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ORIGINAL ARTICLE

Infant locomotive development and its association with adult blood pressure

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Abstract Evidence from animal models suggests that locomotion and blood pressure share common neurophysiological regulatory systems. As a result of this common regulation, we hypothesized that the development of locomotion in human infants would be associated with blood pressure levels in adulthood. The study sample comprised 4,347 individuals

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with measures of locomotive and non-locomotive neuromotor development in infancy and adult blood pressure levels within a longitudinal birth cohort study, the Northern Finland Birth Cohort 1966. Later development in all three stages of locomotive development during infancy was associated with higher systolic and diastolic blood pressure levels at age 31. For age of walking without support, 0.34 (95 % CI 0.07 to 0.60)-mm Hg higher SBP and 0.38 (95 % CI 0.15 to 0.62)-mm Hg higher DBP were estimated for each month of later achievement (P=0.012 for SBP; P=0.001 for DBP). No association was identified for non-locomotive neuromotor development. *Conclusion*: These results highlight the positive sequelae of advanced locomotive development during infancy, suggesting that the common regulatory systems between locomotion and blood pressure may influence the development of raised blood pressure over time.

Keywords Neurodevelopment · Infancy · Child development · Blood pressure · Epidemiology · Cohort studies

Abbreviations

BP	Blood Pressure
DBP	Diastolic blood pressure
SBP	Systolic blood pressure
HR	Heart rate
BMI	Body mass index
MLR	Mesencephalic locomotor region
PPN	Pedunculopontine nucleus

Raised blood pressure (BP) is one of the most important worldwide public health challenges as it is the risk factor attributed to the largest number of deaths globally [24]. It carries a huge economic burden [25]. Future disease projections indicate an alarming increase in prevalence, reaching an estimated 1.56 billion hypertensive people by 2025 [20]. As the impact of hypertension on society escalates, so too does the need to further our understanding of its pathogenesis and to uncover new early predictors of raised BP. Over the last two decades, there has been an increasing appreciation of the importance of the early life determinants of raised BP and hypertension.

While a large number of studies implicate growth during the fetal and postnatal periods as a risk factor for raised BP in adulthood [3, 5, 14], potential links between measures of early life neurodevelopment and later BP have yet to be investigated. This is despite strong neurophysiological evidence accumulated over the last two decades from, primarily, animal models, which suggests that locomotion and BP are closely connected through shared regulatory systems [4, 37]. Studies in mice have identified locomotor activity cycles as the factor with the most dominant influence on BP levels, accounting for up to 70 % of the variation in recorded BP levels [37].

In this study, we investigated the potential life course clinical implications of this common regulation, as this has not yet been investigated in either animal or human studies. Since the development of locomotion in humans occurs during infancy, one of the most crucial periods in terms of neurodevelopment, we hypothesized that the development of locomotion in infants would be associated with raised BP levels in adulthood. This would suggest that the period of

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locomotive development in infancy may be a sensitive neurodevelopmental period for the future development of hypertension. Establishing a link between the development of locomotion in infancy and adult BP would suggest that these common regulatory systems may influence the development of BP over time.

To test this hypothesis, we utilized a longitudinal birth cohort study which followed cohort members prospectively from the antenatal period to adulthood, with assessments of infant locomotive neurodevelopment and adult systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels. We investigated the association between adult BP levels and monthly measurements of the achievement time of three key developmental milestones which largely cover the process of locomotive development in infancy; lifting the body upwards to a standing position, walking with support, and walking without support. To test whether this association was specific to locomotive and not to overall neuromotor development, we explored the association between adult BP and sitting without support—a non-locomotive measure of infant neuromotor development.

