Does Preterm Birth Influence Cardiovascular Risk in Early Adulthood?

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Objective To investigate the effect of preterm birth on risk factors for cardiovascular disease (CVD), independent of birth size.

Study design Observational study using data of 406 healthy participants aged 18-24 years, from the PROgramming factors for Growth And Metabolism and Prematurity and Small for Gestational Age studies. Associations between gestational age (GA), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), blood pressure variability, heart rate (HR), pulse wave velocity, and carotid intima media thickness (cIMT) were studied. To study the differential effects of preterm birth and small birth size for gestational age, these parameters were also analyzed in subgroups born either preterm or term: young adults born small for gestational age with short or normal adult stature, and young adults born appropriate for gestational age with normal adult stature.

Results Subjects born preterm (GA <36 weeks) had higher unadjusted SBP, PP, SBP and DBP variability, and HR, but a lower DBP than subjects born term. GA was inversely associated with SBP, PP, blood pressure variability, and HR, and positively associated with DBP, also after adjustment for confounders. There was no effect of GA on pulse wave velocity and cIMT, a marker of atherosclerosis. Of all the CVD risk factors measured, higher PP affected cIMT the most.

Conclusions Young adults born preterm might have a higher risk for CVD than those born term. *(J Pediatr 2012;161:390-6)*.

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Small size at birth has been associated with an increased risk for developing cardiovascular disease (CVD) in later life.[1] Both preterm birth and poor fetal growth can lead to small birth size. Thus, in unraveling the mechanism of this association, independent effects of gestational age (GA) as well as small birth size for gestational age (SGA) are important to determine.

Increased blood pressure (BP) and arterial stiffness (quantified by pulse wave velocity [PWV][2,3]) are major determinants of CVD, and both preterm birth and SGA birth have been related to these CVD risk factors.[1,4-9]

A recent study showed increased carotid intima media thickness (cIMT), which is a measure of atherosclerosis,[10] in subjects born preterm, however, this was restricted to those with fetal growth restriction.[11] Furthermore, low birth weight has been associated with increased cIMT in young adulthood.[12] Although these results were not adjusted for GA, it was shown that exclusion of young adults born preterm strengthened the association, indicating that the effect of small birth size on cIMT was due to SGA rather than preterm birth. In contrast, others showed that birth weight SDS did not associate with cIMT in young adulthood.[13]

We investigated differences between young adults born either preterm or term, using the following variables: systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP),[14] BP variability,[15,16] heart rate (HR),[17] PWV, and cIMT. We also investigated the influence of GA on these outcomes after adjustment for several confounders, including birth weight SDS and birth length SDS. Additionally, we studied the differential effects of preterm and SGA birth on CVD risk, by subdividing the total population in clinically relevant groups: born small for gestational age (either preterm or term) with short (SGA-S) or normal adult stature (SGA-CU), and born appropriate for gestational age (either preterm or term) with normal adult stature (AGA).

AD	Artery diameter	MR	Multiple linear regression
AGA	Appropriate for gestational age with normal adult stature	PP	Pulse pressure
		PWV	Pulse wave velocity
BP	Blood pressure	SES	Socioeconomic status
cIMT	Carotid intima media thickness	SBP	Systolic blood pressure
CV	Coefficient of variation	SGA	Small birth size for gestational age
CVD	Cardiovascular disease	SGA-S	Small for gestational age with short adult stature
DBP	Diastolic blood pressure		
GA	Gestational age	SGA-CU	Small for gestational age with normal adult stature
HR	Heart rate		
MAP	Mean arterial pressure		

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Methods

The PROgramming factors for Growth And Metabolism (PROGRAM) (n = 323) and Prematurity and Small for Gestational Age (PREMS) (n = 169) study cohorts consist of 492 healthy participants, aged 18-24 years. The PROGRAM and PREMS study cohorts had similar inclusion and exclusion criteria, study center (Erasmus University Medical Center in Rotterdam), and measurements. The only difference was that the PREMS study consists of participants born preterm (GA <36 weeks). Participants were recruited from several hospitals in The Netherlands, where they had been registered because of their small birth size (birth length <−2 SDS),[18] short stature (adult height <−2 SDS),[19] or being born preterm. By using advertisement, healthy subjects born AGA were asked to participate. The participation rate of the PROGRAM/PREMS study cohort was 79.5%.[20] The study population has been previously described in detail.[20,21] Birth data were taken from medical records of hospitals, community health services, and general practitioners. Information regarding socioeconomic status (SES), smoking, and alcohol use was obtained using questionnaires. Education level of the participant was used as socioeconomic indicator to determine SES.[22] The Medical Ethics Committee of Erasmus Medical Center approved the study. Written informed consent was obtained from all participants.

