

Progression of Normotensive Adolescents to Hypertensive Adults

A Study of 26 980 Teenagers

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Abstract—Although prehypertension at adolescence is accepted to indicate increased future risk of hypertension, large-scale/long follow-up studies are required to better understand how adolescent blood pressure (BP) tracks into young adulthood. We studied 23 191 male and 3789 female adolescents from the Metabolic Lifestyle and Nutrition Assessment in Young Adults cohort (mean age: 17.4 years) with BP <140/90 mm Hg at enrollment or categorized by current criteria for pediatric BP and body mass index (BMI) values. Participants were prospectively followed up with repeated BP measurements between ages 25 and 42 years and retrospectively between ages 17 and 25 years for the incidence of hypertension. We identified 3810 new cases of hypertension between ages 17 and 42 years. In survival analyses, the cumulative risk of hypertension between ages 17 and 42 years was 3 to 4 times higher in men than in women. Using Cox regression models adjusted for age, BMI, and stratified by baseline BP, the hazard ratio of hypertension increased gradually across BP groups within the normotensive range at age 17 years, without a discernible threshold effect, reaching a hazard ratio of 2.50 (95% CI: 1.75 to 3.57) for boys and 2.31 (95% CI: 0.71 to 7.60) for girls in the group with BP at 130 to 139/85 to 89 mm Hg. BMI at age 17 years was strongly associated with future risk of hypertension even when adjusted to BP at age 17 years, particularly in boys. Yet, BMI at age 30 years attenuated this association, more evidently in girls. In conclusion, BP at adolescence, even in the low-normotensive range, linearly predicts progression to hypertension in young adulthood. This progression and the apparent interaction between BP at age 17 years and BMI at adolescence and at adulthood are sex dependent. (*Hypertension*. 2010;56:000-000.)

Key Words: blood pressure ■ body mass index ■ hypertension ■ adolescence



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With the growing problem of childhood obesity and the early cardiovascular and metabolic complications that it encompasses, it became increasingly important to reveal obesity-associated risk factors and their tracking from childhood through adolescence to adulthood.¹⁻³ Hypertension is among the classic cardiovascular risk factors, the prevalence of which has been increasing in recent years along with the obesity epidemic,⁴ also in children and adolescents.⁵ With developments in antihypertensive therapy and the appreciation of a lack of a clear threshold effect between blood

pressure (BP) and health risks in adults,⁶ the definition of prehypertension has been proposed as an important predictor for future hypertension and morbidity.⁷ In the pediatric population, a “physiological” increase in BP occurs between ages 11 and 19 years, with systolic BP rising more steeply in boys,⁸ raising the need to define prehypertension in childhood.^{9,10} The ability to track BP levels from childhood to adulthood is supported by significant literature.^{5,11-13} Yet, current literature mainly addressed only the hypertensive and prehypertensive ranges, included relatively short intervals of

Received October 23, 2009; first decision November 10, 2009; revision accepted May 12, 2010.

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Conception and design were conducted by A.T., A.A., A.R., R.P., N.A., D.G., A.S., I.S.; acquisition of data was conducted by A.T., A.A., B.G., N.A., D.G., E.D., D.T., D.G.; analysis and interpretation of data were conducted by A.T., A.A., A.R., R.P., B.G., D.G., E.D., D.T., A.K., A.S., I.S.; and drafting and revising the article were conducted by A.T., A.R., A.A., N.A., E.G., A.K., A.S., I.S.; A.T. and E.D. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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DOI: 10.1161/HYPERTENSIONAHA.109.146415

follow-up, and/or mostly analyzed already hypertensive adolescents.^{9,12}

Similar to these observations, previous studies from the Metabolic Lifestyle and Nutrition Assessment in Young Adults (MELANY), a large follow-up cohort of army personnel,¹⁴ also demonstrated the relevance of prehypertension already at a young age as a strong risk factor for progression to hypertension in early adulthood in men.^{15,16} In addition, overweight and obesity (body mass index [BMI] ≥ 25 kg/m²) has been noted to augment the risk of progression from prehypertension at adolescence to future hypertension,¹⁶ consistent with other studies.⁵ Nevertheless, large-scale long-term follow-up studies describing how hypertension develops over time in young adulthood among the entire normotensive range, including BP <120/80 mm Hg in adolescence, taking into account the current accepted definitions of pediatric BP and BMI,^{2,5,17} are still warranted.⁸

Here we used the MELANY cohort to track BP levels of 17-year-old boys and girls for incidence of hypertension at adulthood across the entire BP range. We followed >25 000 adolescents for the incidence of hypertension by repeated BP measurements during the follow-up period (age: 25 to 42 years).

