When is birthweight at term (≥37 weeks' gestation) abnormally low? A systematic review and meta-analysis of the prognostic and predictive ability of current birthweight standards for childhood and adult outcomes

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Background Health outcomes throughout the life course have been linked to fetal growth restriction and low birthweight. A variety of measures exist to define low birthweight, with a lack of consensus regarding which predict adverse outcome.

Objectives To evaluate the relationship between birthweight standards and childhood and adult outcomes in term-born infants (≥37 weeks' gestation).

Search strategy MEDLINE (1966–January 2011), EMBASE (1980–January 2011), and the Cochrane Library (2011:1) and MEDION were included.

Selection criteria Studies comprising live term-born infants (gestation ≥37 completed weeks), with weight or other anthropometric measurements recorded at birth along with childhood and adult outcomes.

Data collection and analysis Data were extracted to populate 2 × 2 tables relating birthweight standard with outcome, and meta-analysis was performed where possible.

Main results Fifty-nine articles (2 600 383 individuals) were selected. There was no significant relationship between birthweight <2.5 kg (odds ratio [OR] 0.98, 95% confidence intervals [CI] 0.87–1.10) and composite measure of childhood morbidity. Weight <10th centile on the population nomogram showed a small association (OR 1.49, 95% CI 1.02–2.19) for the same outcome. There was no significant association between either of the above measures and adult morbidity. The relationship between other measures and individual outcomes varied.

Author's conclusions The association between low birthweight, by any definition, and childhood and adult morbidity was inconsistent. None of the current standards of low birthweight was a good predictor of adverse outcome.

Keywords Adult morbidity, childhood morbidity, low birthweight, meta-analysis, systematic review.

Introduction

The 'fetal origins hypothesis' suggests that malnourishment *in utero* changes fetal programming, whereby biological pathways are altered, resulting in increased susceptibility to disease. In 1986 Barker et al.[1] demonstrated an inverse relationship between birthweight and adult cardiovascular disease. Since then, numerous studies have evaluated the association between low birthweight and morbidity and mortality throughout the life course.[2–10] However, the

results have not always been consistent.[11–14] The initial evidence for the Barker hypothesis has been criticised for failing to account for important potential confounders such as gestational age and socio-economic class, and as such is not universally accepted.[15]

A number of methods have been used to define low birthweight and to attempt to identify infants who may be at risk of subsequent adverse outcome, including population-based centile charts, the most commonly used threshold being the 10th centile;[16] customised charts where the mother's BMI and ethnicity are used to calculate individualised growth centiles;[17] and ponderal index, which takes into account the neonatal weight and length.[18,19]

The aim of this systematic review was to re-examine the association between low birthweight and adverse outcomes, avoiding the confounding influence of prematurity, by strictly limiting study inclusion to infants of 37 weeks' gestation or more. The findings of this review have been split into two papers. The first, focusing on neonatal outcomes (mortality and morbidity), has been published separately.[20] Birthweight tests were found to be strongly associated with neonatal mortality and morbidity, especially at lower absolute birthweight threshold. The current report focuses on examining the association between low birthweight at term and morbidity and mortality during childhood and adult life.

Methods

Our methodology has been described in detail using the same data sources, search strategy and methodology as in our previous paper[20] and will not be repeated here. Instead we will highlight differences from the previous paper.

Only studies including morbidity diagnosed subsequent to the neonatal period are included in this report. Where morbidity diagnosed in infancy (<1 year) was included, all conditions are permanent (e.g. cerebral palsy) and are assumed to be present through to childhood in survivors.

Meta-analysis was performed using composite and individual outcome measures. When the composite outcome measure was used, care was taken to ensure that each individual was only counted once in each analysis. Where multiple outcomes were reported, we selected the outcome most consistent with other studies; for example, in the childhood morbidity analysis, hypertension was the most commonly reported outcome therefore this was selected primarily, followed by other components of the metabolic syndrome.

Results

As shown in Supporting Information Figure S1, after an initial search of 36 956 citations, we included 92 primary articles in the overall systematic review, of which 59 contained data relating birthweight standards to childhood or adult outcomes.[5,8,9,12,14,21–74] Twenty of the 59 included were added after contact with authors who provided data or information.[12,21–40] 2 600 383 individuals were included in the analyses reported in this manuscript. Details of the included studies are given in Supporting Information Table S1; a list of excluded studies is available from the authors on request. A total of 145 further articles were felt to contain potentially relevant data but either the authors could not be contacted or could not supply data to create 2 × 2 tables, or on clarification regarding the population the study was excluded. If the population was the same but the measure of growth restriction or adverse outcome differed, both studies were included, but care was taken not to include multiple studies reporting from the same population within a single meta-analysis, or within the overall count of the number of individuals included in the review.[39,40,43,44,48,69]

The majority of studies used a population growth chart <10th percentile ($n = 21$) or birthweight <2.5 kg ($n = 23$) as the index test. A wide variety of outcome measures including mortality and morbidity (e.g. hypertension, diabetes mellitus, learning difficulties, cerebral palsy) were reported. For comparison, we grouped outcomes according to age, that is, childhood and adolescent (12 months to 18 years) and adult (>18 years).