Of the 492 participants who entered the study, 86 had incomplete data because the devices to measure BP, cIMT, and PWV were not available at all times, resulting in a total number of 406 eligible subjects for analyses.

Additionally, based on SDSs of birth length and adult height, the subjects were assigned to 1 of 3 subgroups. To increase the statistical power for subgroup comparison, the cut-off values for small birth size and short adult height were set at −2 SDS, and the cut-off values for normal birth size and normal adult height were set at -1 SDS. This resulted in a total of 246 participants who were included in 1 of the 3 subgroups: (1) SGA (birth length <−2 SDS) with a short adult height (<−2 SDS)(SGA-S) (n = 44); (2) SGA (birth length <−2 SDS) with catch-up growth resulting in normal adult height (>−1 SDS)(SGA-CU) (n = 75); and (3) AGA (birth length >−1 SDS) with normal adult height (>−1 SDS)(AGA) (n = 127).

All participants fasted for 12 hours and abstained from smoking and alcohol for 16 hours. Height was measured to the nearest 0.1 cm by a Harpenden stadiometer, weight to the nearest 0.1 kg by a scale (Servo Balance KA-20-150S; Servo Berkel Prior, Katwijk, The Netherlands). All anthropometric measurements were performed twice; the mean was used for analysis.

BP and HR rather were measured after 10 minutes at rest, in the supine position, using the nondominant arm with an automatic device (Accutorr Plus; Datascope Corporation, Montvale, New Jersey[23]) every 5 minutes for 1 hour, and the mean values of these 13 measurements were taken to reflect resting BP and resting HR. Measuring BP using an automatic device has many advantages, however, some factors influence the measurement accuracy such as the underlying algorithms used and size and material of the cuff.[24] The device used in the present study has been validated by the Association for the Advancement of Medical Instrument and the British Hypertension Society, concluding that the device gives accurate measurements in greatest agreement with the mercury standard.[25] The 13 BP measurements were also used to calculate the coefficient of variation (CV).[15,16] PP was calculated as the difference between mean SBP and DBP.[14]

Carotid-femoral PWV was measured in supine position using SphygmoCor (AtCor Medical, Sydney, Australia).[26] A pressure tonometer was used to simultaneously record carotid pulse wave and electrocardiogram. The femoral pulse wave and electrocardiogram were also recorded. Distance traveled by the pulse wave was determined by measuring the distances from sternal notch to the femoral location and from sternal notch to the carotid location of pulse wave recording.[27]

cIMT was measured in supine position by recording of ultrasonographic images of both left and right carotid artery, using one 7.5 MHz linear array transducer (ATL Ultramark IV; Advanced Technology Laboratories, Bethel, Washington).[28] On the R-wave of the electrocardiogram, 3 longitudinal images of the near and far wall of the common carotid artery were frozen and stored on videotape. These frozen images were digitalized and displayed on the screen of a computer using a frame grabber (VP 1400-KIT-512-E-AT; Imaging Technology, Woburn, Massachusetts). The common cIMT was determined as the mean of the mean near and far wall measurements of both the left and right side common carotid artery.[28]

SD-scores for birth length and birth weight were calculated to correct for GA and sex.[18] SD-scores for adult height and adult weight were calculated to correct for sex and age.[19] Variables were log-transformed (natural logarithm) if not normally distributed. ANOVA was used to determine if there were differences between participants born either preterm or term. Using the 13 BP measurements, the CV was calculated to determine the within-subject variation in SBP and DBP with time (BP variability).[15,29]