Methods

Study Population

The MELANY has been conducted at the Israel Defense Forces Staff Periodic Examination Center (SPEC), to which all career service personnel ≥ 25 years of age are referred every 3 to 5 years, as we described previously.^{14,18,19} Briefly, at each visit to the SPEC, participants completed a detailed demographic and lifestyle questionnaire, and a physical examination was performed by a physician. Weight, height, and BP were measured at each visit. Primary care for all Israel Defense Forces personnel between scheduled visits to the center was obtained at designated military clinics, and all medical information was recorded in the same central database, thereby facilitating ongoing, tight, and uniform follow-up. Data on BP measurements at adolescence for all of the participants were obtained from their initial medical evaluation before recruitment for compulsory military service at age 17 to 18 years. Baseline examination was performed in the army recruitment centers, where weight and height were measured, and BMI was calculated. A single BP measurement of the right arm was performed in the seated position, using a mercury sphygmomanometer.¹⁶ Thus, for all of the subjects a baseline BP measurement was recorded at adolescence (mean age: 17.4 ± 0.5 years) with additional repeated BP measurements starting from the age of 25 years, every 3 to 5 years, allowing us to follow the incidence of hypertension. The median time from enrollment (age 17 years) to the end of the follow-up period was 14 years (range: 6 to 25 years).

The institutional review board of the Israel Defense Forces Medical Corps approved this study on the basis of strict maintenance of participants' anonymity during database analyses. The authors are solely responsible for the design of the study, analysis and interpretation of the data, and writing of the article, without any form of censorship or limitation by the Israel Defense Forces.

Inclusion and Exclusion Criteria

Enrolled in this study were 30 254 participants of the MELANY cohort (26 305 men and 3949 women) for whom BP measurement at adolescence (age: 17 to 18) was recorded and who were free of diagnosis of hypertension and were not taking antihypertensive medications at adolescence. We excluded 3114 (11.8%) male and 160 (4.0%) female adolescents with baseline BP ≥ 140 mm Hg systolic and/or 90 mm Hg diastolic or with missing data. Those who

already had hypertension at age 17 years were usually assigned for lifestyle and/or pharmacological treatment and were, therefore, not included in the current analysis. In a subanalysis we have regrouped the study population using the National Heart, Lung, and Blood Institute diagnostic criteria for hypertension in adolescents. For this sub-analysis, an additional 690 participants whose BP at the age of 17 years met the National Heart, Lung, and Blood Institute criteria for hypertension¹⁰ were excluded.

Outcome Determinations

Follow-up examination(s) at the SPEC began at age of 25 years. In total, 7199 participants were assessed once, 17 403 in 2 SPEC visits, 2176 in 3 visits, 195 in 4 visits, and 5 in 5 SPEC visits. BP was measured while participants were in the seated position by a trained medical technician using a mercury sphygmomanometer. The right upper arm was used for all of the measurements. For 30 minutes before measurement, subjects were asked to refrain from smoking, eating, or exercise. Measurements were always performed in the morning at room temperature (20°C to 25°C). If systolic or diastolic measurements were ≥ 140 or ≥ 90 mm Hg, respectively, then the mean of 10-BP measurements, performed over a period of several weeks, was entered into the database before a formal diagnosis of hypertension was made. For participants with BP <140/90 mm Hg measured at the SPEC, no additional measurements were prescribed until the participant's next visit to the examination center. Diagnosis of hypertension between visits to the SPEC could also be made by the participant's primary care physician, using the same diagnostic criteria mentioned above. At the final recorded examination (end of follow-up), all of the participants were censored for the presence or absence of hypertension.¹⁶ The follow-up period began at the first visit of each participant in the SPEC (age: ≈ 25 years). There were 43 participants who developed hypertension between enrollment (age: 17 years) and the beginning of prospective data collection (starting at age 25 years), representing 1.1% of the total number of new cases in this study. Because the exact date of the diagnosis for those individuals was not available for us, these cases were recorded as having hypertension at their first SPEC visit, representing a cumulative incidence for the period between 17 to 25 years. Participants were prospectively followed-up with repeated BP measurements between ages 25 and 42 years for the incidence of hypertension. Forty-three cases were retrospectively diagnosed at age 25 years for the period between 17 and 25 years of age.