Methods

Study population

The Northern Finland Birth Cohort 1966 (NFBC1966) followed pregnancies in the two northernmost provinces of Finland with expected delivery dates in 1966 [31]. Genetic studies suggest the population in these two areas to be ethnically homogeneous [17], with the NFBC1966 being one of the most widely utilized cohorts, globally, in identifying genes associated with blood pressure and other metabolic traits [26, 32]. The study originally included 12,058 live births, and data collection sweeps were performed throughout childhood and in adult life. At 31 years of age, clinical examinations were performed on 6,007 males and females still living in the original target area or the Helsinki capital area [35]. Neither the birth nor the early sociodemographic data differed materially between those attending the clinical examination and the remaining sample [18, 35]. In 2008, medical records containing information on infant neuromotor development were recovered from hospitals for 4,504 of the individuals who attended the clinical examinations at 31 years (75.6 % of eligible). Twins and infants with mental retardation or cerebral palsy were excluded leaving 4,347 individuals, 2,154 males and 2,193 females, for the final analysis. All aspects of the study were reviewed and approved by the Ethics Committee of the University of Oulu and by the respective local research committees. Participants gave written informed consent.

Main study variables

Throughout infancy, the children attended child healthcare centers/clinics on average 10 times for developmental and growth assessment. The achievement dates of the following milestones, relating to locomotive neurodevelopment, were systematically recorded on a monthly chart designed specifically for this purpose: (1) age in months for lifting body upwards to a standing position, (2) walking with support, (3) walking without support. A milestone indicating non-locomotive neuromotor development was also recorded; sitting without support. SBP and DBP levels were measured twice (mean was used in analysis) using a standardized procedure [38].

Early life factors

Family socioeconomic status during early life was based on father's occupational social class, and was classified from I (high) to IV (low), and for farmers by farm size. Information on maternal age and maternal smoking were taken from maternity records or a questionnaire administered during the 6th or 7th month of pregnancy.

Intrauterine and postnatal growth

Intrauterine growth pattern was assessed in two ways: (1) birthweight relative to gestational age (birthweight percentiles were computed for all boys and girls) and (2) ponderal index (birthweight/length^3) as a measure of thinness/nutrition status. Postnatal growth was assessed in terms of both peak weight and peak height velocity during the period of infancy, derived from growth velocity curves [6].

Lifestyle/health factors in adulthood

At 31 years, the individual's own socioeconomic status was based on occupation and employment data. Smoking at 31 was defined as ≥1 cigarette per day; alcohol consumption was evaluated based on the individual's average frequency of alcohol consumption during the last year; frequency of exercise was based on the frequency of light physical activity; administration of an antihypertensive medication was based on how often participants were taking any antihypertensive medication; body mass index (BMI) was calculated based on measured body height (in meters) and weight (in kilograms) (weight/height^2).

Statistical analyses

Linear regression models were used to explore the shape and magnitude of the association between infant locomotive/non-locomotive neuromotor development and adult BP. The effects of potential confounders were examined by multiple regression. Initially, a sex-adjusted regression was run for each

of the measures of infant neuromotor development (model 1), followed by the addition of all potential early life confounders (model 2) and lifestyle/health factors in adulthood (model 3). Possible interactions between locomotive development and sex, family socioeconomic status at birth, BMI in adulthood, and all measures of intrauterine and postnatal growth (birthweight for gestational age, ponderal index, postnatal height/weight growth) were explored. For all analyses, statistical significance was set at the $P<0.05$ level. Participants with missing data, or specific sub-populations which are known to be delayed in their locomotive development, such as twins and individuals suffering from intellectual disability or cerebral palsy, were excluded from the analyses. Peak weight and height growth in infancy had skewed distributions and were log-transformed for analysis. Correlations between the four measures of neurodevelopment were estimated through Pearson's correlation coefficients. Statistical analyses were performed using SPSS (version 20; SPSS, USA).

Results

Our study sample was compared with the whole NFBC1966 cohort and was found to be representative of the whole cohort with no substantive differences observed in several sociodemographic and lifestyle measures and BP. The data of primary interest, adult BP levels and infant neuromotor development, had very similar distributions. Achievement times for all measures of infant neurodevelopment were equal for both sexes and were normally distributed (Table 1). SBP and DBP levels were also normally distributed. All four measures of neurodevelopment were positively correlated, irrespective of whether they were locomotive or non-locomotive ($r^2=0.61$ to 0.82, $P<0.0001$ between locomotive measures; $r^2=0.42$ to 0.56, $P<0.0001$ between the non-locomotive measure and the locomotive measures).