Multiple linear regression (MR)-analysis was performed to determine the association of GA with SBP, DBP, PP, BP variability, HR, PWV, and cIMT independent of birth size. In all MR-models, adjustments were made for birth length SDS, birth weight SDS, adult height SDS, age, sex, SES, smoking, alcohol use, and the interaction term birth length SDS × adult height SDS because the study group had been selected on birth length and adult height (model A). To study the association with SBP, DBP, PP, and BP variability, we additionally adjusted for weight SDS (model B), and HR (model C). To study PWV, we additionally adjusted for mean arterial pressure (MAP) (model B), weight SDS, the interaction term sex × weight SDS and age × weight SDS (model C), and HR (model D). To study cIMT, we additionally adjusted for artery diameter (AD)

(model B) and weight SDS (model C). We tested which parameter (SBP, DBP, PP, BP variability, HR, PWV) was the most important determinant of cIMT, by adding the parameters alternately to the final cIMT-model. All regression coefficients are presented as a percentage for better interpretation of the results. A positive value indicates that the dependent variable is increased by that % for every unit increase of the independent variable.

ANCOVA was used to determine differences in BP among the subgroups corrected for age and sex (model 1), and additionally adjusted for alcohol use, smoking, SES, and weight SDS (model 2). In BP analyses, HR was added to model 2. In HR analyses, SBP was added to model 1. In PWV analyses, MAP and HR were added to model 1, and height SDS was added to model 2 (model 3). In cIMT analyses, AD was added to model 1. AGA subjects born term served as reference group and SGA-S preterm, SGA-S term, SGA-CU preterm, SGA-CU term, and AGA preterm were added as dummy variables. Statistical package SPSS v. 15.0 (SPSS, Inc, Chicago, Illinois) was used for analyses. Results were regarded statistically significant if P was <.05.

Results

The clinical characteristics of the total study population are shown in Tables I and Table II (available at www.jpeds.com). Young adults born preterm had higher unadjusted SBP (P = .007), PP (P < .001), SBP and DBP variability (P = .002 and P < .001, respectively), and HR (P < .001) than subjects born term. Unadjusted DBP was lower in subjects born preterm (P < .001).

GA was inversely associated with SBP (P = .026) and PP (P = .001) after correction for age, sex, SES, smoking, alcohol use, adult height SDS, and birth size. These associations remained significant after additional correction for adult weight SDS (Table III). In contrast with the association between GA and PP, which remained significant after additional correction for HR, the association of GA with SBP disappeared after correction for HR. HR on itself was positively associated with SBP (P < .001) (Table III).

GA was positively associated with DBP after correction for age, sex, SES, smoking, alcohol use, adult height SDS, and birth size (P = .001) (Table III). This association remained significant after additional adjustment for weight SDS and HR (P < .001), which were both positively associated with DBP (P < .001).

Lower GA was associated with a higher CV of both SBP (β (%) = −1.67, P = .003, adj. R^2 = 0.058) and DBP (β (%) = −2.85, P < .001, adj. R^2 = 0.149), after adjustment for age, sex, birth length SDS, birth weight SDS, adult height SDS, SES, smoking, alcohol use, HR, and weight SDS (data not shown).

In MR-analyses, GA was inversely associated with HR after adjustment for age, sex, birth size, adult height SDS, SES, smoking, and alcohol use (β (%) = −0.86, P < .001, adj. R^2 = 0.176). This association remained significant after additional adjustment for weight SDS and SBP (β (%) = −0.76, P < .001, adj. R^2 = 0.213) (data not shown).

After adjustment, GA was not significantly associated with PWV (Table IV). Adult height SDS showed a significant positive association with PWV (P = .029) after adjustment for weight SDS. Smoking, higher MAP, and higher HR, were also related to a higher PWV.