Statistical Analysis

Descriptive statistics included mean \pm SD and proportions (percentage). At baseline, all of the participants were divided into 5 groups in the normotensive and prehypertensive ranges, and classification for the BP group was according to the highest of either systolic or diastolic values (<100/70, 100 to 109/70 to 74, 110 to 119/75 to 79, 120 to 129/80 to 84, and 130 to 139/85 to 89 mm Hg). For comparison of systolic BP, diastolic BP, and BMI between age groups, an ANOVA model was used. We used Cox regression survival analysis models to calculate the cumulative incidence of hypertension stratified by sex and adjusted for both age at baseline (divided into 16 to 17 and 18 to 19 years of age) and BMI as a categorical variable (<25, 25 to 30, and ≥ 30 kg/m²) at baseline and at adulthood. In a Cox regression analysis we calculated hazard ratio with 95% CIs for the association of normal BP at age 17 years with incidence of hypertension at adulthood among the 23 191 men and 3789 women. We then calculated the association of BMI at age 17 years with incidence of hypertension at adulthood, categorized by BMI criteria for adults (BMI of <18.50, 18.50 to 24.99, 25.00 to 29.99, and ≥ 30.00 kg/m²) and by the Centers for Disease Control and Prevention BMI criteria suggested for adolescents (<5th, 5th to 85th, 85th to 95th, and ≥ 95 th percentiles of age- and sex-specific growth charts). We used a general linear model to assess the means and proportions of the population's characteristics across BP groups and to fit the group numbers as a continuous variable to estimate the trend of variables across groups. All of the statistical analyses were performed with SPSS (version 15). $P < 0.05$ was considered significant.

Table 1. Baseline (Age 17) Characteristics of the Study Population Across BP Groups Below the Hypertensive Range (23 191 Men and 3789 Women)

Baseline Variables	Systolic/Diastolic BP Groups at Age 17 y						P for Trend
	Entire Cohort	<100/70 mm Hg	100 to 109/70 to 74 mm Hg	110 to 119/75 to 79 mm Hg	120 to 129/80 to 84 mm Hg	130 to 139/85 to 89 mm Hg	
Men							
n (%)	23 191	367 (1.6)	1962 (8.4)	5103 (22)	10 068 (43.5)	5691 (24.5)	
Age, y	17.41±0.60	17.40±0.54	17.42±0.58	17.40±0.58	17.44±0.58	17.43±0.57	0.603
BMI, kg/m ²	21.23±2.91	20.16±2.38	20.38±2.55	20.73±2.61	21.27±2.88	21.83±3.12	<0.001
Women							
n (%)	3789	153 (4)	623 (16.5)	1027 (27.1)	1479 (39)	507 (13.4)	
Age, y	17.42±0.54	17.43±0.58	17.40±0.54	17.39±0.54	17.42±0.56	17.39±0.54	0.914
BMI, kg/m ²	21.64±3.03	20.86±2.57	20.99±2.61	21.34±2.82	21.76±3.03	22.52±3.44	<0.001

All of the participants with baseline (age 17) BP <140/90 mm Hg were divided into 5 incremental BP categories that include the normotensive and prehypertensive range (adult definition). Classification for the BP group was according to the highest of either systolic or diastolic values.

Results

Of the MELANY population, we identified 23 191 men and 3789 women whose BP at age 17 years was <140/90 mm Hg. Baseline characteristics at adolescence (before recruitment to military service) during the first medical evaluation and distribution of BP values <140/90 mm Hg grouped by increments of 10-mm Hg systolic and 5-mm Hg diastolic BP values are listed in Table 1. Comparing the entire groups of boys and girls, the former had significantly lower mean BMI but higher means of both systolic BP (117.9±9.9 versus 113.6±10.5 mm Hg; *P*<0.001) and diastolic BP (72.7±7.5 versus 71.5±7.6 mm Hg; *P*<0.001). BP in the low-normal range (≤109/74 mm Hg) was two times more prevalent among girls than boys, consistent with previous reports.^{8,20,21}

Repeated BP measurements performed during the follow-up period commencing at age 25 years revealed the dynamics of hypertension development (defined by BP ≥140/90 mm Hg, see “Outcome Determinations” in Methods section). Of 23 191 men and 3789 women, we identified 3810 new cases of hypertension by the age of 42 years. In a Cox regression survival analysis adjusted for age, BMI, and BP values at age 17 years, a sex-differential cumulative risk for hypertension could be observed (Table 2). Within a maximum of 17 years of follow-up, hypertension was 4 times more likely to occur in men than in women. To determine the effect of nonhypertensive BP range at age 17 years on future incidence of hypertension during young adulthood, the same model was conducted, stratified to the 5 baseline BP groups

Table 2. Association of BP <140/90 mm Hg at Age 17 With Incidence of Hypertension at Adulthood Among 23 191 Men and 3789 Women

