

EARLY LIFE ORIGINS OF ADULT HEALTH

Are early life factors responsible for international differences in adult blood pressure? An ecological study

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Background Although low birthweight has been related to higher mean blood pressure in individuals, there have been very few studies on the contribution of the ‘fetal origins hypothesis’ to international variations in mean blood pressure.

Methods Standardized data on mean blood pressure levels in adults aged 20–29 years (available from the INTERSALT study countries) were related to data on mean birthweight and infant mortality rates (IMRs) ~25 years earlier (available from the World Health Organization and the United Nations statistics for 24 of these countries).

Results Population mean systolic pressure was inversely correlated with IMR ($r = -0.66$, $P < 0.001$) and positively correlated with mean birthweight ($r = 0.36$, $P = 0.108$). These correlations were little affected by adjustment either for current body mass index or for current sodium, potassium, and alcohol intake.

Conclusions The directions of these associations suggest that low mean birthweight and high infant mortality are not important determinants of high population mean adult blood pressure levels.

Keywords Blood pressure, birthweight, infant mortality

It has been suggested that factors operating in fetal life are important determinants of cardiovascular disease risk.¹ The principal proxy marker of fetal exposures related to increased cardiovascular risk in most studies has been small size at birth, which has been related to Coronary heart disease (CHD), stroke, and a wide range of vascular risk markers in individuals.¹ However, a second important component of the evidence adduced to support the ‘fetal origins hypothesis’ has been the observation in ecological studies, both on a national and international basis, that infant mortality rate (IMR) is positively correlated with risks of CHD and stroke.^{2–4}

Among established major risk factors for cardiovascular disease, blood pressure has been particularly implicated in the fetal origins hypothesis.¹ It has been consistently shown in studies of individuals that low birthweight is related to higher mean blood pressure levels,⁵ though the magnitude and public health importance of the association is debated.⁶

The geographic differences in mean blood pressure, which occur between populations are marked and of considerable public health importance.⁷ Marked differences between populations in exposures implicated in the fetal origins hypothesis, including birthweight and IMR, are well documented. However, the potential contribution of the fetal origins hypothesis to differences in mean blood pressure levels between populations has not been examined. In order to examine this issue reliably, standardized measurements of blood pressure in different populations are essential. Therefore, we have related published information from the INTERSALT study,⁸ in which standardized blood pressure measurements were made in adults in 32 countries, to independently collected information on mean birthweight and IMR for these countries. If fetal factors were important determinants of blood pressure differences between populations, it would be expected that populations with lower mean birthweights and higher IMRs would tend to have on average higher mean blood pressure levels.

Methods

In the INTERSALT study, standardized measurements of blood pressure, height, weight, and urinary potassium and sodium were

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made in population samples from 52 centres in 32 countries from all major regions of the world during 1986 and 1987.⁸ Each population sample included ~25 men and 25 women in each of four 10 year age strata (20–59 years). Blood pressure was measured twice in the sitting position by an observer who had been trained and tested at one of two co-ordinating centres, using a Hawksley random zero sphygmomanometer; the mean of the two readings was used for analysis. Height and weight were measured using a standard protocol and electrolyte intake was estimated from 24 h urine collections measured in a central laboratory (Leuven, Belgium). Weekly alcohol intake was ascertained from a standard questionnaire.

From published data summaries⁹ we derived sex-standardized estimates of mean systolic pressure, height, body mass index (BMI), weekly alcohol consumption, urinary sodium and potassium in each country for the 20–29 year age group (Table 1). This age group was used in the analysis because it was possible to obtain national data on IMRs and birthweight for most of these countries either for the mid-year of birth of these subjects (1963) or within 10 years either side (1956–1973). Geographic variations in blood pressure at 20–29 years in this study are closely related to variations at older age groups.¹⁰ Information on mean birthweight was available from national birth surveys carried out during the 1960s and collated by the World Health Organization¹¹ for 21 of the INTERSALT countries (Table 1). Information on IMRs was available from United Nations sources¹² for 24 countries included in the INTERSALT study (Table 1). Data on both infant mortality and mean birthweight were available from sixteen countries. To ascertain socioeconomic influences at the time of birth on birthweight and IMRs, correlations with national income were examined. National income was ascertained for 25 of the INTERSALT countries from routine United Nations sources, measured in 1963 for all countries except Brazil (1960) and China (1958).¹³