Lower GA showed a trend toward lower cIMT after adjustment for age, sex, SES, smoking, alcohol use, adult height

Table I. Unadjusted clinical characteristics of the total study population and subgroups

	Total study population		Subgroups					
			SGA-S		SGA-CU		AGA	
	Preterm (n = 163)	Term (n = 243)	Preterm (n = 9)	Term (n = 34)	Preterm (n = 31)	Term (n = 44)	Preterm (n = 63)	Term (n = 64)
Male/female¶	83/80§	92/151	5/4	10/24	15/16	17/27	37/26	26/38
Age (y)	20.8 (1.7)	20.9 (1.7)	21.6 (1.8)	20.6 (1.7)	20.4 (1.9)§	21.4 (1.4)	21.0 (1.6)	20.7 (1.8)
GA (wk)	32.0 (2.2)†	39.2 (1.7)	32.3 (1.5)†	39.3 (1.6)	32.3 (2.1)†	38.3 (1.6)	32.3 (2.4)†	39.4 (1.6)
Birth length SDS	−1.22 (1.9)	−1.46 (1.5)	−3.58 (1.0)	−2.99 (0.9)	−3.16 (0.8)	−2.85 (0.8)	0.38 (0.9)	0.14 (0.7)
Birth weight SDS	−0.42 (1.8)†	−1.12 (1.4)	−2.49 (0.9)	−2.02 (0.9)	−2.11 (1.1)	−2.36 (0.7)	0.79 (1.1)§	0.08 (1.2)
Adult height SDS	−0.42 (1.0)†	−1.03 (1.4)	−2.31 (0.3)	−2.61 (0.6)	−0.10 (0.6)	−0.11 (0.8)	0.13 (0.6)	0.38 (0.9)
Adult weight SDS	−0.28 (1.2)‡	−0.63 (1.4)	−1.08 (1.2)	−1.50 (1.6)	−0.32 (1.2)	0.21 (1.1)	0.27 (0.8)	0.10 (0.9)
SBP (mm Hg)*	112.3 (8.0)§	110.0 (9.0)	109.2 (6.6)	107.8 (10.2)	113.4 (7.2)	112.4 (10.2)	113.1 (8.2)‡	110.1 (7.2)
DBP (mm Hg)	63.3 (5.3)†	66.1 (5.9)	58.2 (3.3)§	66.2 (8.0)	64.5 (5.2)	66.6 (6.1)	63.6 (5.4)§	66.1 (5.0)
PP (mm Hg)*	48.9 (6.2)†	43.8 (5.8)	51.0 (6.1)†	41.7 (5.2)	48.9 (6.0)‡	45.8 (6.7)	49.5 (6.1)†	43.9 (5.5)
CV SBP (%)*	5.17 (1.8)§	4.77 (2.7)	5.90 (1.9)	5.49 (4.4)	5.07 (1.7)	4.42 (1.8)	5.00 (1.5)	4.62 (2.1)
CV DBP (%)*	9.77 (3.2)†	7.98 (3.7)	9.00 (2.1)	8.36 (3.1)	9.64 (2.8)§	7.87 (3.1)	9.21 (3.0)§	7.59 (4.3)
HR (beats/min)	70 (9.1)†	65 (9.0)	67 (9.1)	71 (9.6)	72 (11.0)§	65 (9.1)	69 (8.6)§	64 (8.4)
PWV (m/s)*	7.60 (1.0)	7.59 (0.9)	8.00 (0.8)	7.16 (1.0)	7.65 (1.1)	7.62 (1.1)	7.67 (0.9)	7.76 (1.2)
cIMT (mm)*	0.52 (0.1)	0.52 (0.05)	0.52 (0.1)	0.50 (0.05)	0.52 (0.1)	0.53 (0.1)	0.53 (0.1)	0.52 (0.05)

Values are given as means (SD).
*Log transformed for ANOVA.
†P < .001 compared with term (same subgroup).
‡P < .05 compared with term (same subgroup).
§P < .01 compared with term (same subgroup).
¶χ^2 test used to determine differences between subjects born preterm and term.

