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Small size at birth and greater postnatal weight gain: relations to diminished infant lung function

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METHODS

Study Population

Infants were recruited between May 1999 and October 2002 from a stratified sub-sample of babies born to women participating in the Southampton Women's Survey (SWS). By approaching women registered with particular General Practitioners, the study population was selected to be demographically representative of Southampton. Information obtained by questionnaire from the mother prior to conception included cigarette smoking habits and details of maternal education. At the first ultrasound scan in early pregnancy we calculated gestational age using the woman's menstrual data except where these were uncertain, or where the discrepancy between ultrasound and menstrual data assessments exceeded 14 days; in these circumstances measurements of crown rump length at 7-13 weeks or head circumference and biparietal diameter before 21 weeks determined gestational age. Following application of our dating algorithm, paediatric examination after birth confirmed that no infant showed clinical features of prematurity. All infants were white Caucasian, born at 37 or more weeks' gestation and with no major congenital anomalies or neonatal problems. No mother had gestational diabetes, oligohydramnios, premature rupture of the membranes or other illnesses known to cause fetal lung hypoplasia.

Lung function measurements were made between 5 and 14 weeks of age. 362 women were approached about their infants taking part in the study; 219 (60%) declined to take part and 12 (3%) agreed to take part but were then excluded because of an upper respiratory tract infection within the previous two weeks or other medical grounds, leaving 131 (36%) whose infants had lung function measurements. No infant had previously had a lower respiratory tract illness. To exclude infection or other morbidity, a pediatrician undertook a medical history and examination on the day of testing. Infant feeding practise and the mother's current smoking habits were ascertained by questionnaire. The mothers of the 131 infants who took part tended to be slightly older and better educated than those of infants who did not take part, but maternal smoking and birth weight and length were similar in participants and non-participants.

The Southampton and South West Hants Joint Research Ethics Committee approved the study following careful evaluation by the researchers and ethics committee. The main concerns were of sedating healthy infants - the procedures themselves are safe, and we are unaware of any critical incidents relating to the technical procedures as long as protocols are adhered to. Informed written consent was obtained from a parent, who was invited to be present throughout the measurements.

Anthropometric and respiratory function data collection

The infants' weights at birth and at lung function testing were measured on digital scales. Crown-heel length was measured within 48 hours of delivery and at the time of lung function testing using an infant stadiometer. Maximal occipito-frontal head circumference at birth was measured by marking blank tapes, read off on a metal ruler.

Lung function measurements were recorded in room air with the infant supine, during quiet sleep augmented by chloral hydrate 75-100 mg/kg. Pulse rate and oxygen saturation were monitored throughout. Infant lung function data was collected using RASP software (Physiologic Ltd, Newbury, Berks, UK) and analysed in SQUEEZE (Paul Dixon, London). An inflatable jacket was placed around the infant's chest and abdomen, and connected to a rapid inflation system (Hamid Rassoulian, Medical Physics and Medical Engineering Department, University of Southampton). A clear plastic facemask attached to a Fleisch pneumotachograph (Dynasciences, Blue Bell, CA, USA) measuring airway pressure and flow was placed over the nose and mouth, using malleable putty to create an airtight seal. Tidal breathing data was collected whilst visualising time based plots on a computer monitor. Volume was calculated by digital integration of the flow signal measured by the pneumotachograph. Flow and volume were displayed as real time loops during rapid thoracoabdominal compression (RTC) squeezes, passive inflations and raised volume RTC.