Statistical methods

Statistical analysis was performed using Intercooled STATA 7.0 for Windows software (Stata Corp, Union Station, TX, USA). Correlations between continuous variables, including mean birthweight (kg), systolic blood pressure (SBP) (mm Hg), height (m), BMI (kg/m^2), infant mortality rates IMRs (number of deaths of infants <1 year of age per 1000 live births), mean alcohol consumption (ml/week), national income (converted to US dollars), urinary sodium and potassium (mmol/24 h) were examined. Partial correlation coefficients were used to establish the independent relations of birthweight and infant mortality to blood pressure in later life. The assumption of linearity was verified by observing graphical representations of the data. Independent adjustments for adult height and body size (using mean BMI) were made. Adjustments for electrolyte intake were made using mean urinary sodium and potassium levels, along with weekly alcohol consumption.

Results

Between the INTERSALT countries included in this analysis there was a wide range in mean SBP (97.9–120.6 mm Hg), diastolic blood pressure (DBP) (59.4–75.2 mm Hg) mean birthweight (2.8–3.6 kg) and IMR (16–88 deaths/1000 live births) (see Table 1). IMR and mean birthweight showed a strong

inverse correlation ($r = -0.62$, $P = 0.01$). Mean birth weight was positively correlated and IMR negatively correlated with national income ($r = 0.59$, $r = -0.34$, respectively). Mean SBP showed a modest positive correlation with mean birthweight ($r = 0.36$, $P = 0.108$) (Figure 1) and a stronger inverse correlation with IMR ($r = -0.66$, $P < 0.001$) (Figure 2). These associations were little affected by adjustment for population mean BMI (partial $r = 0.29$, $P = 0.221$; $r = -0.63$, $P = 0.001$, respectively). Additional adjustment for population mean urinary sodium and potassium levels and mean alcohol consumption had minimal effect on the association between IMR and blood pressure ($r = -0.58$, $P = 0.008$), but moderately weakened the association with birthweight ($r = 0.12$, $P = 0.645$). Adjustment for current height had little effect on the relation between infant mortality and systolic pressure ($r = -0.51$, $P = 0.012$) but effectively abolished the relation of birthweight to systolic pressure ($r = -0.04$, $P = 0.854$).

Exclusion of two countries in which INTERSALT populations were highly selected groups (Brazil, Yanamamo Indians; Kenya, Luo tribesmen) did not affect the results appreciably. Replacing mean SBPs for the 20–29 year age group with the overall mean systolic pressures for the 20–59 year age group in these analyses (using the same birthweight and infant mortality data) did not appreciably affect the positive correlation between birthweight and systolic pressure ($r = 0.37$, $P = 0.099$), though the inverse relation between IMR and systolic pressure was markedly weakened ($r = -0.14$, $P = 0.528$).

Current mean BMI showed a strong positive correlation with mean systolic pressure at 20–29 years ($r = 0.44$, $P = 0.014$) which was unaffected by adjustment for birthweight, and attenuated by adjustment for IMR. The regression estimate between mean systolic pressure and BMI (1.6 mm Hg per kg/m^2 , 95% CI 0.4–2.9) is similar to the association observed in individuals in the INTERSALT Study.⁹ There was no evidence of interaction in the associations between birthweight, BMI and systolic pressure in these ecological analyses; in particular there was no suggestion that a combination of low birthweight and high current BMI was associated with particularly high mean blood pressure levels ($P = 0.595$). Similar but weaker associations were observed for diastolic pressure throughout (association with birthweight $r = 0.31$, $P = 0.175$; with IMR $r = -0.47$, $P = 0.021$).

