1. Model definition & assumptions:

To test the relative contributions of age, gender, patient identity, and NIBP on the observed variability of IABP given a non-invasive measurement, we used a hierarchical multilevel mixed effects model.

The constructed model treats the invasive blood pressure as the dependent variable while the non-invasive blood pressure, age and sex are treated as independent variables. Based on patient and population level plots of IBP against NIBP we assume that a cubic polynomial is sufficiently expressive for capturing the relationship between the two variables. The degree of the polynomial was determined after exploration with various options and chosen as it was sufficiently expressive and accurate (validated by inspecting residual plots). For instance, comparing the 3rd degree polynomial with the 5th degree polynomial results in minor differences unimportant in a clinical context (less than 0.1mmHg for example for two different 8 year-old). The age is measured in days, and a log (base e) transformation is applied in order to account for the greater differences observed during development early in life. Sex is included as a binary variable (1 encodes 'male').

Because patients are repeatedly sampled, the correlation structure between the samples from each patient must be taken into account in order to avoid pseudoreplication. Patient level deviations of IBP from their NIBP can occur due to differences in equipment, placement of arterial cannula etc. We assume that such differences can approximately be captured by including a random intercept component in the model.

Formally the model is defined as such (following the notation used Hedeker & Gibbons)

Level-1 (within subjects) model:

$$IBP_{p,i} = b_{0,p} + b_{1,p} \cdot NIBP_{p,i} + b_{2,p} \cdot NIBP^2{}_{p,i} + b_{3,p} \cdot NIBP^3{}_{p,i} + b_{4,p} \cdot log_e(Age)_p + b_{5,p} \cdot Sex + \epsilon_{p,i}$$

Where p is the patient index, $IABP_{p,i}$ and $NIBP_{p,i}$ are the invasive and non-invasive blood pressures measured at the ith time point for patient p. Age is given in days, Sex is a binary variable (1 encodes 'male') and $\varepsilon_{p,i} \sim N(0, \sigma^2)$ is the error term for the ith time point for patient p.

Level-2 (between subjects) model:

$$\begin{aligned} b_{0,p} &= \beta_0 + v_{0,p} \\ b_{1,p} &= \beta_1 \\ b_{2,p} &= \beta_2 \\ b_{3,p} &= \beta_3 \\ b_{4,p} &= \beta_4 \\ b_{5,p} &= \beta_5 \end{aligned}$$

Where $v_{0,p} \sim N(0, \sigma_v{}^2)$ is the random intercept component and β are the population level parameters.

Model Estimation & Validation:

The model was estimated via REML (reduced maximum likelihood) using the lme4 R package (Bates, Douglas, et al.). P-values and confidence intervals were computed via t-tests, using Satterthwaite's method for approximating degrees of freedom [Kuznetsova A., Brockhoff P.B. and Christensen 2017).

Model fit results for Systolic BP

Formula: invasive_bp ~ 1 + noninvasive_bp + noninvasive_bp_squared + noninvasive_bp_cubed + log_age + sex + (1 | id)

Random effects:			
	Groups	Variance	Std.Dev.
	id	98.17	9.908
	Residual	87.08	9.332

Fixed effects:					
	Estimate	Std. Error	df	t value	p value
(Intercept)	4.79E+01	1.84E+00	8.07E+04	25.988	<2e-16
NIBP	-5.34E-01	5.66E-02	8.45E+04	-9.442	<2e-16
NIBP squared	1.18E-02	5.76E-04	8.44E+04	20.464	<2e-16
NIBP cubed	-3.46E-05	1.89E-06	8.43E+04	-18.302	<2e-16
log(age)	3.02E+00	7.20E-02	4.15E+03	41.949	<2e-16
sex	6.72E-01	3.95E-01	2.67E+03	1.704	0.0884

Model fit results for Mean BP

Formula: invasive_bp ~ 1 + noninvasive_bp + noninvasive_bp_squared + noninvasive_bp_cubed + log_age + sex + (1 | id)

Random effects:			
	Groups	Variance	Std.Dev.
	id	33.35	5.775
	Residual	35.78	5.981

Fixed effects:					
	Estimate	Std. Error	df	t value	p value
(Intercept)	4.21E+01	7.84E-01	7.63E+04	53.67	<2e-16
NIBP	-7.16E-01	3.35E-02	9.75E+04	-21.35	<2e-16
NIBP squared	2.03E-02	4.85E-04	9.74E+04	41.89	<2e-16
NIBP cubed	-8.79E-05	2.26E-06	9.73E+04	-38.94	<2e-16
log(age)	1.63E+00	4.01E-02	4.03E+03	40.72	<2e-16
sex	2.37E-01	2.19E-01	2.93E+03	1.08	0.28

Model fit results for diastolic BP

Formula: invasive_bp ~ 1 + noninvasive_bp + noninvasive_bp_squared + noninvasive_bp_cubed + log_age + sex + (1 | id)