Table III. Multiple regression for SBP, DBP, and PP in early adulthood

	SBP						DBP						PP					
	Model A		Model B		Model C		Model A		Model B		Model C		Model A		Model B		Model C	
	β (%)	P	β (%)	P	β (%)	P	β (%)	P	β (%)	P	β (%)	P	β (%)	P	β (%)	P	β (%)	P
GA	−0.246	**.026**	−0.230	**.026**	−0.127	.223	0.451	**.001**	0.462	**.001**	0.631	**<.001**	−1.207	**<.001**	−1.184	**<.001**	−1.167	**<.001**
Birth length SDS	−0.257	.556	−0.496	.227	−0.413	.302	−0.703	.193	−0.866	.104	−0.733	.153	0.293	.664	−0.058	.928	−0.045	.944
Birth weight SDS	0.060	.883	0.155	.690	0.106	.781	0.213	.677	0.361	.475	0.280	.563	−0.466	.465	−0.152	.802	−0.159	.792
Adult height SDS	0.121	.774	−1.021	**.018**	−0.956	**.023**	−0.599	.249	−1.379	**.014**	−1.272	**.018**	1.254	.056	−0.431	.520	−0.421	.531
SES 1	5.180	**<.001**	4.557	**.001**	3.408	**.013**	3.678	**.043**	3.256	.068	1.415	.414	7.354	**.001**	6.425	**.003**	6.238	**.005**
SES 2	1.629	.112	1.159	.228	0.815	.385	2.019	.113	1.695	.176	1.133	.348	1.299	.412	0.634	.681	0.559	.709
Smoking	−1.057	.286	−0.531	.569	−0.096	.917	−1.949	.111	−1.592	.187	−0.890	.448	0.447	.772	1.228	.403	1.298	.380
Alcohol use	2.118	**.045**	1.596	.107	1.449	.133	2.319	.077	1.960	.128	1.720	.164	1.850	.256	1.089	.479	1.065	.489
Adult weight SDS			2.108	**<.001**	2.110	**<.001**			1.442	**.001**	1.447	**<.001**			3.099	**<.001**	3.099	**<.001**
HR					0.176	**<.001**					0.288	**<.001**					0.028	.688
Overall *P* value	**<.001**		**<.001**		**<.001**		**.004**		**<.001**		**<.001**		**<.001**		**<.001**		**<.001**	
R^2 adjusted	0.172		0.272		0.307		0.046		0.079		0.149		0.386		0.452		0.451	

Regression coefficients are shown as a percentage. A positive value indicates that the dependent variable is increased with that percentage for every unit increase of the independent variable. Adjusted for age, sex, and the interaction term birth length SDS × adult height SDS. Bold indicates $P < .05$.
SES 3 (highest socioeconomic class) is used as reference for SES analyses.

SDS, and birth size ($P = .074$) (Table IV). However, this disappeared after adjustment for AD, which was positively associated with cIMT.

Because GA had an effect on several markers that have been previously associated with atherosclerosis, we tested which marker was the most important determinant of cIMT, by adding the markers alternately to model C (data not shown). The effects of SBP (β (%) = 0.16, $P = .002$, adj. $R^2 = 0.198$), DBP (β (%) = .02, $P = .818$, adj. $R^2 = 0.172$), PP (β (%) = 0.48, $P < .001$, adj. $R^2 = 0.228$), SBP variability (β (%) = 0.015, $P = .475$, adj. $R^2 = 0.174$), DBP variability (β (%) = 0.28, $P = .072$, adj. $R^2 = 0.181$), HR (β (%) = −0.06, $P = .352$, adj. $R^2 = 0.176$), and PWV (β = −0.62, $P = .259$, adj. $R^2 = 0.172$) on cIMT were determined. The model with the highest adjusted R^2, thus, explaining the largest proportion of variation in cIMT, was the model including PP.

Unadjusted differences between the subgroups are shown in Table I. Comparison of preterm and term SGA-subgroups, after adjustment for age, sex, alcohol use, smoking, SES, HR, and weight SDS, showed that SGA-S subjects born preterm had a significantly lower DBP ($P = .002$) and a higher PP ($P = .016$) than those born term. Also, SGA-CU subjects born preterm had a lower DBP ($P = .046$), and a higher PP ($P = .028$) and SBP and DBP ($P = .035$ and $P = .004$, respectively) than

