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Influence of Concurrent Obesity and Low Birth Weight on Blood Pressure Phenotype in Youth

Empar Lurbe, Eva Carvajal, Isabel Torro, Francisco Aguilar, Julio Alvarez, Josep Redon

Abstract—The aim of this study was to assess the impact of obesity and low birth weight on both office and ambulatory blood pressure (BP) values, as well as on aortic-derived parameters in youths. A total of 422 white youths, from 10 to 18 years of age, were included. Subjects were divided into 4 groups according to the presence (234; 55%) or the absence (188; 45%) of obesity and according to low (114; 27%) or normal (308; 73%, birth weight. Spacelabs 90207 was used to measure ambulatory BP during a 24-hour period. SphygmoCor radial/aortic transform software was used to estimate aortic pressure waveform. Office, 24-hour, daytime, and nighttime systolic BP values were significantly higher in those subjects with low birth weight who became obese. The lowest BP values were present in nonobese subjects in the absence of low birth weight. In the middle, with similar BP values, were nonobese subjects with low birth weight and obese subjects in the absence of low birth weight. No interaction existed between obesity and low birth weight in the office ($P=0.165$) or ambulatory ($P=0.603$) systolic BP values. Augmentation index, an estimate of the pulse wave reflection, was significantly higher in the nonobese low birth weight group when compared with the other groups after controlling for height, heart rate, and diastolic BP. A significant interaction between low birth weight and obesity ($P<0.005$) existed. In conclusion, although the low birth weight children who become obese have the highest systolic BP values, the presence of obesity blunts the increment of the reflecting wave observed in low birth weight subjects. (*Hypertension*. 2009;53:912-917.)

Key Words: birth weight ■ obesity ■ adolescents ■ blood pressure ■ augmentation index

The need to identify cardiovascular risk factors, including high blood pressure (BP), in children and adolescents is acknowledged more frequently now. In this context, it is important to emphasize that BP values in children represent an important measurable marker of the level of potential cardiovascular risk later in life, despite the known variability of BP readings and the uncertainties related to their accuracy. This strongly supports the importance of performing careful and repeated BP measurements during childhood and adolescence. Therefore, use of ambulatory BP monitoring in this setting appears to be of particular value.

BP phenotype is determined not only by conventional risk factors but also by early life programming based on intrauterine fetal growth retardation.[1–3] During childhood, there is a mismatch between the conditions for which the fetus is programmed in utero and the environment that the child meets. Consequently, BP is influenced both by size at birth[4] as well as by weight gain in childhood.[5] The adverse effects of excessive weight gain on BP, and the association of weight gain with a higher incidence of hypertension later in life, represent major issues in health care.[5–9] Indeed, because of the increasing tendency of obesity to appear during childhood

and to track, to some extent, into adult life,[10,11] children with low birth weight (BW) who become obese could be at particularly high risk for an undesired increase in BP.[12] However, the impact of growth during fetal life and of obesity on BP characteristics has not been addressed previously.

Abnormalities in BP are accompanied by functional changes in the vascular tree, and evidence of early alterations in vascular function has been described in children and adolescents with low BW.[13] These alterations are manifested not only in high BP[14] but also in an increment in BP variability,[15] pulse pressure (PP),[16] and in the impact of reflecting waves on central PP.[13] These intermediate phenotypes can be the expression of functional or structural abnormalities from fetal life.

The aim of the present study was to assess the impact of obesity and low BW on office and ambulatory BP values in normotensive youths. In addition, early functional vascular changes were analyzed as well by using aortic-derived parameters from peripheral recordings: the Sphygmocor method.

Materials and Methods

Obese, white adolescents of both sexes and of European origin, ranging from 10 to 18 years of age, were selected from the Pediatric

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Table 1.   General Characteristics of the Study Groups (n= 422)

Variables	Nonobese Normal BW n=177	Nonobese Low BW n=57	Obese Normal BW n=131	Obese Low BW n=57	P
Sex, male/female	63/114	21/36	60/71	19/38	0.233
Age, y	13.3±0.1	13.5±0.3	13.1±0.1	12.5±0.3*†	0.017
Weight, kg	52.3±0.8	47.3±1.2	73.0±1.1	69.2±1.7*†	0.0001
Height, m	1.60±0.01	1.56±0.01	1.60±0.01†	1.55±0.01*‡	0.001
BMI, kg/m^2	20.4±0.2	19.3±0.3	28.4±0.3*†	28.6±0.5*†	0.0001
BW, kg	3.44±0.03	2.42±0.05*	3.51±0.04†	2.44±0.05*‡	0.0001

Values are mean±SE.