Discussion

In this study, between-country variations in mean birthweight were positively correlated and variations in IMR negatively correlated with mean SBP. Additional adjustment for adult BMI, alcohol consumption, sodium and potassium intake had no important effect on the direction of these associations. Adjustment for height abolished the positive association between birthweight and blood pressure, though it had little effect on the relation between infant mortality and blood pressure.

The ecological analyses presented here combine data from systematic, standardized blood pressure surveys in small population samples with information on birthweight from ad hoc surveys and with routine national information on IMRs. This has the potential weakness that the populations from which blood pressure and early life data are derived are not necessarily the same. The validity of the analyses presented is therefore crucially dependent on the extent to which the data

Table 1 Data included in the analysis, for different countries in the INTERSALT study

Country	Year mean birthweight measured	Sample size	Mean birthweight (SD) kg	IM in 1963 (deaths per 1000 births)	Reliable IM	No. measured at 20-29 Years	Mean SBP (SE) mm Hg	Mean DBP (SE) mm Hg	Mean BMI (SE) kg/m ²	Mean urinary sodium (SE) mmol/24 h	Mean urinary potassium (SE) mmol/24 h
Argentina	1966	200	3.34	62.2	No	50	108.7 (1.5)	70.7 (1.7)	23.4 (0.4)	162.6 (9.8)	52.1 (2.4)
Belgium	-	-	-	27.2	Yes	70	120.6 (1.3)	74.6 (1.2)	23.5 (0.4)	132.1 (6.6)	63.8 (3.0)
Brazil	1961	524	3.18 (0.47)	-	-	97	97.9 (1.0)	62.1 (0.9)	21.8 (0.3)	10.0 (2.3)	77.4 (4.6)
Canada	1973	331 467	3.29	26.3	Yes	98	114.2 (1.0)	74.1 (0.9)	23.8 (0.3)	182.9 (8.2)	54.1 (2.4)
China	1972	5370	3.29	-	-	150	106.4 (0.9)	65.5 (0.8)	21.0 (0.2)	208.2 (7.3)	30.9 (0.8)
Colombia	1965-66	870	3.12 (0.50)	88.2	No	49	108.4 (1.7)	65.1 (1.2)	21.0 (0.4)	217.1 (11.8)	72.2 (3.4)
Denmark	1973	74 857	3.33 (0.57)	19.1	Yes	49	119.2 (1.6)	79.9 (1.3)	23.4 (0.4)	142.9 (7.6)	63.8 (3.0)
England and Wales	1970	16 815	3.31 (0.57)	21.1	Yes	100	115.2 (1.3)	69.8 (1.0)	24.4 (0.4)	151.2 (5.5)	63.1 (2.5)