Variables	Systolic/Diastolic BP Groups at Age 17 y					P for Trend
	<100/70 mm Hg	100 to 109/70 to 74 mm Hg	110 to 119/75 to 79 mm Hg	120 to 129/80 to 84 mm Hg	130 to 139/85 to 89 mm Hg	
Men						
n	367	1962	5,103	10 068	5691	
Person years of follow-up	5655	29 276	75 967	141 607	79 610	
No. of cases	32	217	675	1545	1157	
Incidence, cases/1000 per year	5.66	7.41	8.89	10.91	14.53	<0.001
Hazard ratios						
Crude	1	1.27 (0.87 to 1.86)	1.61 (1.12 to 2.31)	2.19 (1.54 to 3.13)	2.97 (2.08 to 4.24)	<0.001
Age+BMI adjusted	1	1.24 (0.85 to 1.81)	1.53 (1.07 to 2.19)	1.96 (1.37 to 2.79)	2.50 (1.75 to 3.57)	<0.001
Women						
n	153	623	1027	1479	507	
Person years of follow-up	2129	8892	15 129	21 393	7081	
No. of cases	3	21	45	80	35	
Incidence, cases/1000 per year	1.41	2.36	2.97	3.74	4.94	<0.001
Relative risk						
Crude	1	1.51 (0.45 to 5.10)	1.88 (0.58 to 6.06)	2.32 (0.73 to 7.37)	3.34 (1.02 to 0.89)	0.001
Age+BMI adjusted	1	1.36 (0.40 to 4.57)	1.65 (0.51 to 5.32)	1.85 (0.58 to 5.87)	2.31 (0.71 to 7.60)	0.030

Cox regression model was adjusted for age and BMI. *P* value for trend estimates the hazard ratio for future hypertension with mean BP values at each BP group.

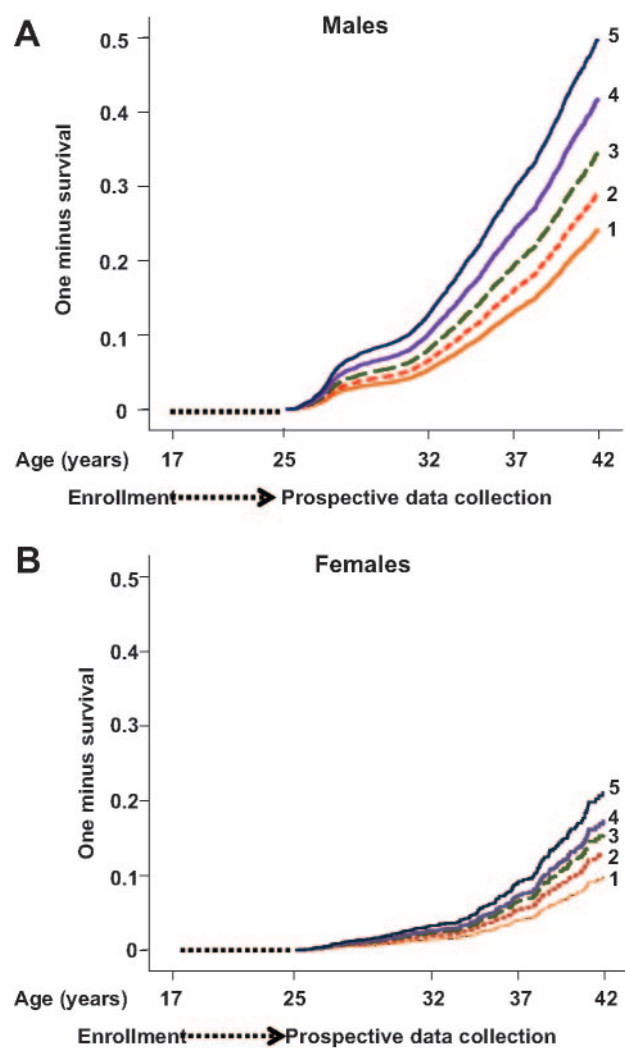


Figure. Survival analysis for progression to hypertension during young adulthood. The incidence of hypertension was assessed in 23 191 nonhypertensive men and 3789 nonhypertensive women followed from age 17 years, across BP groups at adolescence, adjusted for age and BMI, in males (A) and females (B). Adolescent (mean age: 17.4 years) BP groups are as follows: 1, <100/70 mm Hg; 2, 100 to 109/70 to 74 mm Hg; 3, 110 to 119/75 to 79 mm Hg; 4, 120 to 129/80 to 84 mm Hg; 5, 130 to 139/85 to 89 mm Hg. Data were collected prospectively from the age of 25 years. Diagnosis of hypertension between ages 17 and 25 years (43 cases) was recorded retrospectively and was added to the cumulative incidence of hypertension between ages 17 and 42 years.

shown in Table 1, in both boys and girls (Figure, A and B, respectively). In both sexes the cumulative risk of hypertension increased gradually across BP groups at age 17 years, without a clear discernible threshold effect. Incidence rates of hypertension were also calculated for age 17 normotensive and prehypertensive participants, based on the National Heart, Lung, and Blood Institute or the adult criteria, as described in the Methods section. In male adolescents, the incidence rate of hypertension at adulthood was 7.75 and 11.68 cases per 1000 person-years for normotensive and prehypertensives, respectively, using the adult criteria ($P<0.001$), and 9.10 versus 12.03, respectively, using the age- and height-based National Heart, Lung, and Blood

