

## Preterm Birth Is Associated With Increased Blood Pressure in Young Adults: Important Opportunities for Blood Pressure Management

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**W**hen is the appropriate time to begin consideration of management of blood pressure (BP)? Is it at middle to late life when 10-year cardiovascular risk exceeds 7.5%? Is it when BP reaches  $\geq 130/80$  mm Hg? Is it young adulthood, adolescence, or childhood? Maybe the correct time is preconception.

The study, “Preterm Birth Is Associated With Increased Blood Pressure in Young Adult Women,” by Skudder-Hill et al in this issue of the *Journal of the American Heart Association (JAHA)*,<sup>1</sup> is an important confirmation that preterm birth is a risk for adult hypertension for all, including women. Although this study in female volunteers for military service alone may not appear generalizable, their results considered in the context of other studies evaluating this relationship in men are consistent in demonstrating an  $\approx 3$ -mm Hg higher systolic BP in young adults with preterm birth compared with others. Other studies have demonstrated additional risks for adult cardiometabolic and renal diseases, including insulin resistance, obesity, and reduced renal function.<sup>2</sup>

Preterm birth and low birth weight are important contributors to adult health, including BP. Preterm birth is a common and serious problem. Globally, 10% to 11% of all births are premature.<sup>3</sup> Programs to reduce or prevent preterm birth and low birth weight have been successfully implemented in several countries.<sup>4</sup> In the United States and other countries, preterm birth is associated with race, ethnicity, and socioeconomic status.<sup>5</sup> Preterm birth, along with low birth weight and epigenetic factors, are now recognized as important contributors to adult health, including rates of hypertension, chronic kidney disease, and cardiovascular disease.<sup>6,7</sup> This study in young adult European women likely underestimates

the risk in other populations with higher rates of preterm birth and higher rates of adult obesity, such as blacks.

Current BP management guidelines call for the use of nonpharmacological management of patients with a systolic BP 120 to 139 mm Hg and a 10-year calculated risk for cardiovascular disease  $< 7.5\%$ .<sup>8</sup> It is recognized that some in this group will progress to meet the recommended risk threshold for pharmacological treatment, by further elevation of BP, an increase in risk from other recognized risk factors, or a combination of the two.

The TROPHY (Trial of Preventing Hypertension) Study demonstrated that pharmacologic treatment of patients with systolic BP 130 to 139 mm Hg decreases the risk of progressing to higher levels of BP.<sup>9</sup> BP levels in children, adolescents, and young adults track into later life.<sup>10</sup> In addition, compared with other risk factors, young adult BP levels are strong predictors of future cardiovascular events, even at levels below hypertension, as currently defined (Figure).<sup>11</sup> However, pharmacologic therapy is not currently recommended for young adults with low overall 10-year risk in current guidelines because of the lack of evidence from randomized clinical trials and the high estimated number needed to treat to prevent cardiovascular, cerebrovascular, or renal disease.

This association between preterm birth and elevated BP or hypertension has now been demonstrated in several populations<sup>12,13</sup> and has important implications for policy makers, researchers, guideline writers, and clinicians. It may be time to apply the concept of precision medicine to this issue. Precision medicine often implies identification of a specific population within a general population at especially increased risk for adverse outcomes based on genetic differences. However, the principles of precision medicine can be applied outside of genomics. Preterm birth patients can be identified by history and phenotypic characteristics. Preterm birth is an important marker for increased risk for hypertension, insulin resistance, obesity, and chronic kidney disease. Collectively, these preterm birth-associated consequences are a toxic combination, with each risk factor multiplying the impact of the others. There are opportunities to identify those with a history of preterm birth as especially high-risk patients and develop strategies for management different from the general population.