P indicates statistical significance of the differences among groups; *significant differences (*P*<0.05) with the nonobese normal BW group; †significant differences (*P*<0.05) with the nonobese low BW group; ‡significant differences (*P*<0.05) with the obese normal BW group.

Nephrology and Cardiovascular Risk Unit, Consorcio Hospital General, Valencia, Spain, from those who underwent an obesity assessment. Patients with secondary obesity syndromes or with acute illnesses were excluded from the study. Obesity was diagnosed when body mass index (BMI; weight in kilograms divided by height in meters squared) exceeded the 97th percentile for age and sex. The extent of obesity was quantified using Cole's LMS method, which normalizes BMI, and its skewed distribution, by expressing BMI as a standard deviation score. Subjects with severe obesity (*z* score >2.5) were excluded. Nonobese subjects were drawn from a study on normal ambulatory BP monitoring reference values being performed in a pediatric outpatient clinic of the Consorcio Hospital General of the University of Valencia. None of the subjects were taking any medication nor had any clinically manifested illness. In all cases, informed consent was obtained from parents and participants before testing. The study was approved by the ethical committee of the General Hospital, University of Valencia, Spain.

In obese and nonobese subjects, gestational age and BW were obtained from routine obstetric records. Subjects included in the present study were born at term (≥37 weeks), after a normotensive pregnancy. Subjects were divided into 4 groups according to the presence or absence of obesity and according to a BW lower than the 10th percentile for gestational age (low BW) or higher (normal BW).[17]

Clinical Procedures

Body weight was recorded to the nearest 0.1 kg using a standard beam balance scale with the subjects wearing light indoor clothing and no shoes. Height was recorded to the nearest 0.5 cm using a standardized wall-mounted height board.

On the day of ambulatory BP monitoring, trained clinic nurses measured the BP of each subject 3 times consecutively in the seated position, at 5-minute intervals, using a mercury sphygmomanometer. This was done on the nondominant arm, with a cuff and a bladder size adjusted to upper-arm girth.[18] Office BP values were taken as the mean of 3 measurements. Office BP had to be persistently greater than or equal to the 95th percentile of the BP distribution in a normal reference population on ≥3 separate occasions to be considered indicative of a hypertensive condition.[18] All included subjects were normotensive by office measurement. Ambulatory BP monitoring was measured using a validated oscillometric device (Spacelabs model 90207; Spacelabs, Inc.) following a previously described protocol.[19]

The following parameters were calculated for each subject: average of systolic BP, diastolic BP, PP, and heart rate (HR) for office BP; and average of systolic BP, diastolic BP, PP, and HR for ambulatory BP, 24-hour, daytime, and nighttime periods.

Aortic-Derived Parameters

Pressure waveforms were recorded from the radial artery of the wrist of the dominant hand with a high-fidelity micromanometer (SPC-301; Millar Instruments) after being seated and having rested for ≥5 minutes. The waveform data were then processed by the Sphygmo-Cor radial/aortic transform software module (SphygmoCor; PWV

Medical) to produce the estimated aortic pressure waveform.[20,21] The series of estimated aortic waveforms, together with the series of radial waveforms from which these were derived, were each ensemble-averaged over an 8-second period into a single calibrated waveform. The Augmentation Index (AI) is defined as the difference between the second and first systolic peaks expressed in mm Hg or as a percentage of the PP. Although the method has not been validated specifically for children, there are data available that support the validity of the technique in this age group. Vascular properties of the upper-limb vessels vary little with age, in contrast to the changes observed in trunk and lower-limb vessels.[22] This allows for constructs of central aortic pressure derived from the radial waveform, whatever the age, when good quality peripheral pulse tracings are obtained.