Childhood and adolescent outcomes

A Forest plot for the association of measures of low birthweight with childhood and adolescent outcomes is given in Supporting Information Figure S2. Meta-analysis was performed to assess the association of birthweight <2.5 kg with a composite group of adverse outcomes reported in primary studies (including obesity, hypertension, type 1 diabetes mellitus, asthma, hypercholesterolaemia, learning difficulties and strabismus). There was no significant association present (odds ratio [OR] 0.98, 95% confidence interval [CI] 0.87–1.10). A meta-analysis for birthweight <10th centile on the population chart showed a small association that was just significant (OR 1.49, 95% CI 1.02–2.19); however, there was significant heterogeneity present. When limiting the composite outcome analysis to conditions associated with the metabolic syndrome (obesity, hypertension, hypercholesterolaemia) for birthweight <2.5 kg the association remained non-significant (nine studies OR 0.97, 95% CI 0.84–1.18, $I^2 = 0$) and for the population chart <10th centile the association became non-significant (four studies OR 1.01, 95% CI 0.64–1.58, $I^2 = 54$). When the analysis was restricted to learning difficulties or mental handicap, birthweight <3rd centile on the population chart and <10th centile both showed a weak but significant association. When individual outcomes were

considered, there was no significant association between any measure of low birthweight and childhood obesity, hypertension, asthma, visual impairment or psychiatric diagnosis.

Adult outcomes

A Forest plot of odds ratios for the association of measures of fetal growth restriction and adult outcomes is given in Figure 1. A meta-analysis was performed for the association of birthweight <2.5 kg with a composite measure of adult morbidity (including obesity, hypertension, hypercholesterolaemia, type 2 diabetes mellitus, coronary heart disease, and polycystic ovarian syndrome). There was no significant association between birthweight <2.5 kg or birthweight <10th centile on the population chart with this composite outcome. Limiting the composite outcome analysis to conditions associated with the metabolic syndrome (obesity, hypertension, hypercholesterolaemia, coronary heart disease, type 2 diabetes) did not change the results. When individual

morbidities were considered, birthweight <10th centile according to the population chart was significantly associated with adult obesity in a single study (OR 1.86, 95% CI 1.20–2.88). Birthweight <2.5 kg showed a weak association with hypertension, diabetes mellitus or impaired glucose tolerance and cardiovascular mortality. Ponderal index (kg/m³) <24 was also weakly associated with mortality from cardiovascular disease. Childhood or adulthood end stage renal disease showed a significant association with birthweight <10th centile on the population chart.

Quality assessment

The results for the quality assessment are presented in Table 1. The majority of included studies were of cohort design (88%) and most were retrospective studies (58%). Most studies were of high or moderate quality according to our pre-specified criteria. Studies often failed to describe adequately the test or outcome in a way that would make them reproducible, and very few studies described any
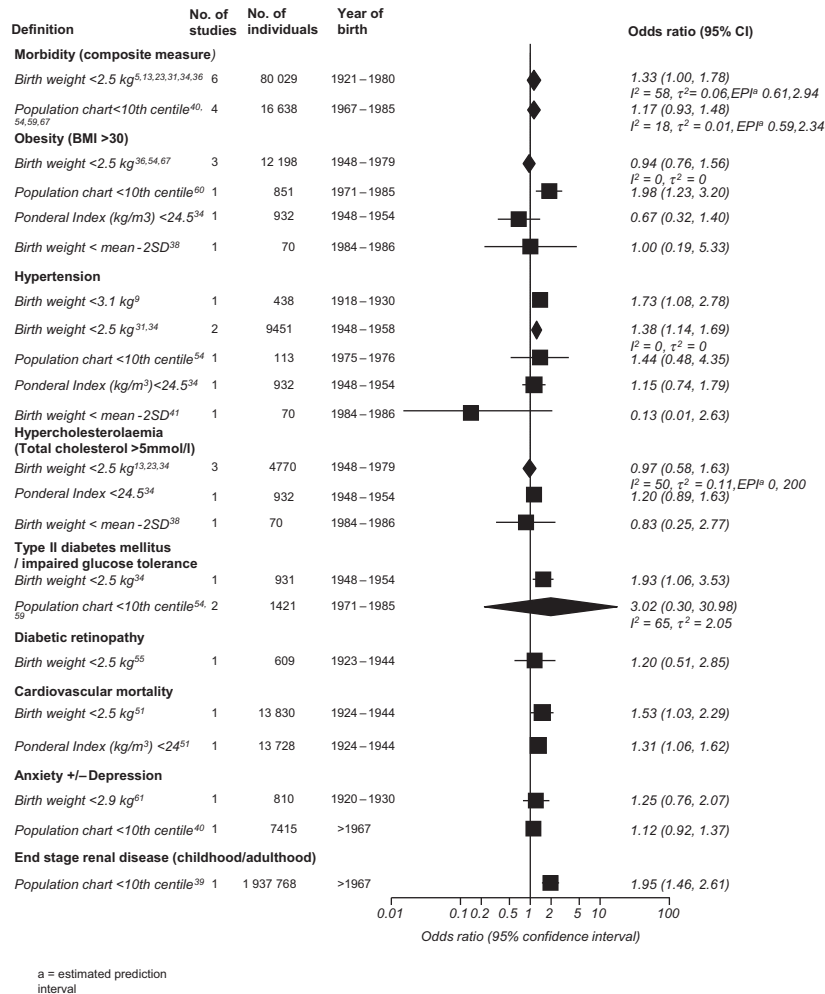

Figure 1. Forest plot of odds ratios for the association between birthweight standards and adult outcomes.