Regression analyses showed a significant sex-adjusted linear association between measures of locomotive development and both SBP and DBP (Table 2). For age of walking without support, 0.31 (95 % CI 0.03 to 0.59)-mm Hg higher SBP and 0.30 (95 % CI 0.06 to 0.55)-mm Hg higher DBP were estimated for each month of later achievement ($P=0.031$ for SBP; $P=0.016$ for DBP). The other two measures of locomotive development, lifting body up to a standing position and walking with support, showed a similar pattern. Adjustment for early life factors, including measures of intrauterine growth, slightly reduced the strength of the association (for SBP only), while adjusting for lifestyle/health factors in adulthood increased the strength of the associations (Table 2). The

Table 1 Characteristics of the available sample in the NFBC1966

Characteristic	Total sample (N=4,347)	Males (N=2,154)	Females (N=2,193)
Predictors and outcomes	*N*	Mean (SD)	Mean (SD)
Blood pressure in adulthood			
SBP (mm Hg)	4,347	130.2 (12.6)	120.2 (12.2)
DBP (mm Hg)	4,343	80.2 (11.2)	75.0 (10.7)
Neuromotor development during infancy			
Sitting without support (month)	3,147	7.2 (1.1)	7.2 (1.1)
Lifting body upwards (month)	3,149	8.4 (1.3)	8.5 (1.4)
Walking with support (month)	3,416	9.1 (1.4)	9.1 (1.4)
Walking without support (month)	3,429	11.7 (1.6)	11.7 (1.6)
Potential confounders/modifiers	*N*	%	%
Early life factors			
Social class (IV & small-area farmers)	4,279	32.9	32.1
Maternal age (>30 years)	4,320	32.4	32.1
Maternal smoking (yes)	4,347	29.5	26.7
BW-GA (≤10 %; small for GA)[a]	4,203	8.3	8.7
BW-GA (≥90 %; large for GA)[a]	4,203	9.9	10.3
Lifestyle/health factors in adulthood			
Smoking (never)	4,278	32.2	38.3
Drinking (at least once monthly)	4,295	79.2	61.1
Exercise (less than once weekly)	4,297	36.1	33.4
BMI (obese, BMI≥30)	4,318	8.6	9.7
Antihypertensive medication (yes)	4,305	1.2	1.4

[a] BW-GA refers to birthweight for gestational age; cut-off was estimated from population with complete data

Table 2 Unadjusted and adjusted linear regression coefficients between locomotive/non-locomotive neuromotor development in infancy and SBP/DBP in adulthood (mm Hg per 1-month later achievement of the milestone)

Neurodevelopmental Milestones		Model 1		Model 2		Model 3	
	n	*β* (95 % CI)	*P*	*β* (95 % CI)	*P*	*β* (95 % CI)	*P*
SBP, mm Hg							
Locomotive neurodevelopment							
Lifting body upwards	2,891	0.56 (0.23 to 0.89)	<0.001	0.46 (0.13, 0.80)	0.006	0.54 (0.23 to 0.86)	<0.001
Walking with support	3,136	0.32 (0.01 to 0.63)	0.042	0.25 (−0.07, 0.56)	0.121	0.35 (0.06 to 0.65)	0.020
Walking without support	3,158	0.31 (0.03 to 0.59)	0.031	0.25 (−0.03, 0.53)	0.080	0.34 (0.07 to 0.60)	0.012
Non-locomotive neurodevelopment							
Sitting without support	2,916	0.06 (−0.33 to 0.45)	0.752	−0.06 (−0.45, 0.34)	0.783	0.06 (−0.31 to 0.44)	0.743
DBP, mm Hg							
Locomotive neurodevelopment							
Lifting body upwards	2,889	0.32 (0.03 to 0.62)	0.033	0.31 (0.01, 0.61)	0.045	0.37 (0.08 to 0.66)	0.011
Walking with support	3,134	0.18 (−0.09 to 0.45)	0.200	0.19 (−0.09, 0.46)	0.190	0.29 (0.02 to 0.55)	0.021
Walking without support	3,156	0.30 (0.06 to 0.55)	0.016	0.31 (0.06, 0.56)	0.015	0.38 (0.15 to 0.62)	0.001
Non-locomotive neurodevelopment							
Sitting without support	2,913	0.03 (−0.32 to 0.37)	0.885	0.01 (−0.34, 0.37)	0.943	0.10 (−0.23 to 0.44)	0.541