Table IV. Multiple regression for PWV and cIMT in early adulthood

	PWV								cIMT					
	Model A		Model B		Model C		Model D		Model A		Model B		Model C	
	β (%)	P	β (%)	P	β (%)	P	β (%)	P	β (%)	P	β (%)	P	β (%)	P
GA	0.147	.460	0.141	.442	0.145	.405	0.261	.145	0.263	.074	0.095	.481	0.091	.506
Birth length SDS	−0.062	.935	−0.061	.932	0.400	.553	0.493	.461	0.113	.847	−0.084	.875	−0.063	.906
Birth weight SDS	−0.101	.890	0.193	.776	−0.104	.872	−0.173	.787	−0.330	.550	−0.234	.643	−0.254	.615
Adult height SDS	0.005	.995	−0.041	.952	1.556	**.032**	1.574	**.029**	0.502	.372	−0.337	.519	−0.235	.676
SES1	2.064	.259	0.740	.755	2.540	.268	1.365	.555	0.531	.775	0.432	.799	0.461	.786
SES2	−1.814	.317	−3.084	.066	−2.453	.126	−2.725	.087	1.488	.271	1.538	.213	1.575	.204
Smoking	2.343	.185	4.006	**.017**	3.770	**.017**	4.136	**.009**	0.645	.623	1.214	.313	1.179	.328
Alcohol use	−0.116	.950	−0.552	.749	0.600	.716	0.443	.787	0.757	.586	1.001	.431	1.053	.410
AD											10.66	**<.001**	10.85	**<.001**
Adult weight SDS					5.496	.376	6.247	.312					−0.202	.636
MAP			0.638	**<.001**	0.740	**<.001**	0.692	**<.001**						
HR							0.192	**.015**						
Overall *P* value	**<.001**		**<.001**		**<.001**		**<.001**		.099		**<.001**		**<.001**	
R^2 adjusted	0.108		0.236		0.317		0.329		0.019		0.183		0.181	

Regression coefficients are shown as a percentage, a positive value indicates that the dependent variable is increased with that percentage for every unit increase of the independent variable. Adjusted for age, sex, and the interaction term birth length SDS × adult height SDS. Bold indicates $P < .05$.
The model with PWV as dependent variable is additionally adjusted for the interaction terms age*adult weight SDS and gender*adult weight SDS.
SES 3 (highest socioeconomic class) is used as reference for SES analyses.

Table V. Subgroup analyses of BP, PP, BP variability, HR, PWV, and cIMT compared with AGA term controls

	SGA-S preterm		SGA-S term		SGA-CU preterm		SGA-CU term		AGA preterm		
	β (%)	P	β (%)	P	β (%)	P	β (%)	P	β (%)	P	R^2 adjusted
SBP											
Model 1	−2.67	.355	−0.45	.802	2.47	.149	1.20	.464	1.02	.486	0.129
Model 2*,†	−3.00	.256	0.09	.959	−0.12	.937	−0.34	.819	−1.33	.300	0.314
DBP											
Model 1	−12.9	**<.001**	0.27	.901	−1.45	.469	0.63	.745	−4.57	**.005**	0.107
Model 2*,†	−14.3	**<.001**	−0.75	.721	−5.57	**.003**	−1.02	.554	−7.66	**<.001**	0.318
PP											
Model 1	12.9	**.008**	−1.95	.483	8.34	**.002**	2.87	.371	9.36	**<.001**	0.358
Model 2*,†	14.4	**.003**	0.71	.817	8.08	**.005**	0.87	.729	8.17	**<.001**	0.396
CV SBP											
Model 1	34.2	**.038**	24.4	**.013**	8.73	.303	−9.94	.182	8.91	.204	0.057
Model 2*,†	32.5	.055	20.4	.060	6.60	.470	−11.1	.145	7.55	.300	0.051
CV DBP											
Model 1	36.4	**.042**	23.0	**.028**	30.4	**.003**	2.95	.730	29.8	**<.001**	0.109
Model 2*,†	38.5	**.037**	22.5	.053	29.1	**.007**	0.89	.917	28.2	**.001**	0.127
HR											
Model 1‡	9.13	.083	10.1	**.002**	13.5	**<.001**	0.67	.811	8.72	**.001**	0.234
Model 2*,‡	4.52	.377	5.11	.138	9.58	**.002**	−0.79	.774	7.70	**.002**	0.283
PWV											
Model 1§	0.07	.990	−6.96	**.019**	−4.73	.101	−5.59	**.033**	−4.47	.060	0.275
Model 2*,§	−2.24	.681	−11.2	**<.001**	−5.10	.070	−4.90	.055	−3.65	.114	0.342
Model 3*,§,¶	2.48	.691	−6.41	.145	−4.48	.114	−4.18	.106	−3.22	.163	0.348
cIMT											
Model 1‖	2.25	.374	1.35	.525	1.75	.409	2.28	.261	1.82	.298	0.132
Model 2*,‖	2.57	.503	0.03	.989	1.43	.522	2.31	.265	2.02	.260	0.131