Table 1. Methodological quality of studies included in systematic review of birthweight standards for childhood and adult outcomes

Quality item	No. (%) of studies, *n* = 59		
	Yes	No	Unclear
Cohort study design	52 (88)	7 (12)	0
Population adequately described	59 (100)	0	0
Consecutive recruitment	21 (36)	11 (18)	27 (46)
Prospective recruitment	21 (36)	34 (58)	4 (7)
Appropriate outcome measure	59 (100)	0	0
Outcome measure blinded	10 (17)	1 (2)	48 (81)
>90% of individuals had outcome measure	14 (24)	40 (68)	5 (8)
Index test and outcome measure described	34 (57)	4 (7)	21 (36)
Intervention between index test and outcome	4 (7)	0	55 (93)
Quality classification			
High	28 (46)	–	–
Medium	24 (41)	–	–
Low	8 (13)	–	–

interventions that were performed between the time of the birthweight measurement and the outcome test. Where possible, a subgroup analysis using only high quality studies was performed and the results are presented in Table 2.

Subgroup analyses

The results for subgroup analyses within the meta-analysis groups for each age group and birthweight standard are presented in Table 2. When childhood morbidity was considered, there was no significant association between birthweight <2.5 kg or the population chart <10th centile in any of the subgroups analysed. There was a significant association between birthweight <2.5 kg and adult morbidity when high-quality studies were considered (OR 1.39, 95% CI 1.14–1.69); however, only two studies were included in this analysis.

Predictive ability of standards of low birthweight to predict childhood and adult outcomes

Only two measures of low birthweight met our pre-specified criteria for calculation of predictive values for childhood morbidity. Customised chart <1st centile had a high specificity (0.99; 95% CI 0.97–1.00) but poor sensitivity (0.06; 95% CI 0.04–0.11) for childhood cerebral palsy.[49] A customised chart <5th centile had a specificity of 0.90 (95% CI 0.87–0.93) and a sensitivity of 0.25 (95% CI 0.19–0.31) for the same outcome.[49] The positive likelihood ratio was 5.6 (95% CI 2.04–15.34) for <1st centile and 2.57 (95% CI 1.78–3.72) for <5th centile. The corresponding negative likelihood ratios were 0.95 (95% CI 0.91–0.98) and 0.83 (95% CI 0.77–0.90).

Birthweight as a continuous variable

Seven papers reported regression analysis using birthweight as a continuous outcome.[9,12–14,26,28,47] These studies looked at adult hypertension (age 50 and 60 years) and hypercholesterolaemia, childhood obesity and hypertension, and composite childhood metabolic risk index. Only one found a significant association. Andersson et al.[9] performed logistic regression to examine the association between birthweight and hypertension (defined as treatment for hypertension and/or systolic BP ≥160 mmHg and/or diastolic BP >95 mmHg). At age 60, the OR was 0.96 (95%

Table 2. Subgroup analysis according to birthweight standard and outcome, where possible, for study quality, ethnicity, year of birth of study population and singleton population

Birthweight standard	No. of studies	Subgroup	Odds ratio (95% CI)	Estimated prediction interval (EPI)	I^2, τ^2
Childhood morbidity					
Birthweight <2.5 kg	5[12,22,24,25,28]	Singleton	0.95 (0.63–1.44)	–	$I^2 = 0$, $\tau^2 = 0$
Birthweight <2.5 kg	5[23,25,28,32,33]	High quality studies	0.82 (0.63–1.07)	–	$I^2 = 0$, $\tau^2 = 0$
Birthweight <2.5 kg	7[12,24,25,26,28,32,33]	Ethnicity >90% White European	0.99 (0.68–1.44)	–	$I^2 = 0$, $\tau^2 = 0$
Population chart <10th centile	4[8,22,63,74]	Singleton	1.35 (0.82–2.24)	0.15–12.24	$I^2 = 90$, $\tau^2 = 0.20$
Population chart <10th centile	8[22,30,45,56,62,63,66,74]	High quality studies	1.65 (0.96–2.83)	0.31–8.86	$I^2 = 89$, $\tau^2 = 0.40$
Population chart <10th centile	2[22,30]	Year of birth ≥1990	0.67 (0.35–1.31)	–	$I^2 = 76$, $\tau^2 = 0.19$
Population chart <10th centile	3[58,63,73]	Ethnicity White European	1.67 (1.40–1.98)	–	$I^2 = 0$, $\tau^2 = 0$
Adult morbidity					
Birthweight <2.5 kg	4[5,23,31,36]	Singleton	1.41 (0.80–2.47)	0.14, 13.82	$I^2 = 70$, $\tau^2 = 0.20$
Birthweight <2.5 kg	2[31,34]	High-quality studies	1.39 (1.14–1.69)	–	$I^2 = 0$, $\tau^2 = 0$

CI 0.92–0.99, $P = 0.028$ for change in risk of hypertension per 100 g birthweight).

Direct comparison of absolute versus population centiles

Only one study compared two birthweight standards in the same population. For type 1 diabetes in childhood, birthweight <2.5 kg had an OR of 0.68 (95% CI 0.22–2.12), and a population chart <10th centile an OR of 0.46 (95% CI 0.26–0.82).[22]

Publication bias

The Peters test was performed where there were ten or more studies included in the meta-analysis (population <10th centile and childhood morbidity and birthweight <2.5 kg for the same outcome). There was no statistically significant small study effect in either of the groups analysed (P-value 0.326–0.996).