Separate models were run for each of the measures of infant neuromotor development

Model 1—adjusted only for sex (crude/unadjusted)

Model 2—adjusted for sex + early life factors at pregnancy/birth (family socioeconomic status at birth, maternal age, maternal smoking, birthweight for gestational age)

Model 3—adjusted for sex + early life factors at pregnancy/birth (family socioeconomic status at birth, maternal age, maternal smoking, birthweight for gestational age) + lifestyle/health factors in adulthood (individual's socioeconomic status in adulthood, frequency of exercise, smoking, drinking, taking antihypertensive medication, body mass index)

association between locomotive development in infancy and adult BP is continuous and graded throughout the entire range of locomotive development (Fig. 1). Sitting without support, which reflects a measurement of neurodevelopment which is non-locomotive, was not associated with either SBP (P=0.752) or DBP (P=0.885), despite its strong correlation with the three locomotive milestones.

To further test whether the infant neuromotor development—adult BP association is confounded by the well-established infant growth—adult BP association [5], we performed further analyses where we adjusted for all possible combinations of the following variables for which an association with adult BP has previously been reported: birthweight for gestational age (measure of intrauterine growth), ponderal index at birth (measure of neonatal thinness/under-nutrition), and velocity of weight and height growth during infancy (measures of postnatal growth derived from growth velocity curves) [6, 34]. The associations remained statistically significant (data not shown).

There were no significant interactions between infant neuromotor development and sex, family socioeconomic status, birthweight for gestational age, ponderal index, postnatal height/weight growth, and body mass index (BMI) in adulthood on the relationship with adult BP. Therefore, no additional analyses were performed for these factors.

Discussion

Overall, utilizing a well-characterized population-based birth cohort with detailed measures of neuromotor development throughout infancy and BP measurements in adulthood, we found the following: (1) a linear association between development of locomotion and adult SBP/DBP; (2) no evidence that this association is substantively confounded (or explained) by measures of intrauterine/postnatal growth or lifestyle/health factors in adulthood; (3) the association is continuous and graded throughout the entire range of neuromotor development, including the normal variation of development; (4) a non-significant association for non-locomotive neuromotor development.

Since key measures of intrauterine and postnatal growth had only a small impact on the strength and significance of the association observed (and only for SBP) and because tests for interaction/moderation between the observed association and all of the available measures of intrauterine/postnatal growth showed that growth does not moderate or interact with the locomotive development—BP association, our findings suggest explanations independent of growth-related mechanisms. Because the association was observed across the entire range of locomotive development, it is not driven by extreme values (i.e., very early or vary late developers).