Statistical Analysis

Values were expressed as mean±SE for each study group. The differences in BP mean values among the different groups were assessed through analysis of variance covariate by sex and height. Bonferroni correction was applied in the case of multiple comparisons. Multiple linear regression analyses were performed using office and ambulatory BP values as dependent variables, with age, sex, obesity, and low BW as independent variables. Two-way analysis of variance for multiple comparisons was used to compare the 24-hour BP circadian pattern. The difference in AI values within groups was examined using analysis of variance covariate by height, HR, and office diastolic BP. A formal test was performed to assess whether an interaction of BP values or aortic-derived parameters exists between obesity and low BW. Values of 2-sided *P*<0.05 were set as the minimum level of statistical significance throughout the article.

Results

Characteristics of the Study Population

A total of 422 young white subjects were included in the study, of whom 188 (45%) were obese and 234 (55%) were normal weight. The low BW were 57 (30.0%) obese subjects and 57 (24%) nonobese subjects. The general characteristics of the study population are shown in Table 1. Although no differences in terms of sex were observed between groups, differences appeared in age and height. No differences in BW were observed between the 2 groups with low BW. BMI differences were not found between the 2 nonobese groups. Although there were no between-group differences for sex distribution, all comparisons were also adjusted by sex because of the known differences between boys and girls in this age group.

BP and HR Values

The means of the systolic BP, diastolic BP, PP, and HR for office and ambulatory 24-hour, daytime, and nighttime peri-

Table 2.   Office and Ambulatory BP Values and HR of Study Groups

Variables	Nonobese Normal BW n=177	Nonobese Low BW n=57	Obese Normal BW n=131	Obese Low BW n=57	P
Office BP					
Systolic BP, mm Hg	102.1±0.7	103.0±1.3	104.7±0.8*	108.6±1.3*†‡	0.0001
Diastolic BP, mm Hg	58.1±0.6	57.6±1.0	61.2±0.7*†	61.3±1.0*†	0.0001
PP, mm Hg	44.0±0.6	45.5±1.2	43.6±0.8	47.3±1.1*‡	0.036
HR, bpm	77.9±1.1	74.8±1.1	82.5±1.0*	79.0±1.5†	0.021
24-Hour ambulatory BP					
Systolic BP, mm Hg	111.5±0.6	114.0±1.0*	112.9±0.7	116.3±1.0*‡	0.001
Diastolic BP, mm Hg	65.1±0.4	66.4±0.7	63.9±0.4*†	65.0±0.7	0.018
PP, mm Hg	46.4±0.4	47.6±0.8	48.9±0.5*	51.2±0.8*†‡	0.0001
HR, bpm	79.6±0.6	76.6±1.1*	81.1±0.7‡	80.3±1.1‡	0.006
Daytime ambulatory BP					
Systolic BP, mm Hg	115.2±0.6	117.5±1.1	116.7±0.8	119.8±1.1*‡	0.005
Diastolic BP, mm Hg	69.3±0.4	70.5±0.8	68.1±0.5	68.7±0.8†	0.074
PP, mm Hg	45.9±0.5	47.0±0.8	48.6±0.5*	51.1±0.8*†‡	0.0001
HR, bpm	84.5±0.7	80.9±1.2*	85.0±0.8†	84.3±1.2	0.046
Nighttime ambulatory BP					
Systolic BP, mm Hg	102.7±0.6	105.1±1.1*	104.0±0.7	107.8±1.1*‡	0.0001
Diastolic BP, mm Hg	55.2±0.4	56.4±0.8	54.4±0.5†	56.8±0.8‡	0.040
PP, mm Hg	47.4±0.5	48.7±0.8	49.6±0.5*	51.1±0.8*†	0.001
HR, bpm	61.2±0.7	65.7±1.2*	73.6±0.8*†	71.6±1.2†	0.0001

Values are adjusted for height and sex and expressed as mean±SE.

P indicates statistical significance of the differences among groups; *significant differences (*P*<0.05) with the nonobese normal BW group; †significant differences (*P*<0.05) with the nonobese low BW group; ‡significant differences (*P*<0.05) with the obese normal BW group.

ods for the groups adjusted by sex and height are shown in Table 2. Significant differences in systolic BP, diastolic BP, or PP were observed within groups. However, the differences were more prominent for systolic BP than were those observed for diastolic BP. Office, 24-hour, daytime, and nighttime systolic BP values were significantly higher in those subjects with low BW who became obese, as shown in Table 2. The lowest BP values were present in nonobese subjects in the absence of low BW. In the middle, with similar BP values, were the nonobese subjects with low BW and the obese subjects in the absence of low BW. Despite these differences among the groups, no interaction existed between obesity and low BW in the office (*P*=0.165) or ambulatory (*P*=0.603) systolic BP values. Differences among groups were also observed for ambulatory HRs, with the highest values belonging to the 2 obese groups.