Discussion

Main findings

For outcomes in childhood, there was a significant association between birthweight <10th centile according to population chart and a composite measure of morbidity. However, when this analysis was restricted to a singleton population, or for metabolic outcomes, it became non-significant. When individual measures were considered, there was no significant association between any measure of low birthweight and childhood obesity, hypertension or asthma. For adult outcomes, there was no consistent association seen between birthweight standards and adult health, although individual studies showed a weak association between birthweight <2.5 kg and hypertension, cardiovascular mortality and diabetes. The predictive ability of customised centile charts (<1st centile and <10th centile) for childhood cerebral palsy was calculated. The likelihood ratios indicated that both were poor tests.[75]

Our analysis for the relationship between birthweight standards and neonatal outcomes has already been published.[20]

Strengths and limitations

This review provides the best available evidence, at the time of writing, regarding the association between different measures of low birthweight at term and adverse outcomes. No other review has attempted to compare different definitions of low birthweight to inform clinical practice. The strength of our review and the validity of our inferences lie in the methodology used. We have complied with existing guidelines for the reporting of systematic reviews of diagnostic and observational studies.[76,77] We have used the most up-to-date techniques for performing and interpreting meta-analysis.[78–80] Every effort was made to obtain the most complete data set possible through contact with authors and experts in the field.

There are several limitations to our review. Although every effort was made to control for potential confounding factors through subgroup analysis, due to the quality and reporting of the primary studies this was not always possible. We strictly limited our review to infants born at 37 weeks' gestation or more; however, the method of estimating gestation in the primary studies was often inaccurate. Very few studies used ultrasound measurement of crown–rump length at 10–13 weeks' gestation, which is the most accurate method.[81] Due to poor reporting in the primary studies, our ability to perform subgroup analysis according to ethnicity was limited. Although our results did not differ much when limited to a White European population, it is known that Black African or Caribbean and Asian populations have smaller babies, and therefore it is likely that the same thresholds would not give the same results in all ethnic backgrounds.[82] We did not analyse according to social class; however, previous epidemiological studies that have accounted for this have found that the association between birthweight and cardiovascular risk factors persisted across social groups, suggesting that known and unknown confounding variables do not affect this relationship.[83]

Comparing different standards of birthweight through analyses using different populations may not give a true result. However, no studies reported more than two standards in the same population, and only one study compared absolute birthweight and population centile charts, in which neither showed a significant association, limiting our ability to deal with this issue. Unfortunately, no meta-analysis was possible for certain birthweight standards or outcomes, for example, the ponderal index, or customised centile charts.

With regard to the outcomes examined, we recognise that our age categories were very broad and that the risks and severity of the conditions differ across the life course. However, due to the nature of the reporting in the primary studies it was not possible to examine this further with the data available. We did not restrict the outcomes included, but we found that some health outcomes, such as cancer, were poorly represented in the included studies. However, we are confident that our searches were robust and that nothing further could have been done to address this.

Interpretation

There is a vast literature exploring the relationship between low birthweight and adverse outcomes, using different methodologies to do so. Other systematic reviews performed in this field using birthweight as a continuous variable have shown mixed results. Owen et al.[35] examined the association between birthweight and blood cholesterol level, and found a weak association; however, this analysis did

not exclude pre-term infants. Huxley et al.[2] found an inverse association between birthweight and systolic blood pressure in children, adolescents and adults, but again did not exclude pre-term infants from the analysis. Whincup et al. found mixed results in the relationship between type II diabetes mellitus and birthweight. Nine of 31 studies included in their systematic review showed a significant inverse relationship between birthweight and this outcome but again, prematurity was not excluded.[84]

The original literature published in support of the Barker hypothesis has been criticised for failing to control for potential confounding factors within their analysis, including prematurity.[15] We have made every effort to consider these, and the findings with regard to childhood and adult health outcomes linked with the metabolic syndrome have been inconsistent. Where a composite outcome was used, no significant association with childhood or adult morbidity was seen. No significant association was present for childhood diabetes, hypertension or obesity. Weak associations were seen between birthweight and adult hypertension, diabetes and cardiovascular mortality, but the results are based on one or two studies.

While low birthweight is significantly associated with neonatal mortality and morbidity,[20] the associations between all measures of low birthweight assessed and childhood and adult health outcomes were inconsistent. Where a significant association was present, no single measure of low birthweight appeared superior to the others examined to recommend their use, and for the two standards where sensitivity, specificity and likelihood ratios were calculated, the predictive value was low. This highlights that current birthweight standards are poor predictors of adverse childhood and adult outcomes. Considering childhood cerebral palsy as an example: the prevalence of this condition is 1–2.4 per 1000 in children born at or near term.[85] Using the positive likelihood ratio 5.6 (for birthweight on customized chart <1st centile to predict this outcome), the odds of a baby with a birthweight under this centile developing cerebral palsy are $0.0024 \times 5.6 = 0.013$, that is, 1%. The negative likelihood ratio is 0.95, therefore being born above this centile does not significantly change the risk in comparison with the background prevalence.