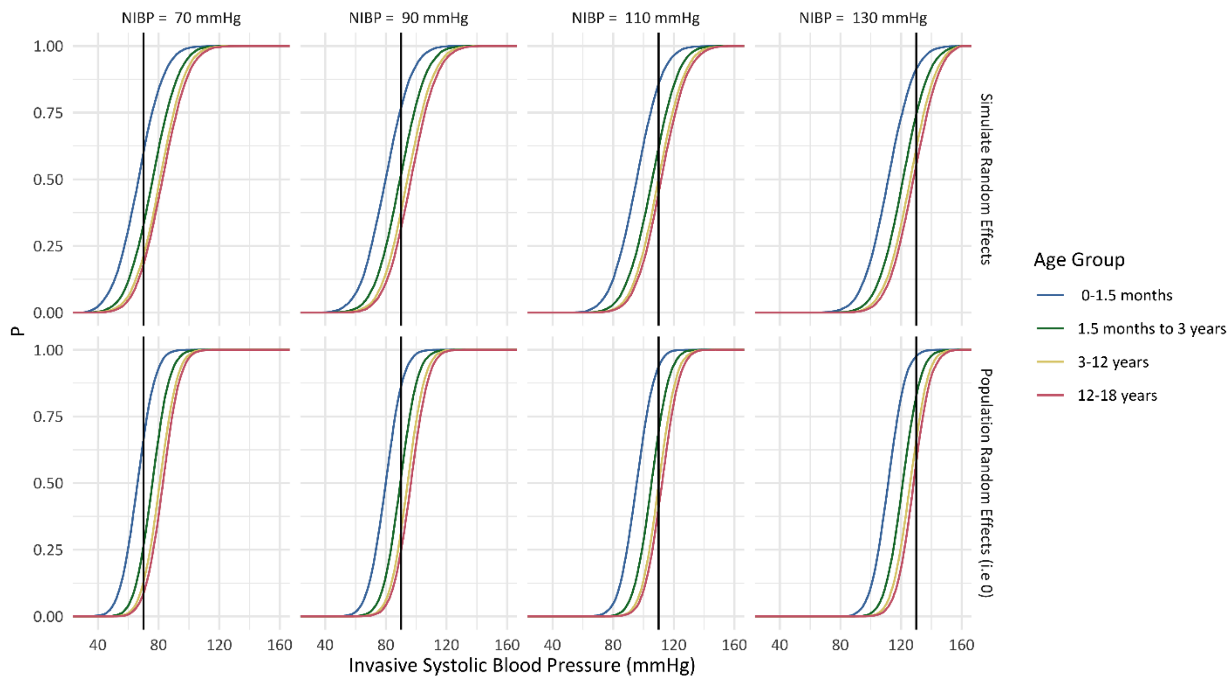
Random effects:			
	Groups	Variance	Std.Dev.
	id	28.21	5.311
	Residual	33.77	5.811

	Estimate	Std.Error	df	t value	p value
(Intercept)	3.54E+01	5.30E-01	4.43E+04	66.83	<2e-16
NIBP	-6.35E-01	2.45E-02	1.02E+05	-25.88	<2e-16
NIBP squared	1.89E-02	4.06E-04	1.02E+05	46.51	<2e-16
NIBP cubed	-8.94E-05	2.13E-06	1.02E+05	-41.87	<2e-16
log(age)	1.48E+00	3.66E-02	3.89E+03	40.51	<2e-16
sex	2.14E-01	2.00E-01	2.97E+03	1.07	0.285

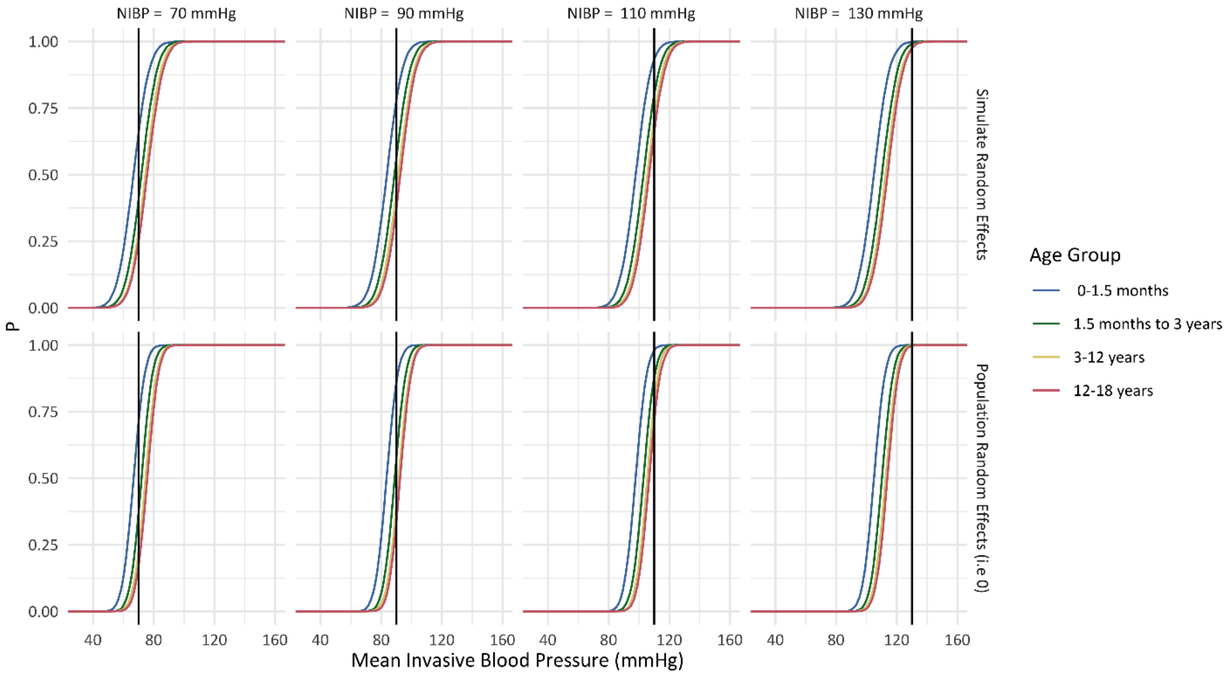
Cumulative Distributions of IABP as a function of observed NIBP