Respiratory rate was measured during quiet tidal breathing prior to any respiratory manoeuvres. To record partial expiratory flow volume (PEFV) curves, a stable end expiratory level was established over at least five breaths before performing an RTC manoeuvre. To find optimal jacket pressure (Pj), a series of RTC manoeuvres was performed starting with an initial jacket pressure of 3 kPa, increasing or decreasing in increments of 1 kPa until the lowest pressure to achieve the best $\dot{V}max_{FRC}$ was identified. At least three RTC manoeuvres were performed at this Pj and the $\dot{V}max_{FRC}$ calculated from the PEFV curve. Four sets of passive inflations were recorded by manual respiratory inflations at 3.0 kPa (air flow 11 L/min) using a Neopuff Infant Resuscitator (Fisher and Paykel Healthcare Ltd.) connected to the pneumotachograph via a T-piece. Up to eight passive inflations were applied to obtain 2-3 relaxed inflations. C_{rs} (ml/kPa) was calculated using SQUEEZE software (Paul Dixon, London) from the resultant passive flow-volume curves and the airway opening pressure measured during occlusion. Raised volume RCT (RVRTC) curves were recorded using a technique adapted from Feher *et al* [E1], again manually inflating the infant's lungs using the Neopuff Resuscitaire at an inflation pressure of 3.0 kPa. Once respiratory muscle relaxation was achieved as indicated by visual inspection of the flow-volume trace, the jacket was inflated to the previously determined optimal jacket pressure at the end of a passive inspiration, producing a forced expiration. The resultant forced expiratory flow-volume curve was used to calculate $FEV_{0.4}$ and forced vital capacity (FVC).

Data interpretation

The criteria for accepting a run of tidal breathing were that the breathing was regular, with a coefficient of variation below 10%, and with no significant drift or leak. All RTC and raised volume RTC flow-volume curves were visually inspected prior to analysis. PEFV loops were considered suitable for measurement of $\dot{V}max_{FRC}$ if a) they were preceded by at least three tidal breaths with a stable end expiratory level (EEL), b) PEF was achieved before 30% of expired volume, with forced expiration extending beyond previous EEL, c) there was a jacket lead time of <0.05 sec and jacket inflation time <100 msec and d) there was no leak, no excessive braking and no glottic closure in the last half of expiration. Passive inflations were accepted if regular in appearance with a stable EEL, no sign of early inspiration or late inflation, no leak and coefficient of variation for all parameters within 5%. Raised volume curves were considered suitable for analysis if a) the inflations were totally relaxed, b) the EEL was a good fit for the time constants and c) jacket inflations were initiated within 100 msec of end inspiration and inflation time was <100 msec. As with RTC curves, raised volume curves were only accepted if there was no sign of significant glottic closure, no leaks and PEF occurred before 30% of inspired volume had been expired.

Statistical analysis

Analysis focused on the lung function measurements of $FEV_{0.4}$, C_{rs}, $\dot{V}max_{FRC}$ and respiratory rate. All these variables were positively skewed and logarithmic transformation was applied to normalise them. Multivariate linear regression was used to relate the lung function variables to the factors of interest. $FEV_{0.4}$ measurements were also analysed adjusting for FVC by including it as a covariate in the regression analyses. Due to the logarithmic transformation the results are presented as percentage change in the lung function measurement associated with a unit change in the factor of interest, together with back-transformed means of the logged variables.

Infant weights, head circumferences and crown-heel lengths at birth were adjusted for sex by conversion to standard deviation (SD) scores compared to standard reference values for British children[E2]. Likewise, weights and lengths at lung function testing were adjusted for the infant's age and sex to produce standard deviation scores that indicate the degree to which an infant is heavier or longer than infants of the same age and sex in Britain[E2]. The SD scores for weight gain between birth and test were derived using the method of Cole[E3]. Published data allowed us to derive conditional SD scores for weight gain,[E2] but comparable data were not available for crown-heel length. The weight gain scores are conditional upon the infant's birthweight and take account of regression to the mean. All SD scores were derived using Excel spreadsheets available from the Child Growth Foundation (12 Mayfield Avenue, London W4 1PW, UK).

References

E1. Feher A, Castile R, Kisling J, Angelicchio C, Filbrun D, Flucke R, Tepper R. Flow limitation in normal infants: a new method for forced expiratory maneuvers from raised lung volumes. J Appl Physiol 1996; 80:2019-2025.

E2. Freeman JV, Cole TJ, Chinn S, Jones PR, White EM, Preece MA. Cross sectional stature and weight reference curves for the UK, 1990. Arch Dis Child 1995; 73:17-24.

E3. Cole TJ. Conditional reference charts to assess weight gain in British infants. Arch Dis Child 1995; 73:8-16.

Legends for online figures

Figure E1. Distribution of characteristics of the study population at birth

Figure E2. Geometric means of lung function measurements by thirds of birthweight and weight gain SD scores. Means for $FEV_{0.4}$ and $\dot{V}max_{FRC}$ are adjusted for age and those for C_{rs} are adjusted for age and sex. Respiratory rate means are unadjusted.