Future research is necessary to identify a birthweight standard which can predict adverse health outcomes. First, it is important to compare the different standards across the same population to enable an unbiased comparison, and to further explore the standards which were less frequently reported. This could be performed through individual patient data meta-analysis, where multiple definitions of fetal growth restriction could be compared across the same population, and factors such as ethnicity more adequately assessed.[86] Another option would be to perform further analysis on the large Scandinavian birth registries, which record a variety of birth anthropometry that can be linked to health outcomes.[87] If a standard with high predictive ability is not identified, then birthweight in combination with other factors should be explored to predict adverse outcome in clinical practice. Future research in this field should consider and adequately report potential confounding factors, including prematurity. The importance of improving the quality of prognosis research has recently been highlighted.[88]

Conclusion

None of the current definitions of low birthweight has a good enough predictive ability for adverse outcome to recommend their superiority in clinical practice. Although the association between low birthweight and neonatal mortality is strong, the association between low birthweight and childhood and adult morbidity is inconsistent. Further research, as outlined above, is required to identify the optimum definition of low birthweight that can predict adverse outcomes.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Characteristics of studies included in systematic review of low birthweight standards and childhood and adult outcomes.

Figure S1. Study selection process for systematic review of the prognostic and predictive ability of current birthweight standards for short and long term outcomes.

Figure S2. Forest plot of odds ratios for the association between birthweight standards and childhood outcomes. ■

References

1 Barker DJ, Osmond C. Infant mortality, childhood nutrition and ischaemic heart disease in England and Wales. *Lancet* 1986;1:1077–81.

2 Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *J Hypertens* 2000;18:815–31.

3 Leon DA, Lithell HO, Vagero D, Koupilova I, Mohsen R, Berglund L, et al. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915–29. *BMJ* 1998;317:241–5.

4 Martyn CN, Barker DJP, Osmond C. Mothers' pelvic size, fetal growth, and death from stroke and coronary heart disease in men in the UK. *Lancet* 1996;348:1264–8.

5 Rich-Edwards J, Stampfer MJ, Manson J, Rosner B, Hankinson SE, Colditz GA, et al. Birthweight and risk of cardiovascular disease in a cohort of women followed up since 1976. *BMJ* 1997;315:396.

6 Law CM, Shiell AW. Is blood pressure inversely related to birthweight? The strength of evidence from a systematic review of the literature. *J Hypertens* 1996;14:935–41.

7 Nobili VA. Low birthweight and catch-up-growth associated with metabolic syndrome: a ten year systematic review. *Pediatr Endocrinol Rev* 2008;6:241–7.

8 Jelliffe-Pawlowski LLH. Neurodevelopmental outcome at 8 months and 4 years among infants born full-term small-for-gestational-age. *J Perinatol* 2004;24:505–14.

9 Andersson SWL. Blood pressure and hypertension in middle-aged women in relation to weight and length at birth: a follow-up study. *J Hypertens* 2000;18:1753–61.

10 Da Silveira VMF, Horta BL. Birthweight and metabolic syndrome in adults: meta-analysis. *Rev Saude Publica* 2008;42:10–8.

11 Newsome CA, Shiell AW, Fall CH, Phillips DI, Shier R, Law CM, et al. Is birthweight related to later glucose and insulin metabolism? A systematic review *Diabet Med* 2003;20:339–48.

12 Catalano PM, Farrell K, Thomas A, Huston-Presley L, Mencin P, de Mouzon SH, et al. Perinatal risk factors for childhood obesity and metabolic dysregulation. *Am J Clin Nutr* 2009;90:1303–13.

13 Libby G, McEwan SR, Morris AD, Belch JJF. No difference in the association between birthweight and total cholesterol for males and females. A SHARP (Scottish Heart and Arterial Disease Risk Prevention) study. *Vasc Med* 2008;13:271–4.

14 Libby GM. Birthweight does not predict blood pressure in a young working population: a SHARP (Scottish Heart and Arterial Disease Risk Prevention) Study. *Ann Epidemiol* 2008;18:298–301.

15 Wilson J. The Barker hypothesis – an analysis. *Aust N Z J Obstet Gynaecol* 1999;39:1–7.

16 Ferdynus C, Quantin C, Abrahamowicz M, Platt R, Burguet A, Sagot P, et al. Can birthweight standards based on healthy populations improve the identification of small-for-gestational-age newborns at risk of adverse neonatal outcomes? *Pediatrics* 2009;123:723–30.

17 Gardosi J. Intrauterine growth restriction: new standards for assessing adverse outcome. *Best Pract Res Clin Obstet Gynaecol* 2009;23:741–9.

18 Walther FJ, Ramaekers LH. The ponderal index as a measure of the nutritional status at birth and its relation to some aspects of neonatal morbidity. *J Perinat Med* 1982;10:42–7.

19 Botero D, Lifshitz F. Intrauterine growth retardation and long-term effects on growth. *Curr Opin Pediatr* 1999;11:340–7.

20 Malin GL, Morris RK, Riley RD, Teune M, Khan KS. When is birthweight at term abnormally low? A systematic review and meta-analysis of the association and predictive ability of current birthweight standards for neonatal outcomes. *BJOG* 2014;121:515–26.

21 Lamb MM, Dabelea D, Yin X, Ogden LG, Klingensmith GJ, Rewers M, et al. Early-life predictors of higher body mass index in healthy children. *Ann Nutr Metab* 2010;56:16–22.

22 Algert CS, McElduff A, Morris JM, Roberts CL. Perinatal risk factors for early onset of Type 1 diabetes in a 2000–2005 birth cohort. *Diabet Med* 2009;26:1193–7.

23 Amigo H, Bustos P, Alvarado ME, Barbieri M, Bettiol H, da Silva AAM, et al. Size at birth and lipoprotein concentrations in adulthood: two prospective studies in Latin American cities. *J Epidemiol Community Health* 2010;64:855–9.