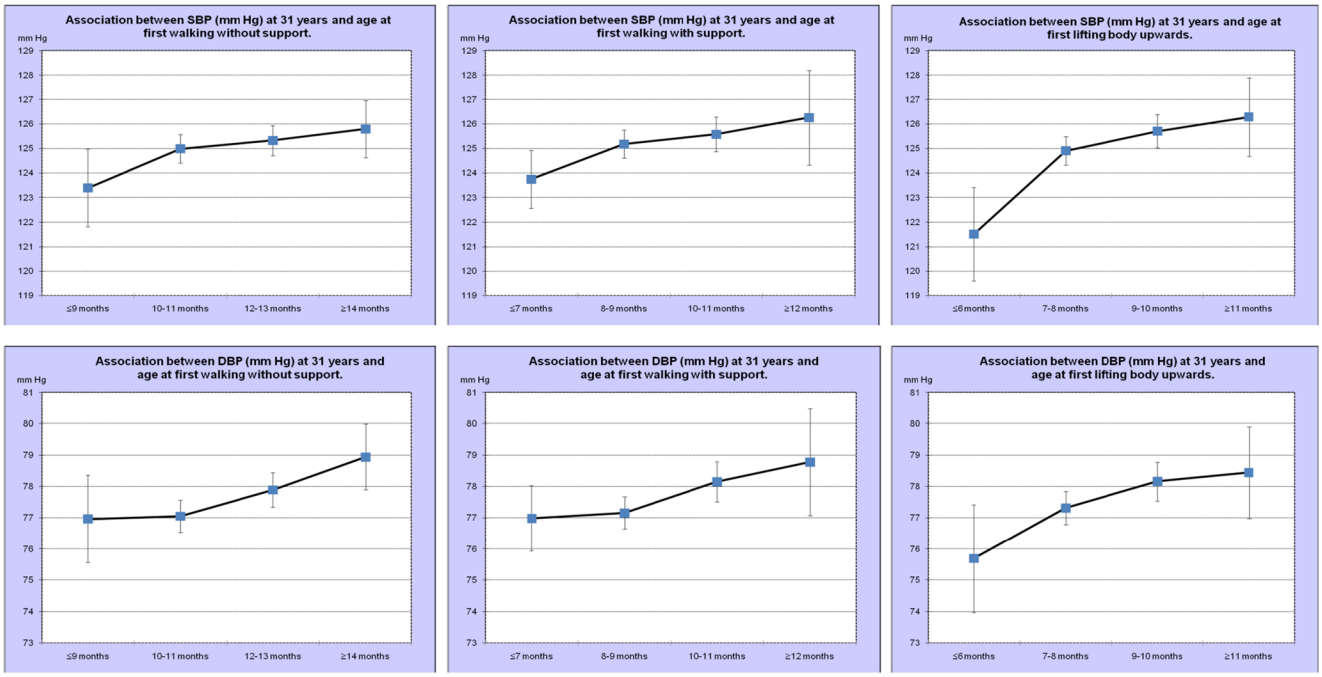

Fig. 1 Association between SBP and DBP (mm Hg) at 31 years and locomotive development during infancy (months to date of achievement). The 95 % confidence intervals for means are shown for the whole population. Adjusted for all covariates (model 3)

Our study has several strengths. It is based on a large, prospective, population-based cohort of a genetically homogeneous population. Participants known to be delayed in their neuromotor development or to have high BP in adulthood due to abnormalities or multiple births were excluded. Trained personnel collected infant development data systematically at frequent intervals. Three different measures of locomotive development during infancy were assessed, and all measures showed consistent and significant associations. Data were available on all the potentially important early and later life confounders/moderators, which were included in the models.

Studies focusing on the associations between early growth measures and BP have shown that the association amplifies with age [11]. This may also be the case for the infant locomotive development—BP association, as SBP and DBP levels in this study were measured at 31 years of age, when BP levels have not yet started to diverge markedly. Our findings were observed across the entire range of locomotive development suggesting implications for the whole population, not just the extremes.

Our findings derive support from a strong evidence base which has accumulated over the last few decades, primarily from animal models and has identified that: i) locomotion and BP share common neurophysiological regulatory systems, and ii) the administration of substances, such as glucose and a high-salt diet, which are known to increase BP, induce a concurrent decrease in various aspects of locomotion.