Finland	1966	11 931	3.44 (0.57)	18.2	Yes	100	116.7 (1.2)	75.2 (1.2)	23.2 (0.4)	151.3 (5.8)	72.5 (2.4)
Germany	1973	63 330	3.36 (0.59)	26.9	Yes	94	117.2 (1.2)	72.1 (0.9)	22.6 (0.3)	165.5 (7.3)	70.9 (2.3)
Hungary	1970	151 819	3.15	42.9	Yes	50	117.6 (1.6)	79.4 (1.5)	23.8 (0.5)	181.2 (10.2)	47.1 (2.8)
Iceland	-	-	-	17.0	Yes	50	116.0 (1.8)	69.1 (1.6)	23.4 (0.4)	132.1 (7.4)	60.0 (3.0)
India	1962-70	2940	2.81 (0.28)	77.6	No	100	107.2 (1.0)	70.3 (1.0)	20.6 (0.2)	177.3 (6.7)	44.7 (1.5)
Italy	1965	963 653	3.45 (0.57)	40.1	Yes	200	113.2 (0.8)	72.9 (0.7)	23.9 (0.3)	168.1 (4.2)	55.3 (1.3)
Japan	1960	1 598 909	3.1	23.2	Yes	149	113.4 (1.0)	67.8 (0.9)	21.7 (0.2)	172.7 (5.3)	43.4 (1.3)
Kenja	1971	3160	3.16	-	-	42	110.8 (1.6)	67.5 (1.4)	20.4 (0.3)	53.4 (5.7)	33.0 (3.4)
Malta	1965	2517	3.40 (0.53)	34.2	Yes	50	116.4 (1.6)	76.4 (1.3)	24.5 (0.5)	151.3 (7.9)	61.5 (3.8)
Mexico	1968-70	2113	3.03 (0.53)	68.5	Yes	46	108.3 (1.3)	71.7 (1.6)	23.9 (0.5)	129.3 (10.5)	38.3 (3.0)
Netherlands	1961-1966	10 144	3.47	15.8	Yes	50	119.6 (1.8)	78.8 (1.1)	22.3 (0.4)	151.6 (9.4)	71.4 (3.4)
Northern Ireland	-	-	-	27.0	Yes	50	116.8 (1.7)	71.0 (1.7)	24.0 (0.5)	153.6 (9.1)	53.2 (3.5)
Papua New Guinea	1962	6819	2.85	-	-	46	111.6 (1.7)	61.9 (1.3)	22.8 (0.3)	37.1 (4.7)	77.5 (6.1)
Poland	1974	619 872	3.28 (0.65)	48.7	Yes	100	116.4 (1.3)	74.4 (0.9)	23.6 (0.3)	175.7 (7.5)	49.3 (1.8)
Portugal	-	-	-	73.1	Yes	50	113.4 (1.3)	74.3 (1.5)	22.7 (0.4)	184.9 (10.5)	64.8 (3.7)
South Korea	1956-60	1489	3.63 (0.57)	-	-	50	109.8 (1.7)	71.3 (1.7)	20.9 (0.3)	204.2 (11.0)	49.1 (2.2)
Soviet Union	1975	-	-	30.9	Yes	47	106.3 (1.4)	72.4 (1.3)	23.4 (0.4)	126.9 (6.4)	40.2 (1.9)
Spain	-	-	-	40.5	Yes	100	113.6 (1.1)	68.2 (1.1)	23.0 (0.6)	173.1 (6.7)	62.9 (1.9)
Tawain	1965-68	25 814	3.13 (0.49)	26.4	Yes	44	113.4 (1.9)	73.6 (1.7)	21.8 (0.3)	138.7 (8.3)	33.0 (2.6)
Trinidad and Tobago	-	-	-	40.9	Yes	46	112.3 (1.5)	72.6 (1.7)	24.3 (0.6)	98.9 (8.3)	36.0 (2.4)
USA	-	-	-	25.2	Yes	287	114.2 (0.8)	74.3 (0.6)	25.9 (0.4)	125.8 (3.5)	39.0 (1.2)
Zimbabwe	-	-	-	-	-	50	115.4 (1.7)	76.3 (1.7)	24.0 (0.4)	148.0 (9.2)	36.4 (1.6)

