other factors.

It is well established that there is a positive relationship between initial level of BP and subsequent rise of BP in adulthood,[31] a phenomenon known as horse racing.[32] This would indicate that the familial differences found in our study might be expected, if anything, to increase further later in life. In addition, is has been shown in adulthood (age $>$25 years) that prolonged differences in BP have a substantial impact on risk of heart disease.[33] For example, differences in systolic BP of 9, 14, and 19 mm Hg were reported to be associated with subsequent 34%, 46%, and 56% differences in 10-year risk of stroke and with 21%, 29%, and 37% differences in 10-year risk of coronary heart disease, respectively. The longitudinal association between high BP in childhood and cardiovascular disease much later in life has not yet been demonstrated. However, recent studies have shown a significant relationship between BP in childhood and levels of atherosclerosis in young adulthood.[34,35] The familial differences in offspring in our study, amounting to a projected 2.72 mm Hg systolic BP and 8.47 mm Hg diastolic BP at 45 years of age, may lead to material differences in risk of stroke and coronary heart disease in the far future. It should be added that BP is not the only cardiovascular risk factor that shows familial aggregation over time. We have shown previously in this cohort that increased parental lipid levels are associated with persistently and substantially higher lipid levels in their offspring.[27] Familial aggregation of multiple cardiovascular risk factors already present at an early age seems to persist over time in the offspring, as described here. Moreover, it has been reported that clusters of cardiovascular risk factor levels show tracking in unselected young populations.[36] Our findings add to the current knowledge in several ways. The impact of parental BP was present over the whole distribution of parental BP levels, meaning the lower the parental BP, the lower the BP levels of the offspring. Furthermore, our data suggest that the impact of parental BP starts at an early age and that it is strong and long lasting. Cardiovascular high-risk profiles in the young may be better predictors of elevated risk profiles in adulthood and eventually of cardiovascular endpoints than single risk factors. Because our data show that on a group level parental BP characterizes offspring BP throughout youth into young adulthood, actual parental BP levels may play an important role in assessing cardiovascular risk in childhood.

In conclusion, the results of this study indicate that actual parental BP is an important predictor of BP development from childhood into young adulthood. This is important when constituting cardiovascular risk profiles for children and young adults.

## Acknowledgments

We thank Joke Jansen for measuring the BP diligently for more than 18 years and for contacting the EPOZ participants. We thank Toos Stehmann, Pauli van Eldik, and Inge Haumersen for the meticulous measurements in EPOZ 2002.

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