Significant differences in 24-hour systolic BP circadian pattern among the 4 groups (*P*=0.003) are shown in Figure 1. Obese low BW subjects had the highest systolic BP values over the 24 hours, whereas the nonobese subjects in the absence of low BW had the lowest values. In between these 2 extreme groups, there were the systolic BP values of the other 2 groups: nonobese low BW and obese in the absence of low BW. No differences in circadian variability were observed among the 4 groups.

Using a multiple regression analysis, the influence of obesity and low BW on the office and ambulatory systolic BP were assessed adjusting for age and sex. Whereas the pres-

ence of obesity in these children was significantly associated with office systolic BP, both obesity and low BW were independently associated with ambulatory systolic BP, 24-hour BP, and daytime and nighttime BP (Table 3; *P*<0.01). When current BMI and BW were introduced into the model as continuous variables, both parameters were significantly associated with office systolic BP (*P*<0.05). In a similar model with ambulatory systolic BP as the dependent variable, BW only achieved borderline significance (*P*<0.091), whereas BMI remained nominally significant (*P*<0.001). However, it should be noted that because participants were originally selected from the extremes of the BW distribution, a model that includes BW as a continuous variable may introduce statistical error.
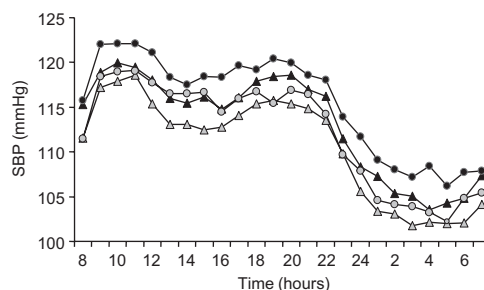

Figure 1. Ambulatory systolic BP (SBP) patterns in adolescents grouped by obesity and BW: nonobese normal BW (△), nonobese low BW (○), obese normal BW (▲), and obese low BW (●). Values are adjusted for sex and height.

Table 3. Factors Related to Office and Ambulatory Systolic BP Estimated by Multiple Regression Analysis

Variables	β	SD	P	R^2
Office systolic BP, mm Hg				0.11
Age, y	0.868	0.261	0.001	
Sex, female vs male	−4.895	0.984	0.0001	
Obese, yes vs no	3.754	0.971	0.0001	
Low BW, no vs yes	−1.505	1.082	0.165	
24-Hour systolic BP, mm Hg				0.11
Age, y	0.482	0.206	0.02	
Sex, female vs male	−4.308	0.777	0.0001	
Obese, yes vs no	1.825	0.767	0.018	
Low BW, no vs yes	−2.446	0.854	0.004	
Daytime systolic BP, mm Hg				0.08
Age, y	0.490	0.229	0.033	
Sex, female vs male	−4.058	0.864	0.0001	
Obese, yes vs no	1.948	0.852	0.023	
Low BW, no vs yes	−2.200	0.949	0.021	
Nighttime SBP, mm Hg				0.09
Age, y	0.183	0.216	0.396	
Sex, female vs male	−4.046	0.812	0.0001	
Obese, yes vs no	1.768	0.801	0.028	
Low birth weight, no vs yes	−2.656	0.892	0.003	

Aortic-Derived Parameters

The aortic-derived parameters were analyzed in a subsample total of 149 subjects, of whom 73 (49%) were obese and 76 (51%) had normal weight. In the low BW group, there were 32 (44%) obese subjects and 34 (45%) nonobese ones. The

general characteristics of the patients in each of the 4 subgroups did not differ from the total study population (data not shown).