24 Burke V, Beilin LJ, Blake KV, Doherty D, Kendall GE, Newnham JP, et al. Indicators of fetal growth do not independently predict blood pressure in 8-year-old Australians – a prospective cohort study. *Hypertension* 2004;43:208–13.

25 Cornelius MD, Goldschmidt L, Willford JA, Leech SL, Larkby C, Day NL. Body Size and Intelligence in 6-year-olds: are offspring of teenage mothers at risk? *Matern Child Health J* 2009;13:847–56.

26 Gardner DS, Hosking J, Metcalf BS, Jeffery AN, Voss LD, Wilkin TJ. Contribution of early weight gain to childhood overweight and metabolic health: a longitudinal study (EarlyBird 36). *Pediatrics* 2009;123:e67–73.

27 Hands B, Kendall G, Larkin D, Parker H. Perinatal risk factors for mild motor disability. *Intl J Disabil Dev Educ* 2009;56:317–31.

28 Hindmarsh PC, Bryan S, Geary MPP, Cole TJ. Effects of current size, postnatal growth, and birth size on blood pressure in early childhood. *Pediatrics* 2010;126:e1507–13.

29 Kindlund K, Thomsen SF, Stensballe LG, Skytthe A, Kyvik KO, Backer V, et al. Birthweight and risk of asthma in 3–9-year-old twins: exploring the fetal origins hypothesis. *Thorax* 2010;65:146–9.

30 Kuhle S, Allen AC, Veugelers PJ. Perinatal and childhood risk factors for overweight in a provincial sample of Canadian Grade 5 students. *Int J Pediatr Obes* 2010;5:88–96.

31 Li L, Law C, Power C. Body mass index throughout the life-course and blood pressure in mid-adult life: a birth cohort study. *J Hypertens* 2007;25:1215–23.

32 McKinney PA, Parslow R, Gurney KA, Law GR, Bodansky HJ, Williams R. Perinatal and neonatal determinants of childhood type 1 diabetes: a case-control study in Yorkshire, U.K. *Diabetes Care* 1999;22:928–32.

33 Menezes AMB, Hallal PC, Horta BL, Araujo CLP, Vieira MD, Neutzling M, et al. Size at birth and blood pressure in early adolescence: a prospective birth cohort study. *Am J Epidemiol* 2007;165:611–6.

34 Mi JC, Cheng H, Zhao X-Y, Hou D-Q, Chen F-F, Zhang K-L. Developmental origin of metabolic syndrome: interaction of thinness at birth and overweight during adult life in Chinese population. *Obes Rev* 2008;9 (Suppl 1):91–4.

35 Owen CG, Whincup PH, Odoki K, Gilg JA, Cook DG. Birthweight and blood cholesterol level: a study in adolescents and systematic review. *Pediatrics* 2003;111:1081–9.

36 Pandolfi C, Zugaro A, Lattanzio F, Necozione S, Barbonetti A, Colangeli MS. Low birthweight and later development of insulin resistance and biochemincal/clinical features of polycystic ovarian syndrome. *Metab, Clin Exp* 2008;57:999–1004.

37 Pearce MS, O'Sullivan JJ. Relationship between birthweight and blood pressure variability in children. *J Hum Hypertens* 2003;17:677–80.

38 Salonen MK. Tracking serum lipid levels and the association of cholesterol conceentrations, blood pressure and cigarette smoking with carotid artery intima-media thickness in young adults born small for gestational age. *Circ J* 2010;74:2419–25.

39 Vikse BE, Irgens LM, Leivestad T, Hallan S, Iversen BM. Low birthweight increases risk for end-stage renal disease. *J Am Soc Nephrol* 2008;19:151–7.

40 Berle JO, Mykletun A, Daltveit AK, Rasmussen S, Dahl AA. Outcomes in adulthood for children with foetal growth retardation. A linkage study from the Nord-Trondelag Health Study (HUNT) and the Medical Birth Registry of Norway. *Acta Psychiatr Scand* 2006;113:501–9.

41 Bilge I, Poyrazoglu S, Bas F, Emre S, Sirin A, Gokalp S, et al. Ambulatory blood pressure monitoring and renal functions in term small-for-gestational age children. *Pediatr Nephrol* 2011;26:119–26.

42 Chaudhari S, Kulkarni S, Barve S, Pandit AN, Sonak U, Sarpotdar N, et al. Neurologic sequelae in high risk infants – a three year follow up. *Indian Pediatr* 1996;33:645–53.

43 Evensen KA, Vik T, Helbostad J, Indredavik MS, Kulseng S, Brubakk AM, et al. Motor skills in adolescents with low birthweight. *Arch Dis Child Fetal Neonatal Ed* 2004;89:F451–5.

44 Evensen KA, Lindqvist S, Indredavik MS, Skranes J, Brubakk AM, Vik T, et al. Do visual impairments affect risk of motor problems in preterm and term low birthweight adolescents? *Eur J Paediatr Neurol* 2009;13:47–56.

45 Evensen KAI, Steinshamn S, Tjonna AE, Stolen T, Hoydal MA, Wisloff U, et al. Effects of preterm birth and fetal growth retardation on cardiovascular risk factors in young adulthood. *Early Hum Dev* 2009;85:239–45.