Institute criteria ($P<0.001$). For female adolescents, the incidence of hypertension was 2.56 and 3.79 per 1000 person-years for normotensive and prehypertensives, respectively, using the adult criteria ($P=0.013$) and 3.06 and 3.28 for normotensive and prehypertensives, respectively, using the age- and height-based criteria ($P=0.797$). Using the incremental age 17 BP categories (as in Table 1), a Cox regression model further adjusted to BMI at age 17 years suggested an attenuation effect exerted by BMI in both women and men, with hazard ratio in the top group (age 17 BP of 130 to 139/85 to 89 mm Hg) decreasing from 3.34 to 2.31 in women and from 2.97 to 2.5 in men (Table 2). Nevertheless, increasing age 17 BP in both sex groups remained linearly associated with higher hazard ratio for future hypertension even when adjusted for age 17 BMI (P of trend <0.001 for men and at 0.030 for women).

To better dissect out the role of BMI at age 17 years as a predictor of hypertension in young adults, the study population was divided into classic categories of BMI (underweight, normal weight, overweight, and obese) at age 17 years, both by the adult criteria (BMI of <18.50, 18.50 to 24.99, 25.00 to 29.99, and ≥ 30.00 kg/m²; Table 3, top panel) and by the Centers for Disease Control and Prevention BMI criteria suggested for adolescents (<5th, 5th to 85th, 85th to 95th, and ≥ 95 th percentiles of age- and sex-specific growth charts; Table 3, bottom panel). Remarkably, in men a progressive increase in the risk of hypertension was observed across the BMI categories at the age of 17 years, with a significant increase observed already in the normal weight group as compared with BMI <18.5 kg/m² or ≤ 5 th percentile. In contrast, among women a significant relationship between age 17 BMI and the risk of subsequent hypertension was observed more pronouncedly among overweight and obese adolescents. Interestingly, a strong attenuation of the effect of BMI at age 17 years on the risk for future hypertension was observed by BMI values at adulthood, particularly among girls. In boys, although the risk was attenuated by further adjusting the model to BMI at age 30 years, age 17 BMI remained an independent predictor for hypertension. Among adolescent girls, only BMI of ≥ 30 kg/m², or ≥ 95 th percentile, were associated with elevated risk of hypertension when adjusting for BMI at adulthood (Table 3, top and bottom, respectively).

Discussion

There is a wealth of epidemiological data supporting a correlation between BP at childhood and adolescence with the incidence of hypertension at adulthood (^{5,11–13} and references within). Using a large cohort of >25 000 adolescents, a prolonged follow-up (up to the age of 42 years), and the current diagnostic criteria for BP and BMI among adolescents,^{9,10} this study substantiates and adds to previous observations as follows. First, mean BP values are higher among male adolescents than among female adolescents despite lower mean BMI. The incidence rate of hypertension during early adulthood is 2- to 3-fold higher among men in all of the categories of BP <140/90 mm Hg. Second, increasing age 17 BP within the current definitions of normal BP and prehypertension is linearly associated with higher risk of hyperten-

Table 3. Association of BMI at Age 17 With Incidence of Hypertension at Adulthood, Stratified by BMI Criteria for Adults or Adolescents

Adjustments	Adult Criteria, Men					Adult Criteria, Women				
	Underweight, <18.50	Normal Weight, 18.50 to 24.99	Overweight, 25.00 to 29.99	Obese, ≥30.00	P for Trend	Underweight, <18.50	Normal Weight, 18.50 to 24.99	Overweight, 25.00 to 29.99	Obese, ≥30.00	P for Trend
Age	1	1.45 (1.29 to 1.62)	3.07 (2.67 to 3.53)	4.12 (3.25 to 5.22)	<0.001	1	1.44 (0.79 to 2.61)	4.39 (2.33 to 8.29)	8.08 (3.02 to 21.67)	<0.001
Age and BP	1	1.39 (1.24 to 1.55)	2.8 (2.44 to 3.23)	3.65 (2.87 to 4.63)	<0.001	1	1.39 (0.76 to 2.53)	4.09 (2.15 to 7.76)	7.23 (2.68 to 19.51)	<0.001
Age, BP, and BMI at adulthood	1	1.28 (1.14 to 1.44)	2.09 (1.78 to 2.45)	2.59 (2.02 to 3.33)	<0.001	1	1.05 (0.25 to 4.39)	1.69 (0.39 to 7.18)	4.81 (1.13 to 20.53)	<0.001