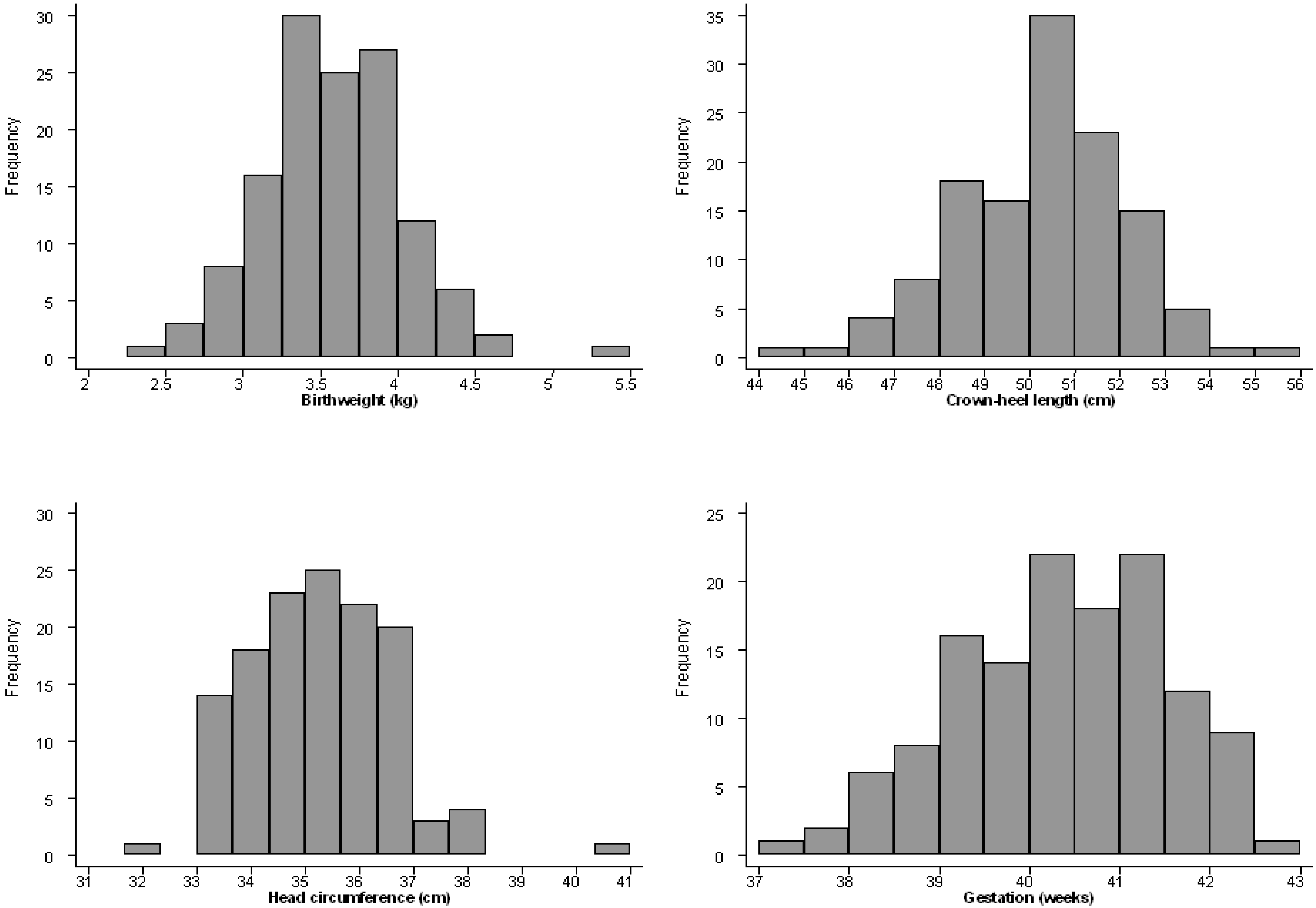
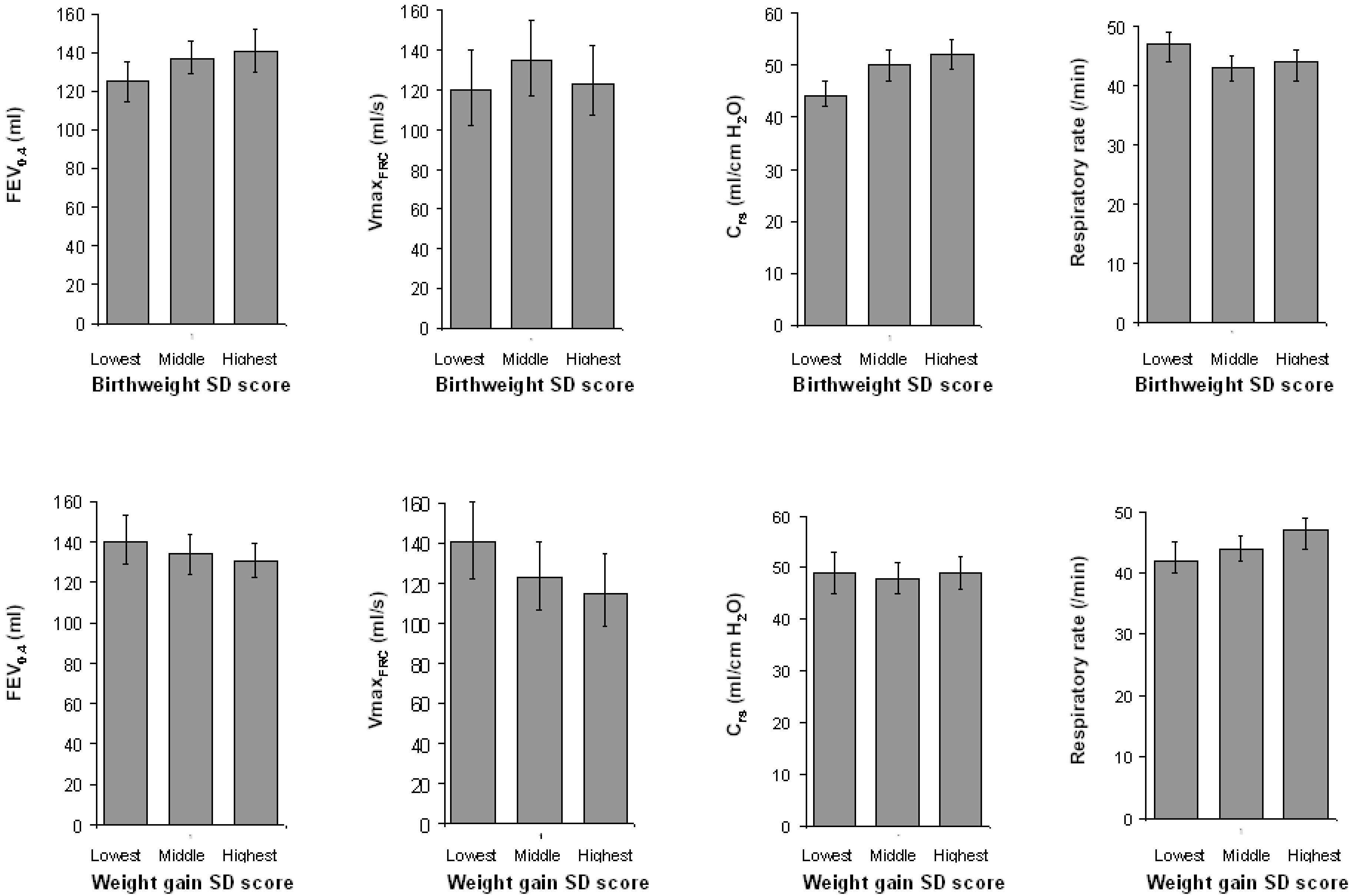

Frequency
Birthweight (kg)
Frequency
Crown-heel length (cm)
Frequency
Head circumference (cm)
Frequency
Gestation (weeks)

Figure E1



FEV$_{0.4}$ (ml)
Vmax$_{FRC}$ (ml/s)
C$_{rs}$ (ml/cm H$_2$O)
Respiratory rate (/min)
Lowest
Middle
Highest
Birthweight SD score
Weight gain SD score

Figure E2