The office- and the aortic-derived parameters of the 4 groups are shown in Table 4. Office systolic BP and diastolic BP were similar, as described above, for the total population. The derived aortic systolic and diastolic values were significantly higher in the obese groups when compared with those of the nonobese groups, the higher values being those corresponding to the obese low BW group. The AI, the parameter used to estimate the pulse wave reflection expressed in mm Hg or by the percentage of aortic PP, was significantly higher in the nonobese low BW group when compared with the other groups (Table 4). These differences between the low BW group and the other groups remained significant after controlling for height, HR, and office diastolic BP (Figure 2). A significant interaction between low BW and obesity ($P<0.005$) existed. Likewise, the amplification phenomenon from central to peripheral vascular tree, calculated by using the radial to aortic PP ratio, tended to be lower in the low BW groups when compared with that of the other BW groups, although the differences were not statistically significant.

Discussion

The present study, performed in normotensive youths, shows that low BW children who become obese have not only the highest office and ambulatory systolic BP values but also the highest for PP. The impact of each of the 2 conditions, low BW and obesity, seems to be additive because no interaction between the 2 has been found. In contrast, the highest impact for reflecting wave in central aortic pressure, as assessed by

Table 4. Aortic-Derived BP Parameters in Study Population (n=149)

Variables	Nonobese Normal BW n=42	Nonobese Low BW n=34	Obese Normal BW n=41	Obese Low BW n=32	P
BMI, kg/m^2	21.9±0.5	21.4±0.6	29.4±0.4*†	30.2±0.7*†	0.0001
Office BP					
Systolic BP, mm Hg	103.4±1.3	105.0±1.5	108.4±1.3*	110.2±1.5*†	0.003
Diastolic BP, mm Hg	58.8±1.1	57.7±1.3	63.4±1.7*†	64.2±1.3*†	0.0001
PP, mm Hg	44.6±1.4	46.6±1.6	44.5±1.4	44.8±1.6	0.728
HR, bpm	77.8±1.5	74.5±1.7	83.0±2.2†	78.0±2.8	0.035
Aortic BP					
Systolic BP, mm Hg	87.1±1.2	88.4±1.4	91.4±1.3*	92.7±1.4*†	0.01
Diastolic BP, mm Hg	60.4±1.1	58.8±1.3	64.9±1.2*†	65.4±1.3*†	0.0001
PP, mm Hg	26.7±1.0	29.7±1.1	26.5±1.0	27.4±1.3	0.168
Ratio peripheral/aortic PP	1.69±0.1	1.60±0.3	1.70±0.1	1.66±0.1	0.137
AI					
Unadjusted, %	95.9±3.48	115.5±3.80*	99.5±3.40†	98.9±3.90†	0.001
Adjusted, %	96.8±3.20	112.5±3.70*	102.1±3.30†	97.7±3.70†	0.009
Unadjusted, mm Hg	−0.98±0.8	3.4±0.9*	−0.15±0.8†	−0.28±0.9†	0.002
Adjusted, mm Hg	−0.79±0.7	2.63±0.8*	0.50±0.7	−0.54±0.8†	0.014

BP values are adjusted for height and sex and expressed as mean±SE.
AI is adjusted for height, HR, and diastolic BP.
P is statistical significance of the differences among groups; *significant differences ($P<0.05$) with the nonobese normal BW group;
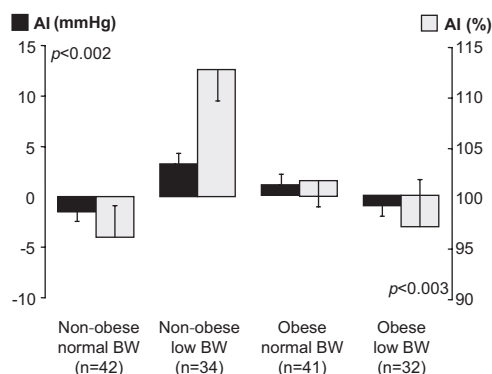†significant differences ($P<0.05$) with the nonobese low BW group.

Figure 2. AI expressed in mm Hg (closed bars) or by the percentage of aortic PP (open bars) and their corresponding SE. Values are adjusted for height, HR, and office diastolic BP. Significant differences were present across the 4 groups (AI in mm Hg, $P=0.002$; AI as a percentage, $P=0.003$).

AI, was only observed in low BW in the absence of obesity. The presence of obesity blunts the increment of the reflecting wave observed in low BW subjects. These findings of the AI may suggest that the mechanisms implicated in BP elevation differ between low BW and obesity, but that they can act together resulting in the higher BP values observed in low BW children who become obese. These findings suggest that subjects with a lower BW and subsequent greater weight gain tend to be at higher risk for developing cardiovascular disease or hypertension.