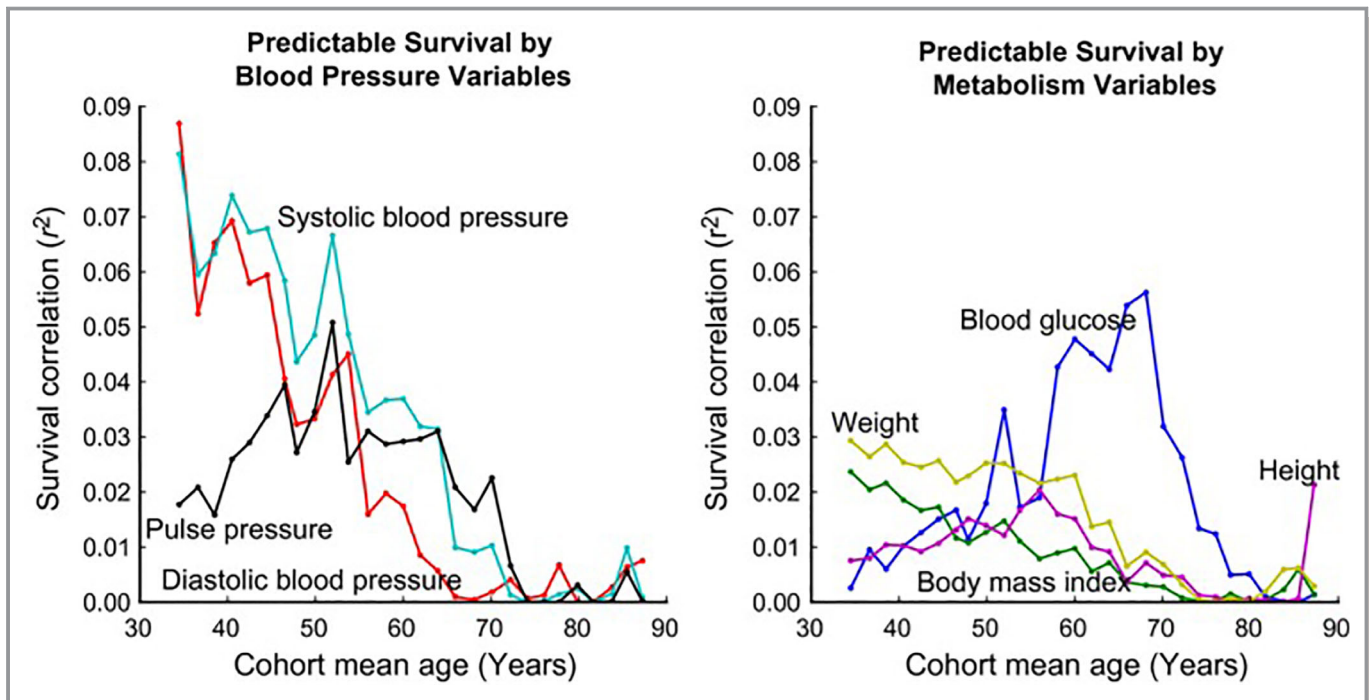
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**Figure.** Predicting all-cause mortality from basic physiological features in the FHS (Framingham Heart Study).<sup>11</sup> The individual variables' ability to predict survival changes over time. Blood pressure, body mass index, and weight are predictive of mortality primarily from the ages of 35 to 60 years, whereas blood glucose is most predictive from the ages of 57 to 73 years.

At the policy level, certain groups can be identified as being at higher risk for preterm birth on the basis of race, ethnicity, age, and socioeconomic status. Principles used successfully in countries around the world<sup>4</sup> can and should be applied in countries with higher preterm birth rates, including the United States. The costs of contraception and improved prenatal care are small compared with the healthcare costs of the second and third generation for cardiovascular disease and kidney disease. Health management policies, including policies related to contraception access and care for pregnant women, may prevent hypertension in future generations.

There are large opportunities for research beginning with social science and evaluation of social determinants of preterm birth. Strategies specific to country, race, ethnicity, language, and culture need investigation.