46 Fitzhardinge PM, Steven EM. The small-for-date infant. II. Neurological and intellectual sequelae II. Neurological and intellectual sequelae. *Pediatrics* 1972;50:50–7.

47 Hemachandra AHK. The association between intrauterine growth restriction in the full-term infant and high blood pressure at age 7 years: results from the Collaborative Perinatal Project. *Int J Epidemiol* 2006;35:871–7.

48 Indredavik MS, Vik T, Evensen KAI, Skranes J, Taraldsen G, Brubakk AM. perinatal risk and psychiatric outcome in adolescents born preterm with very low birthweight or term small for gestational age. *J Dev Behav Pediatr* 2010;31:286–94.

49 Jacobsson BA. Cerebral palsy and restricted growth status at birth: population-based case-control study. *BJOG* 2008;115:1250–5.

50 Johnson CC. Nueroblastoma: case control analysis of birth characteristics. *J Natl Cancer Inst* 1985;74:789–92.

51 Kajantie E, Osmond C, Barker DJP, Forsen T, Phillips DIW, Eriksson JG. Size at birth as a predictor of mortality in adulthood: a follow-up of 350 000 person-years. *Int J Epidemiol* 2005;34:655–63.

52 Kotecha SJ, Watkins WJ, Heron J, Henderson J, Dunstan FD, Kotecha S. spirometric lung function in school-age children: effect of intrauterine growth retardation and catch-up growth. *Am J Respir Crit Care Med* 2010;181:969–74.

53 Larroque B. School difficulties in 20 year olds who were born small for gestational age at term in a regional cohort study. *Pediatrics* 2001;108:111–5.

54 Levitt NSL. Impaired glucose tolerance and elevated blood pressure in low birth rate weight, nonobese, young South African adults: early programming of cortisol axis. *J Clin Endocrinol Metab* 2000;85:4611–8.

55 Liew G, Wang JJ, Klein R, Duncan BB, Yeh HC, Brancati FL, et al. Birthweight is not related to risk of diabetic retinopathy in type 2 diabetes: the atherosclerosis risk in communities study. *Curr Eye Res* 2008;33:193–8.

56 Low JA, Handley-Derry MH, Burke SO, Peters RD, Pater EA, Killen HL, et al. Association of intrauterine fetal growth retardation and learning deficits at age 9 to 11 years. *Am J Obstet Gynecol* 1992;167:1499–505.

57 Low JA, Galbraith RS, Muir D, Killen H, Pater B, Karchmar J, et al. Intrauterine growth retardation: a study of long-term morbidity. *Am J Obstet Gynecol* 1982;142:670–7.

58 Lurbe E, Carvajal E, Torro I, Aguilar F, Alvarez J, Redon J. Influence of concurrent obesity and low birthweight on blood pressure phenotype in youth. *Hypertension* 2009;53:912–7.

59 Meas T, Deghmoun S, Alberti C, Carreira E, Armoogum P, Chevenne D, et al. Independent effects of weight gain and fetal programming on metabolic complications in adults born small for gestational age. *Diabetologia* 2010;53:907–13.

60 Meas T, Deghmoun S, Armoogum P, Alberti C, Levy-Marchal C. Consequences of being born small for gestational age on body composition: an 8-year follow-up study. *J Clin Endocrinol Metab* 2008;93:3804–9.

61 Nelson KB, Broman SH. Perinatal risk factors in children with serious motor and mental handicaps. *Ann Neurol* 1977;2:371–7.

62 Nobili VM, Marcelli M, Marchesini G, Vanni E, Manco M, Villani A, et al. Intrauterine growth retardation, insulin resistance, and nonalcoholic fatty liver disease in children. *Diabetes Care* 2007;30:2638–40.

63 O'Keeffe MJ, O'Callaghan M, Williams GM, Najman JM, Bor W, O'Keeffe MJ, et al. Learning, cognitive, and attentional problems in adolescents born small for gestational age. *Pediatrics* 2003;112:301–7.

64 Pathai S, Cumberland PM, Rahi JS. Prevalence of and early-life influences on childhood strabismus findings from the Millennium Cohort Study. *Arch Pediatr Adolesc Med* 2010;164:250–7.

65 Paz I, Gale R, Laor A, Danon YL, Stevenson DK, Seidman DS. The cognitive outcome of full-term small for gestational age infants at late adolescence. *Obstet Gynecol* 1995;85:452–6.

66 Peng Y. Outcome of low birthweight in China: a 16 year longitudinal study. *Acta Paediatr* 2005;94:843–9.

67 Plante LA. Small size at birth and later diabetic pregnancy. *Obstet Gynecol* 1998;92:781–4.

68 Rahiala E, Tenhola S, Vanninen E. Ambulatory blood pressure in 12 year old children born small for gestational age. *Hypertension* 2002;39:909–13.

69 Sommerfelt KA, Andersson HW, Sonnander K, Ahlsten G, Ellersten B, Markestad T, et al. Behavior in term, small for gestational age preschoolers. *Early Hum Dev* 2001;65:107–21.

70 Strauss RS. Adult functional outcome of those born small for gestational age: twenty-six year follow up of the 1970 British birth cohort. *JAMA* 2000;283:625–32.

71 Thompson C, Syddall H, Rodin I, Osmond C, Barker DJP. Birthweight and the risk of depressive disorder in late life. *Br J Psychiatry* 2001;179:450–5.