Adjustments	Pediatric Criteria, Men					Pediatric Criteria, Women				
	Underweight, ≤5th	Normal Weight, 5th to 85th	Overweight, 85th to 95th	Obese, ≥95th	P for Trend	Underweight, ≤5th	Normal Weight, 5th to 85th	Overweight, 85th to 95th	Obese, ≥95th	P for Trend
Age	1	1.53 (1.29 to 1.79)	3.17 (2.62 to 3.83)	4.34 (3.48 to 5.40)	<0.001	1	2.06 (0.51 to 8.35)	5.83 (1.39 to 24.43)	12.98 (2.61 to 64.4)	<0.001
Age and BP	1	1.52 (1.29 to 1.80)	3.14 (2.60 to 3.79)	4.28 (3.44 to 5.34)	<0.001	1	2.06 (0.52 to 8.34)	5.82 (1.39 to 24.41)	13.08 (2.63 to 65.13)	<0.001
Age, BP, and BMI at adulthood	1	1.39 (1.17 to 1.65)	2.27 (1.84 to 2.78)	2.95 (2.33 to 3.74)	<0.001	1	1.09 (0.25 to 4.39)	2.17 (0.79 to 22.16)	4.15 (1.10 to 49.34)	<0.001

For adult criteria, n=26 980. Cox regression analysis is shown for the incidence of hypertension in a cohort of nonhypertensive adolescents with BP <140/90 mm Hg (Adult Criteria). The population study was divided into baseline BMI levels based on the adult criteria (<18.5, 18.5 to 25.0, 25.0 to 30.0, and ≥30.0 kg/m²). For pediatric criteria, subanalysis included 26 290 nonhypertensive participants with BP below the 95th percentile for age, sex, and height according to the National Heart, Lung, and Blood criteria (Pediatric Criteria). BMI groups were based on the Centers for Disease Control and Prevention criteria for BMI in the pediatric population (<5th, 5th to 85th, 85th to 95th, and ≥95th of the BMI growth charts for age and sex).

sion in early adulthood in both sexes, without a discernible threshold effect. Third, BMI at adolescence is a strong determinant of future hypertension for both boys and girls, even when adjusting for age 17 BP or BMI at age 30 years. Yet, for boys, a strong interaction between BP levels and BMI at age 17 occurs throughout the BMI range, whereas in girls this interaction mainly manifests in the overweight-obese BMI range. Fourth, nevertheless, age 17 BP, even well below the hypertensive range, remains a predictor of hypertension risk at young adulthood, independent of BMI at adolescence or at adulthood.

Several limitations and strengths in our study warrant consideration. Age 17 determinations of BP are a single-visit measurement, and although performed after rest, could generally be viewed as being performed in a more stressful setting than usual. This may explain the rather high prevalence of prehypertension (BP ≥120/80 mm Hg). Yet, this limitation may in fact result in increasing the predictive value of such a baseline measurement, as detailed below. In addition, although most of the study participants hold military office jobs (rather than front field soldiers), it is possible that a higher-stress environment contributed to the high risk of hypertension, particularly among men. Yet, as mentioned in previous published studies on this population,^{14,18} anthropometric, BP, and biochemistry values were very similar to other Western populations of young adults in the literature.^{22–25} An added limitation is the rather basic information available from the age 17 database, precluding the assessment of additional potential confounders. The strengths of the study include the large cohort, a tight long follow-up with repeated measurements from age 25 years, and measured (rather than reported) height and weight at age 17 years.

It has been extensively debated how BP should be measured to be reliable. It is generally accepted that patients should be unstressed. Moreover, in clinical studies many have argued for requiring multivisit, repeated measurements, to determine the “true” BP value, and repeated high-range BP

measurements were particularly predictive of future hypertension.²⁶ Here, relying on a vast mass screening setup, a single-visit measurement has been performed, potentially resulting in misclassification in BP stratification, particularly because the environment of an army recruitment center is likely more stressful than “normal life.” Despite this limitation, our results suggest that such single-visit determination in a “nonrelaxed environment” may still be valuable for predicting the future development of hypertension. This is highly reminiscent of the higher true hypertension rates eventually diagnosed among persons with an elevated BP response to a medical environment (“white-coat hypertension”).^{27,28} Regardless of the mechanisms for this trait, it seems to be operational in adults, children, and, as in this study, also in adolescents.