Data on birthweight from WHO, infant mortality from the UN, and blood pressure from the INTERSALT study. SD, standard deviation; SE, standard error.

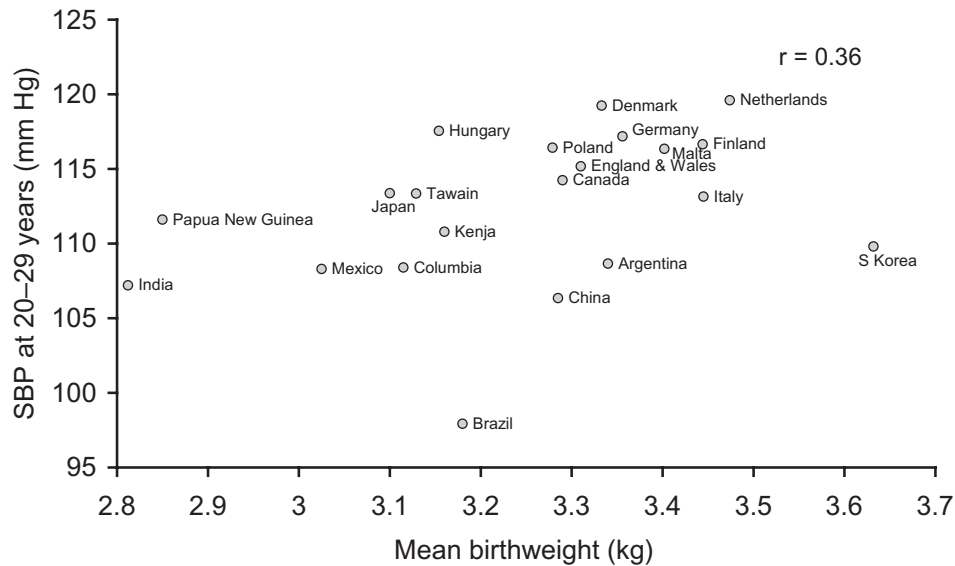


Figure 1 Association between SBP at 20-29 years and mean birthweight, for different countries included in the INTERSALT study

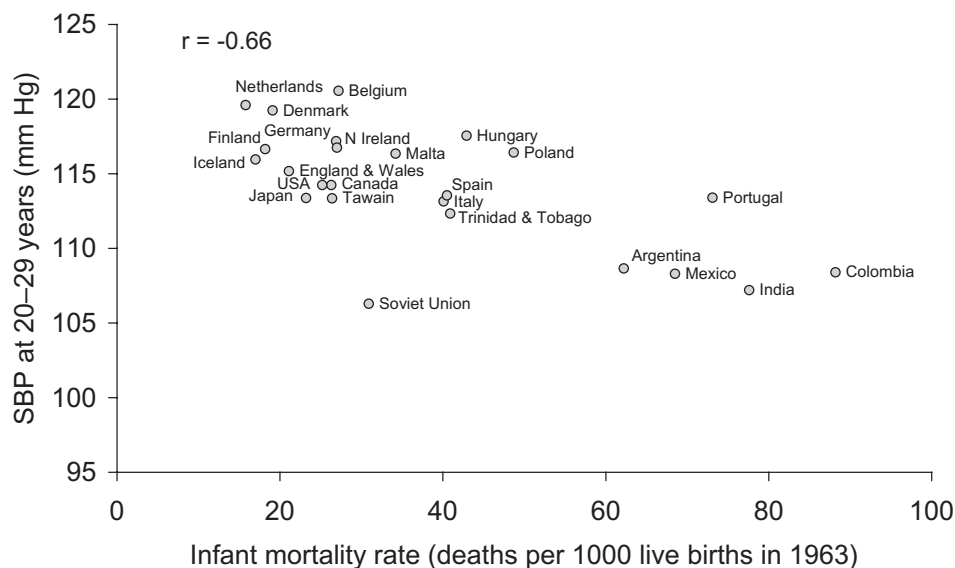


Figure 2 Association between SBP at 20-29 years and infant mortality, for different countries included in the INTERSALT study

on infant mortality, birthweight, and blood pressure are representative of that of the populations to which they refer. The majority of IMRs were based on reliable whole population data (Table 1),¹² with only a small number ($n = 3/24$) being from estimated data or from civil registers that are incomplete and of unknown reliability;¹² exclusion of these three estimates had little effect on the results. The validity of the data on IMRs is supported by the expected inverse association with national income. The validity of the information on mean birthweight from population samples is supported by the strong positive association with national income and by the strong inverse association with IMR, both parameters based on national data. The representativeness of the information on blood pressure from INTERSALT is supported by several lines of evidence. First,

the patterns of blood pressure variation observed in INTERSALT correspond closely with those in earlier population-based studies in individual countries, showing particularly high mean blood pressure levels in industrialized countries and in the Caribbean and particularly low mean levels in 'unacculturated' populations in Brazil and Kenya.^{14,15} Second, the variations in mean blood pressure levels in middle-aged subjects in the INTERSALT samples show a positive correlation with stroke mortality ($r = 0.26$). Third, other characteristics of the INTERSALT population samples, particularly their mean BMI, correlate strongly ($r = 0.63$) with data from national surveys in the same countries collated by the International Association for the Study of Obesity, again suggesting that they are representative (R. Leach, personal communication).