Similar to figure 4 in the manuscript, below we derive using these models and simulated patient populations cumulative Systolic, Mean and Diastolic Invasive BP histograms for various measured NIBP pressures and different age groups (age for each simulated population was chosen as the median for each age group). X-axis is Systolic BP (mmHg, bin size 1mmHg) while on the y-axis we show the fraction of samples with a BP below the value in the X-axis

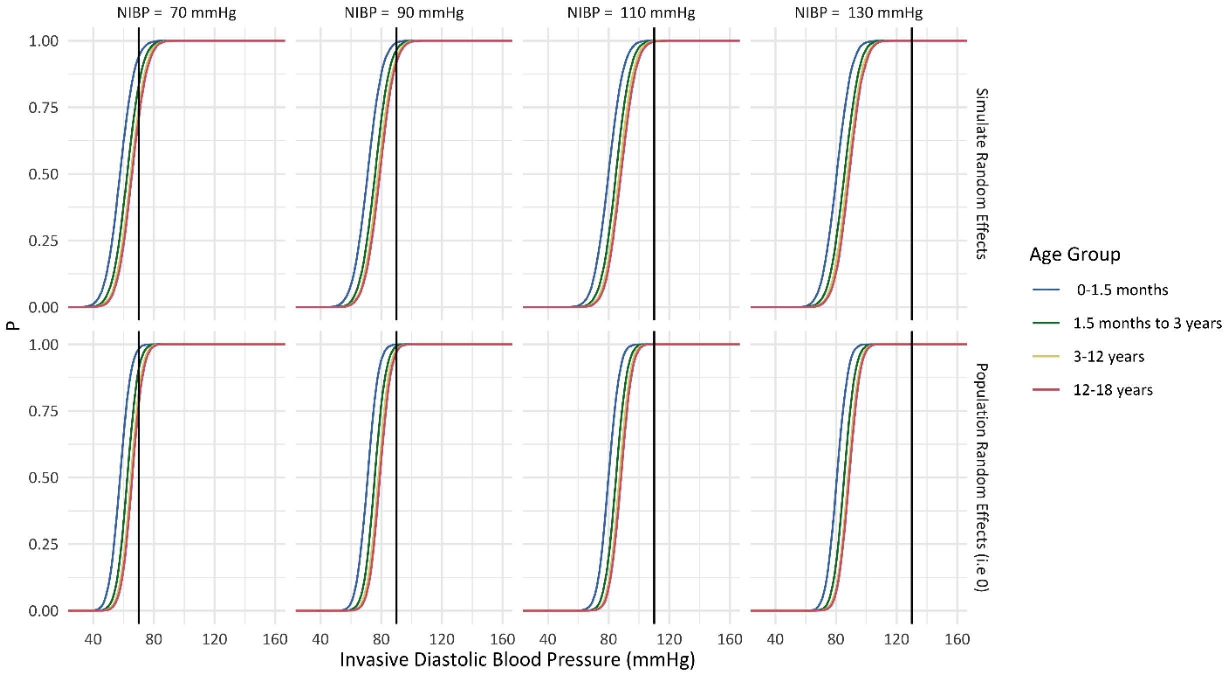
Systolic BP



<u>Mean BP</u>


NIBP = 70 mmHg
NIBP = 90 mmHg
NIBP = 110 mmHg
NIBP = 130 mmHg
Simulate Random Effects
Population Random Effects (i.e 0)
P
1.00
0.75
0.50
0.25
0.00
40
80
120
160
Mean Invasive Blood Pressure (mmHg)
Age Group
0-1.5 months
1.5 months to 3 years
3-12 years
12-18 years

Diastolic BP



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