The progression of normotensive boys and girls to hypertensive young adults occurs with sex-differential kinetics, magnitude, and association with BMI. Sex hormones are likely involved in this sex-differential effect, with several mechanisms proposed to function as early as in utero (“fetal programming”),^{29,30} as well as during adult life.³¹ Several previous studies demonstrated an increasing incidence of adult hypertension based on the European BP categories of the normotensive range (optimal, normal, and high-normal).^{16,32} Here we show that, even beyond these predefined categories and within the normotensive BP range, both sexes exhibit a linear progression in the risk of hypertension in young adulthood with increasing BP values. The association of incident hypertension and BMI is also well described.^{33,34} Yet, here we show that the strength of this association is also sex dependent, exhibiting a larger effect on boys than on girls. Moreover, in girls, much of the risk associated with BMI at age 17 years may be mediated by its prediction of BMI at adulthood. Jointly, these findings support an individualized definition of “normal BP” at adolescence, taking into account sex and BMI, similar to both the European and American guidelines for the definition of

normotension and prehypertension in children and adolescents.^{10,17} This notion is similar to that proposed recently for fasting blood glucose levels: within the normal fasting plasma glucose range, an 8-fold variability in the incident risk of future type 2 diabetes mellitus in young adults could be recognized, influenced by family history of the disease, fasting triglyceride levels, and BMI.^{14,35}

Perspectives

There is a pressing need to better understand cardiovascular risk factors in young adulthood, particularly in the face of the obesity epidemic that also affects children and adolescents. The present study used a large-scale, prolonged follow-up cohort to determine the interplay among sex, BP, and BMI at late adolescence in determining the risk for hypertension in early adulthood. Substantiating previous studies and guidelines, this study demonstrates that males have higher mean BP values already in adolescents and exhibit higher incidence rates and kinetics of hypertension before age 42 years. The results also demonstrate that a linear increase in the incident risk of hypertension occurs throughout the entire BP range at late adolescence, without a clear threshold effect, whether adult or pediatric criteria are used. BMI at this age also determines hypertension risk but in girls mainly manifests in the overweight and obese range, where much of its effect can be attributed to its association with BMI at age 30 years. Finally, the study demonstrates the potential predictive value of even a single BP measurement. Thus, along with existing guidelines, these findings call for high awareness for pediatricians in using an integrated individualized assessment that incorporates sex and late adolescence BP and BMI in predicting the risk of hypertension in young adulthood, an age group that frequently escapes continuous medical attention.

Sources of Funding

This study was supported by a grant from the Talpiot Medical Leadership Program, Chaim Sheba Medical Center, Tel-Hashomer, Israel (to A.T.) and by the Israeli Defense Forces Medical Corps.

Disclosures

None.

References

- Baker JL, Olsen LW, Sorensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. *N Engl J Med*. 2007;357:2329–2337.
- Steinberger J, Daniels SR, Eckel RH, Hayman L, Lustig RH, McCrindle B, Mietus-Snyder ML. Progress and challenges in metabolic syndrome in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; and Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2009;119:628–647.
- Varness T, Allen DB, Carrel AL, Fost N. Childhood obesity and medical neglect. *Pediatrics*. 2009;123:399–406.
- Chockalingam A, Campbell NR, Fodor JG. Worldwide epidemic of hypertension. *Can J Cardiol*. 2006;22:553–555.
- Muntner P, He J, Cutler JA, Wildman RP, Whelton PK. Trends in blood pressure among children and adolescents. *JAMA*. 2004;291:2107–2113.
- Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, for the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–1252.
- Moran A, Jacobs DR Jr, Steinberger J, Steffen LM, Pankow JS, Hong CP, Sinaiko AR. Changes in insulin resistance and cardiovascular risk during adolescence: establishment of differential risk in males and females. *Circulation*. 2008;117:2361–2368.
- Falkner B, Gidding SS, Portman R, Rosner B. Blood pressure variability and classification of prehypertension and hypertension in adolescence. *Pediatrics*. 2008;122:238–242.
- National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114:555–576.
- Sun SS, Grave GD, Siervogel RM, Pickoff AA, Arslanian SS, Daniels SR. Systolic blood pressure in childhood predicts hypertension and metabolic syndrome later in life. *Pediatrics*. 2007;119:237–246.
- Maggisano V, Chiarotti F, Botunac I, Campanella C, Galletta G, Loizzo A. Adolescence as possible critical temporal window for blood pressure short term monitoring in boys and girls. *Eur J Epidemiol*. 2005;20:517–524.
- Bao W, Threefoot SA, Srinivasan SR, Berenson GS. Essential hypertension predicted by tracking of elevated blood pressure from childhood to adulthood: the Bogalusa Heart Study. *Am J Hypertens*. 1995;8:657–665.
- Tirosh A, Shai I, Tekes-Manova D, Israeli E, Pereg D, Shochat T, Kochba I, Rudich A. Normal fasting plasma glucose levels and type 2 diabetes in young men. *N Engl J Med*. 2005;353:1454–1462.
- Grossman A, Grossman C, Barenboim E, Azaria B, Goldstein L, Grossman E. Pre-hypertension as a predictor of hypertension in military aviators: a longitudinal study of 367 men. *Aviat Space Environ Med*. 2006;77:1162–1165.
- Israeli E, Korzets Z, Tekes-Manova D, Tirosh A, Schochat T, Bernheim J, Golan E. Blood-pressure categories in adolescence predict development of hypertension in accordance with the European guidelines. *Am J Hypertens*. 2007;20:705–709.
- Lurbe E, Cifkova R, Cruickshank JK, Dillon MJ, Ferreira I, Invitti C, Kuznetsova T, Laurent S, Mancia G, Morales-Olivas F, Rascher W, Redon J, Schaefer F, Seeman T, Stergiou G, Wuhl E, Zanchetti A. Management of high blood pressure in children and adolescents: recommendations of the European Society of Hypertension. *J Hypertens*. 2009;27:1719–1742.
- Tirosh A, Rudich A, Shochat T, Tekes-Manova D, Israeli E, Henkin Y, Kochba I, Shai I. Changes in triglyceride levels and risk for coronary heart disease in young men. *Ann Intern Med*. 2007;147:377–385.
- Tirosh A, Shai I, Bitzur R, Kochba I, Tekes-Manova D, Israeli E, Shochat T, Rudich A. Changes in triglyceride levels over time and risk of type 2 diabetes in young men. *Diabetes Care*. 2008;31:2032–2037.
- Wang X, Poole JC, Treiber FA, Harshfield GA, Hanevold CD, Snieder H. Ethnic and gender differences in ambulatory blood pressure trajectories: results from a 15-year longitudinal study in youth and young adults. *Circulation*. 2006;114:2780–2787.
- Elliott WJ, Black HR. Prehypertension. *Nat Clin Pract Cardiovasc Med*. 2007;4:538–548.
- Juonala M, Viikari JS, Hutri-Kahonen N, Pietikainen M, Jokinen E, Taittonen L, Marniemi J, Ronnema T, Raitakari OT. The 21-year follow-up of the Cardiovascular Risk in Young Finns Study: risk factor levels, secular trends and east-west difference. *J Intern Med*. 2004;255:457–468.
- Urbina EM, Srinivasan SR, Kietlyka RL, Tang R, Bond MG, Chen W, Berenson GS. Correlates of carotid artery stiffness in young adults: the Bogalusa Heart Study. *Atherosclerosis*. 2004;176:157–164.
- Stamler J, Stamler R, Neaton JD, Wentworth D, Daviglius ML, Garside D, Dyer AR, Liu K, Greenland P. Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and life expectancy: findings for 5 large cohorts of young adult and middle-aged men and women. *JAMA*. 1999;282:2012–2018.