Further studies to understand the mechanism(s) of the association between preterm birth and higher adult BP are needed. Previous investment in basic science hypertension research has resulted in much progress in understanding the mechanisms of essential hypertension. However, a clear understanding of the mechanism of the preterm birth/hypertension relationship remains uncertain. In the HAPI (Health of Adults Born Preterm Investigation), young adults born preterm had smaller kidneys, higher urine albumin/creatinine ratios, higher angiotensin I levels, and higher BP compared with term controls.<sup>14</sup> One hypothesis is that the smaller nephron mass of children born prematurely causes impaired renal pressure natriuresis, leading

to increased susceptibility to factors that elevate BP, such as sodium intake and obesity, among others. The study by Skudder-Hill et al<sup>1</sup> and several others suggest elevated BP manifests early in life in young adulthood. Both kidney size and renal function are abnormal as preterm-born infants mature as adults.

Other potential mechanisms noted by Skudder-Hill et al include immature development of arterial wall elastin, cardiac underdevelopment, and increased aortic wave reflection associated with central aortic systolic pressure elevation.<sup>1</sup>

Clinician scientists have an opportunity to explore early intervention trials in this selected group of patients with preterm birth. Using a trial design similar to the TROPY Study,<sup>9</sup> early treatment with pharmacologic agents could theoretically prevent the increase in BP or reduction in renal function, which occur with aging (or other stimuli, such as weight gain) in those born preterm. If these studies prove positive, a longer-term study of cardiovascular outcomes should be performed. Important questions in preterm birth-associated BP issues that need to be addressed with clinical trials include the following: Can progression of BP elevation with age be eliminated or reduced with aggressive therapy (lifestyle and pharmacotherapy with a goal systolic BP of 120 mm Hg)? Can nephron loss be prevented or slowed with aggressive BP treatment from an early age? Can cardiovascular and renal events be reduced in patients with a history of preterm birth, including patients with obesity and insulin resistance, prediabetes mellitus, or diabetes mellitus?

This issue of preterm birth–associated hypertension presents a challenging dilemma for guideline writers. Contemporary guideline writers remain highly dependent on evidence from randomized clinical trials for making recommendations. This may be an area for consideration of recommendations beyond the evidence provided by randomized clinical trials using the principles of precision medicine. The 2018 American College of Cardiology/American Heart Association cholesterol guidelines incorporated the use of “risk enhancers” (ie, genetic and acquired characteristics associated with increased risk that serve to individualize treatment and favor therapy that is more aggressive).<sup>15</sup> Similar to risk-enhancing factors for cholesterol management, future hypertension guidelines may consider high-risk features, such as preterm birth, to inform patient-clinician discussions beyond population-derived risk scores.

Clinicians need not wait on the results of these research studies to act on premature birth–associated hypertension. Obstetricians and others caring for women of childbearing age can appropriately use contraception and other family planning methods to reduce the risk of unplanned pregnancies, especially in younger women. In caring for pregnant women, prenatal care should focus on allowing birth to occur at full term and not prematurely. Indeed, the best intervention to prevent preterm birth–associated hypertension is prevention of premature births. Encouragingly, programs to reduce or prevent preterm birth and low birth weight have been successfully implemented in several countries.<sup>4</sup>

Clinicians caring for children, adolescents, and young adults who have a history of preterm birth should pay careful attention to BP measurement and monitoring renal function. Effective use of office BP measurement, home measurement, and ambulatory BP measurement is especially important in these high-risk patients. From an early age, clinicians should encourage use of lifestyle therapy in these patients, including regular exercise, control of weight and waist circumference, a diet high in vegetable and fruit content, reduced sodium, avoidance of tobacco, and limitation of alcohol intake. In addition, using their own clinical judgment, clinicians can lean toward early use of pharmacotherapy in these high-risk patients.

The contribution of premature birth as a significant contributor to hypertension is clear from the study by Skudder-Hill et al<sup>1</sup> and other studies. Now is the time to act on prevention and management of preterm birth–associated hypertension.

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## Disclosures

None.

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