Epidemiological studies have repeatedly documented the association between fetal growth impairment, low BW, and BP elevation, and even hypertension,[23] although not all are in agreement that BW has a relationship with BP level later in life.[24] In children and adolescents, the contribution of intrauterine environment, as reflected by BW, to ambulatory BP has also been observed.[14] Subjects with the lowest BW tend not only to have the highest systolic BP values and variability[15] but also the highest PP values.[16] These BP phenotypes become manifested early in life, because a rapid rise in BP during the first weeks after birth has been observed in low BW newborns.[4] All of these abnormalities may be the expression of functional or structural abnormalities established from fetal life as a consequence of an adverse intrauterine environment.

Considering low BW as one expression of a cardiovascular risk syndrome, studies of the functional characteristics of the vascular tree offer an opportunity to further clarify the underlying susceptibility long before structural vascular disease has been established. Indeed, evidence of early alterations in vascular function has been described.[25] An increment in the AI, a quantitative measure of the contribution of wave reflection to the central pressure waveform, was described previously in low BW by our group,[13] and it has been confirmed in the present study performed on a different subset of subjects. The inverse relationship was independent of other determinants of wave reflection such as height, HR, and office diastolic BP. These results are also in concordance with a previous report in adults that described an inverse relationship between BW and pulse wave velocity, a marker

of aortic elasticity and one of the main determinants of reflecting waves.[26]

The impact of low BW on growth during early childhood, a time when excessive weight gain may predispose to later overweight or obesity, is not well established. However, the contribution of childhood body weight gain to BP values in low BW children is a matter of concern. In infants born at term, upward percentile crossing for weight was associated with higher later BP, insulin resistance, and risk for obesity.[27]

The impact of overweight and obesity on BP values has been well established. Substantial clinical and epidemiological evidence supports the influence of obesity on BP levels, even early in life.[28,29] Obesity increases BP values across age, race, and sex. Furthermore, a significant reduction in BP values is achieved after losing weight. In the present study, significantly higher BP values, office as well as ambulatory, were observed in obese subjects when compared with those of subjects in the normal percentile of BMI. Obesity-associated BP elevation is characterized by increased vascular volume as a consequence of increased sodium reabsorption in the kidney.[30] Despite the large bulk of evidence of BP elevation in obese subjects, few studies have analyzed the characteristics of the reflecting wave associated with obesity. No differences in AI have been observed across tertiles of BMI in healthy subjects,[31] nor has obesity been related to lower peripheral wave reflection in subjects with or without type 2 diabetes mellitus.[32] The results from these studies are in agreement with the present results, in which not only the obese children have a "normal" AI, but obesity also blunts the increased AI observed in low BW children. However, the results may not be representative of the entire population at risk, and it cannot be generalized to non-whites at present.

The role of wave reflections as an early change in the evolution of vascular disease is being recognized increasingly,[3] and the incremental value of AI may be relevant in normotensive youths. For the first time, the effect of both low BW and obesity on BP values and on the AI has been explored early in the natural history of functional vascular alterations. On becoming obese, low BW children have significantly higher office and ambulatory BP values. However, the AI values are near those observed in nonobese subjects with normal BW. The precise mechanisms that lead to this apparent discrepancy in the AI cannot be inferred from the data of the present study. Perhaps volume overload in the obese subjects blunts the impact of the reflecting waves in the pulse wave contour, reducing the elevation of the systolic peak over the wave shoulder. Nevertheless, BP values are the highest in low BW subjects who have become obese. Prospective studies may be useful in assessing the features of vascular loading beyond those obtained from BP measurements.

Clinical Perspectives
The presence of these abnormalities of BP phenotype and vascular function may be expressions of early vascular ageing susceptibility because the structural and mechanical properties of the large arteries can be permanently affected by altered hemodynamic stress early in life. Low BW children and adolescents who became obese have higher BP values early in life even when the impact of reflecting waves in

central BP parameters is diminished when compared with those of nonobese low BW children. The addition of obesity to low BW increases the risk of vascular complications later in life. Consequently, overweight and obesity should be prevented, especially in low BW children.

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Disclosures

None.

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