Regression coefficients are shown as a percentage. A positive percentage indicates that the dependent variable is increased with that percentage compared with AGA term controls. Bold indicates $P < .05$.
All models are adjusted for age and sex and additionally adjusted for: *Alcohol use, smoking, SES, and adult weight SDS, †HR, ‡SBP, §MAP, ¶adult height SDS, and ‖AD.

those born term. There were no significant differences in SBP between preterm and term SGA-subgroups.

After adjustment for age, sex, alcohol use, smoking, SES, SBP, and weight SDS, SGA-CU subjects born preterm had a higher HR than those born term ($P = .009$). There was, however, no significant difference in HR between SGA-S subjects born preterm or term. After adjustment for confounders, PWV and cIMT also did not differ significantly between subjects born preterm or term, in any of the subgroups.

Table V shows comparisons of SBP, DBP, PP, BP variability, HR, PWV, and cIMT of the subgroups after adjustment for possible confounders, with AGA subjects born term as reference group. In the final model, all preterm subgroups had a significantly lower DBP, but higher PP and DBP variability than the reference group. After correction, there were no differences in SBP variability and cIMT. SGA-CU and AGA subjects born preterm had a higher HR than the reference group (AGA, born term). SGA-S and SGA-CU subjects born term had a lower PWV than the reference group, but this significant difference disappeared after correction for adult height SDS.

Discussion

Higher BP in adults born preterm than in healthy controls has been reported.[30] Also, in the present study, lower GA was associated with higher SBP, but this disappeared after adjustment for HR. These findings suggest that the reported elevated SBP in subjects born preterm is associated with an increased HR, indicating that both might share an underlying determinant. The mechanisms underlying these associations remain unknown,[31] but might be explained by preterm birth being associated with an increased cardiac output, which might eventually lead to hypertension.[32] In contrast, we showed a lower DBP in young adults born preterm, which remained significant after adjustment for several confounders. Lower DBP has been associated with less risk for CVD,[33] although this was controversial in other studies.[34]

We report an increased PP in young adults born preterm. This new finding is in line with a study showing an inverse association between GA and PP in children.[35] Elevated PP has been associated with increased risk for atherosclerosis, already in young adulthood.[14,33] This was confirmed by our study showing that of all determinants of CVD examined, the effect of PP on cIMT was most pronounced, in contrast to the nonsignificant effect of DBP on cIMT. In addition, variability of SBP and DBP was higher in participants born preterm. Higher variability of BP in time has also been associated with CVD.[15,16]

Although one would expect a lower HR in combination with a higher PP, young adults born preterm had a higher HR than those born term. This finding is supported by previous studies.[36-38] Johansson et al hypothesized that an increased HR could be ascribed to altered sympathoadrenal function in subjects born small, either preterm or SGA.[38] In the present study, higher HR was only found in subjects born preterm, regardless of birth weight. This implies that there is an effect of preterm birth on HR, rather than an effect

of SGA birth. Determination of resting HR is of importance because it is associated with CVD.[17] Unfortunately, the present study does not include tests to determine neural regulatory mechanisms. For future research it would be interesting to carry out spectral analyses in young adults born preterm, to determine whether the increased HR and BP variability are due to sympathovagal imbalance.[39,40]

We did not find an association of preterm birth with PWV. Adult height SDS was, however, positively associated with PWV. This association also explains the difference in PWV between SGA-S subjects born term and AGA subjects born term, as this difference disappeared after correction for height SDS. Only limited studies investigated the association between adult height SDS and PWV. One study showed a positive association between height and PWV in healthy children.[41]

There was also no effect of preterm birth on cIMT. Previous studies reported controversial results regarding the association of cIMT with GA, preterm birth, and birth size.[12,13] These studies, however, did not adjust for AD, which is likely to be a confounder in the relationship of GA and birth size with cIMT. Also, it might well be that an effect of GA on cIMT will arise at an older age.