The analyses presented in this report suggest that at a population level, higher birthweight and lower IMRs are correlated with higher mean blood pressure levels. The findings are consistent with the earlier evidence from epidemiological studies on the distribution and determinants of blood pressure, especially those documenting the characteristics of low blood pressure populations, which tended to be living on the margins of subsistence, with characteristics suggesting that average birthweights would be low and infant mortality high.^{16,17} Ecological data of this kind requires cautious interpretation, being particularly prone to confounding.^{18–21} However, the results do suggest that low birthweight and high IMRs, and their close correlates, are not the major determinant or determinants of variations in mean adult blood pressure levels between populations. There was also no evidence to suggest that the combination of low birthweight with later obesity was strongly related to the development of high population mean blood pressure, as has been suggested by some studies in individuals,²² although statistical power for such an analysis was limited in this ecological investigation. Both the exposure measures in this study (birthweight and infant mortality) are crude markers, influenced by a wide range of factors (birthweight by the intrauterine environment and by fetal and maternal genes, IMR by fetal nutrition and by the post-natal environment).^{1,23} However, both measures have been important in providing epidemiological evidence relating potentially prenatal exposures to cardiovascular risk which provide the basis of the fetal origins hypothesis; although crude, they have not so far been superseded by other more specific measures.²³

These ecological observations do not exclude an important influence of fetal factors on blood pressure levels at the individual level. Studies in individuals generally provide stronger evidence about causality than ecological ones.^{18–21} Moreover, the factors responsible for variation in blood pressure between populations may differ from those responsible for variation between individuals.⁷ It therefore remains possible that correlates of low

birthweight are important determinants of blood pressure levels in individuals, although recent reports have suggested that the association between low birthweight and raised blood pressure may have been influenced by publication bias and may not be as strong or have the public health importance originally ascribed to it.⁶ The results also do not exclude an important role for fetal factors at a population level operating through pathways other than blood pressure. Several previous studies have shown positive ecological correlations between infant mortality early in the 20th century and cardiovascular disease (particularly stroke) both within and between countries.^{2–4} The results of our present analyses suggest that such relations are not mediated through blood pressure, which was inversely related to IMR. This suggests that other causal pathways (for example, involving childhood infection) might be important.² Alternatively, the pattern of relationships between infant mortality and blood pressure may not be the same for subjects born in the 1960s as was the case in earlier years.

It is not possible from the current analyses to explain why higher mean blood pressure levels are correlated with higher mean birthweight and with lower IMRs. The explanation may well lie in the strong correlations between birthweight, IMR, and post-natal factors. IMR showed strong negative correlations with BMI and nutritional markers in adult life (particularly alcohol intake and sodium intake); birthweight showed strong positive correlations with these factors and with adult height. The complete disappearance of the positive relation between birthweight and blood pressure after adjustment for height would be consistent with a post-natal explanation for the direction of these associations. Such an explanation would also be consistent with the results of studies examining the effect of migration on blood pressure, which have generally pointed to the dominant influence of the post-migration environment (usually in practice the adult environment) on population blood pressure levels in adult life.^{14,23}

KEY MESSAGES

What do we know?

- Low birthweight has been related to higher mean blood pressure in individuals.
- Although there are marked variations in mean blood pressure between populations, the contribution of the fetal origins hypothesis to these variations remains unknown.

What does this paper add?

- Higher population mean blood pressure levels in adulthood are correlated with higher mean birthweight and lower infant mortality rates.
- The directions of these associations do not suggest that exposures related to the fetal origins hypothesis are major determinants of between-population differences in blood pressure.
- It is likely that post-natal rather than prenatal factors are the most important determinants of population blood pressure levels in adult life.

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