72 Uvebrant P, Hagberg G. Intrauterine growth in children with cerebral palsy. *Acta Paediatr* 1992;81:407–12.

73 Walther FJ, Ramaekers LH. Language development at the age of 3 years of infants malnourished in utero. *Neuropediatrics* 1982;13:77–81.

74 Wei JN, Li HY, Chang CH, Sung FC, Li CY, Lin CC, et al. Birthweight and type 1 diabetes among schoolchildren in Taiwan – a population-based case-controlled study. *Diabetes Res Clin Pract* 2006;74:309–15.

75 Deeks JJ, Altman DJ. Diagnostic tests 4. Likelihood ratios. *BMJ* 2004;329:168–9.

76 Khan KS, Dinnes J, Kleijnen J. Systematic reviews to evaluate diagnostic tests. *Eur J Obstet Gynecol Reprod Biol* 2001;95:6–11.

77 Stroup FD, Berlin JA, Morton SC, Olkin I, Williamson D, Drummond R, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA* 2000;283:2008–12.

78 Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005;58:982–90.

79 Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. London: The Cochrane Collaboration, 2008.

80 Macaskill P, Gatsonis C, Deeks J, Harbord RM, Takwoingi Y. Analysing and presenting results. In: Deeks J, Bossuyt P, Gatsonis C, editors. *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy, Version 1.0*. London: The Cochrane Collaboration; 2010. [http://srdta.cochrane.org/]. Accessed 20 October 2014.

81 NCC-WCH. *Antenatal Care: Routine Care for the Healthy Pregnant Woman*, 2nd edn. 2008 [http://guidance.nice.org.uk/CG62/NICEGuidance/pdf/English]. Accessed 3 February 2014.

82 Gardosi J. Ethnic differences in fetal growth. *Ultrasound Obstet Gynecol* 1995;6:73–4.

83 Phillips DIW. Birthweight and adulthood disease and the controversies. *Fetal Matern Med Rev* 2006;17:205–27.

84 Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa SK, et al. Birthweight and risk of type 2 diabetes: a systematic review. *JAMA* 2008;300:2886–97.

85 Nelson KB. The epidemiology of cerebral palsy in term infants. *Ment Retard Dev Disabil Res Rev* 2002;8:146–50.

86 Khan KS, Bachmann LM, ter Riet G. Systematic reviews with individual patient data meta-analysis to evaluate diagnostic tests. *Eur J Obstet Gynecol Reprod Biol* 2003;108:121–5.

87 Knudsen LB, Olsen J. The Danish medical birth registry. *Dan Med Bull* 1998;45:320–3.

88 Riley RD, Hayden JA, Steyerberg EW, Moons KGM, Abrams K, Kyzas PA, et al. Prognostic research strategy (PROGRESS) 2: prognostic factor research. *PLoS Med* 2013;10:e1001380.

Chance or destiny?

STEVEN S WITKIN, WILLIAM J. LEDGER DISTINGUISHED PROFESSOR, USA

BJOG PERSPECTIVES

BJOG INSPIRED

In the early 1980s I was a young assistant professor of immunology at the Sloan Kettering Institute for Cancer Research in New York City. My research focused primarily on looking for evidence of retroviruses in breast cancer, and examining whether exposure to semen altered immunity and susceptibility to cervical and prostate cancer. The director of Sloan Kettering was the prominent immunologist, Robert A. Good, and he forcefully transmitted to anyone within earshot the underlying role of immunology in disease. Unexpectedly and suddenly, Dr Good was fired. It very soon became clear that anyone associated with him was also no longer welcome. Dr Good was relocating to a cancer institute in Oklahoma and he asked me to join him there; however, I felt that it was best for me and for my young family to remain in New York. Through my semen studies I had developed an association with J Michael Bedford, a leading reproductive biologist. Dr Bedford was a professor in the Department of Obstetrics and Gynecology at Cornell Medical College, located just across the street from Sloan Kettering. Luckily, he had an opening in his lab and so I became an assistant professor of obstetrics and gynaecology. My first years in the Bedford lab involved studying mechanisms of immune-mediated infertility and determining why some women developed antisperm antibodies.

The chairman of the department was William J Ledger, considered by many to be the father of modern infectious disease in obstetrics and gynaecology. Dr Ledger was a founding member of the Infectious Diseases Society for Obstetrics and Gynaecology, and he encouraged me to attend their annual meetings. At that time, most of the presentations involved comparing the efficacy of two different antibiotics on various gynaecological infections, and were not very stimulating to me and also to Dr Ledger. He had the foresight to propose that immunological studies on women with infections could provide new insights into disease mechanisms and lead to novel treatments. He established what I believe was the first division of immunology in a US obstetrics and gynaecology department, and asked me to run the laboratory. I began to work closely with Dr Ledger, and under his extraordinary guidance and encouragement I began my education in obstetrics and gynaecology and to study the role of immunology, first in gynaecological infections and later in non-infectious disorders affecting pregnant and non-pregnant women.

Now more than 30 years later, I am the William J Ledger distinguished professor of infection and immunology in obstetrics and gynaecology. I have trained numerous fellows from all over the world in obstetrics and gynaecology immunology, and many have made significant contributions in this area of investigation. If Dr Good had not been deposed and Dr Ledger had not seen the potential of immunology for obstetrics and gynaecology, my future would have been very different and none of the contributions from my laboratory would have seen the light of day. Was my career path just chance or destiny?

Disclosure of interests
No conflicts of interest to disclose. ∎