The great contrasts in birth size and adult stature in our study population enabled performing comparisons of clinically relevant subgroups. These comparisons showed that the effect of preterm birth on CVD risk can not be ascribed to SGA birth and/or catch up growth. We found significant differences in DBP, PP, and DBP variability, between the preterm subgroups and term AGA controls, irrespectively of SGA birth. The preterm groups had a significantly higher resting HR, except for the preterm SGA-S subgroup. There were no differences in CVD risk parameters between the SGA-groups born term and the healthy controls.

We acknowledge that the Datascope Accutorr Plus to determine BP during 1-hour uses an algorithm to compute SBP and DBP. Although it has shown to be in greatest agreement with the mercury standard, this should be taken into account. Future studies are warranted to reproduce our results using directly measured SBP and DBP. We also acknowledge that our study population consists of subjects without serious postnatal complications and did not include extreme prematurely born subjects. Whether our results can be generalized to subjects with complications, such as broncho-pulmonary dysplasia, requires further research. Furthermore, it would be of additional value to include family history, as a risk factor of atherosclerosis, in our analyses. Unfortunately, we did not have sufficient information to assess family history in our cohort of young adults. However, none of the subjects who fully completed the questionnaires mentioned a family history of CVD.

Our data show that young adults born preterm might have a higher risk to develop CVD because of a higher SBP, resting HR, and a higher PP and BP variability in time. Although we show that young adults born preterm have a lower DBP than adults born term, the lower DBP contributes to an increased PP in these subjects. Because the prevalence of preterm birth and survival is rapidly increasing, our results are of clinical relevance for an increasing number of subjects and are thus of major importance for public health. ■

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Table II. Unadjusted clinical characteristics of the total study population and subgroups

	Total study population		Subgroups					
			SGA-S		SGA-CU		AGA	
	Preterm (n = 163)	Term (n = 243)	Preterm (n = 9)	Term (n = 34)	Preterm (n = 31)	Term (n = 44)	Preterm (n = 63)	Term (n = 64)
GA median (IQR)	32 (29-34)	40 (38-40)	32 (32-34)	40 (38-41)	33 (31-34)	38 (37-40)	34 (32-36)	40 (40-41)
BMI	22.2 (3.4)	22.4 (3.5)	23.5 (3.6)	23.1 (5.0)	21.5 (3.7)	23.2 (3.6)	22.7 (2.7)	21.8 (2.8)
Alcohol users (%)†	84.5‡	75.7	77.8	76.5	80.7	80.0	88.9	78.1
Smokers (%)†	27.0	25.5	22.2	20.6	19.4	35.0	27.0	20.3
SES¶ (%)								
1	13.0	9.4	14.3	13.3	14.3	15.6	7.5	3.2
2	30.5‡	20.8	28.6	33.3	39.3	21.9	26.4§	6.5
3	56.5	69.8	57.1	53.3	46.4	62.5	66.0	90.3
MAP (mm Hg)*	83.4 (7.3)	83.3 (7.7)	81.7 (5.2)	81.9 (8.2)	84.0 (7.7)	86.3 (9.4)	84.4 (7.4)	83.0 (5.8)
AD (mm)	6.66 (0.4)	6.66 (0.5)	6.49 (0.4)	6.38 (0.4)	6.65 (0.4)	6.76 (0.4)	6.77 (0.4)	6.79 (0.5)
cIMT/AD	0.08 (0.01	0.08 (0.01)	0.08 (0.01)	0.08 (0.01)	0.08 (0.01)	0.08 (0.01)	0.08 (0.01)	0.08 (0.01)

BMI, body mass index.
Values are given as means (SD), except when indicated otherwise.
*Log transformed for ANOVA.
†χ^2 test used to determine differences between subjects born preterm and term.
‡$P < .05$ compared with term (same subgroup).
§$P < .01$ compared with term (same subgroup).
¶SES (1 = lowest, 3 = highest).