Studies on, primarily, animal models have documented three regions in the brain, namely the mesencephalic locomotor region (MLR), the subthalamic locomotor region (STLR), and the lateral hypothalamic area (LHA), as being common regulators of locomotion and BP. These common regulatory systems are hypothesized to influence both BP levels and locomotion in parallel; experiments in animal models have shown that stimulation of the MLR affects locomotion and BP in direct proportion to each other [4, 9, 13, 15, 28]. Experiments in rats have indicated that the relation between locomotion and BP in the MLR common regulatory region appears to be restricted to walking as, even at running and galloping speeds of locomotion, the level of BP increase elicited by MLR stimulation plateaus at the level of walking speed [9]. However, this cardiorespiratory response can also occur in the absence of overt movements or muscle contractions [9, 36]. Without somatosensory feedback, HR and BP responses are not modulated, and they keep increasing in a linear fashion [9].

On a neurofunctional level, this mechanism involves neurons that target both the locomotor and cardiovascular systems when activated. In rats, cholinergic neurons in the pedunculopontine nucleus (PPN), which is part of the MLR, have been shown to project to the ventrolateral medulla and lateral parafascicular thalamus (which projects to the motor cortex and striatum) [23, 29]. In humans, stimulation of the thalamus and the basal ganglia (subthalamus or substantia nigra) increase heart rate and mean arterial pressure [29]. The ventrolateral medulla acts on sympathetic reflexes that are important for the control of arterial blood pressure. Poor control may produce a range of cardiovascular complications,

including hypertension [8]. It is possible that such complications originate during the most dynamic period of neurodevelopment, infancy, [22] if during this period either the locomotor or cardiovascular systems are not maturing normally, as the PPN is thought to optimize locomotor and cardiovascular responses [30].

Additional links between BP regulation and locomotor activity relate to the sleep-wake cycle and circadian rhythm variation observed in BP levels, with studies in mice indicating that locomotor activity contributes strongly to the circadian variation in BP [21]. Locomotor activity cycles have been identified as the factor with the most dominant influence on BP levels in mice, accounting for up to 70 % of the variation in levels recorded [37]. The circadian rhythms observed in both locomotor activity and BP are believed to be controlled by an internal biological clock located in the suprachiasmatic nucleus (SCN), as SCN-lesioned rats have significantly reduced locomotor activity and increased BP levels [33]. A rodent model study which explored the effects of neonatal cerebral hypoxia-ischemia on circadian rhythms when the animals became adults identified a decreased locomotor activity accompanied with increased SBP and DBP [2].

Supportive evidence also exists from recent studies involving exposure to a high-sugar or a high-salt diet, which is known to elicit raised BP levels in adulthood [1, 7]. Separate studies on healthy full-term newborn infants, as well as on preterm neonates, have documented how the administration of glucose or sucrose results in less vigorous locomotion [12, 19], with one study finding that the effect of glucose administration is limited only to locomotive neurodevelopment, without affecting non-locomotive neuromotor development [12]. A rodent study focusing on high-salt diet exposure found rats to exhibit increased BP levels and decreased intensity levels of locomotor activity [27].

Despite the emphasis placed on the identification and provision of early intervention for developmentally delayed children [10], examining the potential for advancing early locomotive neurodevelopment has generated very limited academic interest. Few studies have aimed to evaluate the potential benefits of specific rearing practices, estimating that they can speed up the achievement of independent locomotion by 1 to 2 months [16, 39]. Since the medium- or long-term benefits of early achievement of locomotion through interventional approaches have not yet been examined, an evidence-based discussion of potential practical implications of the identified association is not possible. However, our findings implicate a novel mechanism for the life course development of blood pressure levels, which may be further examined, hence increasing the understanding of pathways leading to raised blood pressure levels, with clinical/therapeutic implications.

In conclusion, this study adds to the evidence of the early life determinants of adult disease by identifying infant locomotive development as a novel early life predictor of adult blood pressure levels. Our findings highlight the need for future research to focus on elucidating the mechanisms which may explain this novel association, as it may carry important clinical implications for the entire life course.

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Competing interests The authors have no conflicts of interest to disclose.

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