25. Diez Roux AV, Jacobs DR, Kiefe CI. Neighborhood characteristics and components of the insulin resistance syndrome in young adults: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Diabetes Care*. 2002;25:1976–1982.
26. Shear CL, Burke GL, Freedman DS, Webber LS, Berenson GS. Designation of children with high blood pressure: considerations on percentile cut points and subsequent high blood pressure—the Bogalusa Heart Study. *Am J Epidemiol*. 1987;125:73–84.
27. Ugajin T, Hozawa A, Ohkubo T, Asayama K, Kikuya M, Obara T, Metoki H, Hoshi H, Hashimoto J, Totsune K, Satoh H, Tsuji I, Imai Y. White-coat hypertension as a risk factor for the development of home hypertension: the Ohasama Study. *Arch Intern Med*. 2005;165:1541–1546.
28. Strandberg TE, Salomaa V. White coat effect, blood pressure and mortality in men: prospective cohort study. *Eur Heart J*. 2000;21:1714–1718.
29. Grigore D, Ojeda NB, Alexander BT. Sex differences in the fetal programming of hypertension. *Gen Med*. 2008;5(suppl A):S121–S132.
30. Lawlor DA, Smith GD. Early life determinants of adult blood pressure. *Curr Opin Nephrol Hypertens*. 2005;14:259–264.
31. Gilbert JS, Nijland MJ. Sex differences in the developmental origins of hypertension and cardiorenal disease. *Am J Physiol Regul Integr Comp Physiol*. 2008;295:R1941–R1952.
32. Franklin SS, Pio JR, Wong ND, Larson MG, Leip EP, Vasan RS, Levy D. Predictors of new-onset diastolic and systolic hypertension: the Framingham Heart Study. *Circulation*. 2005;111:1121–1127.
33. Vogt B, Bochud M, Burnier M. The association of aldosterone with obesity-related hypertension and the metabolic syndrome. *Semin Nephrol*. 2007;27:529–537.
34. Gerber LM, Stern PM. Relationship of body size and body mass to blood pressure: sex-specific and developmental influences. *Hum Biol*. 1999;71:505–528.
35. Nichols GA, Hillier TA, Brown JB. Normal fasting plasma glucose and risk of type 2 diabetes diagnosis. *Am J Med*. 2008;121:519–524.



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JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Hypertension. published online June 14, 2010;
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

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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