to stop doing something else); so if they do not work, we should not waste resources on them. But it can be an uphill struggle to do rigorous evaluations of interventions that relate to parenting because they carry a veneer of being "obviously" good. We all want to be better parents, and we all want parenting to be better—for paediatricians, it is almost an article of faith. However, even though there is good evidence that some parenting programmes seem to work does not mean that every parenting programme will be effective. Each has to be evaluated on its merits.

So to the methodology. Glazebrook *et al* used a cluster-randomisation technique, a crossover design, pairing of units to account for socioeconomic variation, and two demographically different regions of the UK (Trent and the South West). This allowed them to maximise power,

minimise cross-contamination between groups, allow for deprivation and generalise the findings. Trials of this kind require a huge investment of time and money, but the pay-off for the National Health Service is even bigger, given that no unit could now plausibly make a bid to introduce PBIP in its hospital. Indeed it should also have the effect of increasing the care with which any other proposed parenting programme should be scrutinised before introducing it. We have to wonder whether the other trials in the Cochrane review were as well designed as this. If they had been, would the meta-analyses have come up with such unequivocal positive findings?

When a study that is as well designed and powerful as this one fails to show any effect of the intervention, it is important to look critically again at other studies that purport to show benefits of

analogous interventions. Above all, what this study adds to the literature is that every parenting intervention programme should be evaluated with the same rigour. Glazebrook *et al* have set the standard to which others must aspire.

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SGA and SIDS: causality or association

Small for gestational age infants and sudden infant death syndrome: a confluence of complex conditions

Carl E Hunt

Perspective on the paper by Malloy (see page 473)

"All illnesses have some hereditary contribution. Genetics loads the gun and environment pulls the trigger" (Francis Collins, Director, National Human Genome Research Institute, National Institutes of Health, 2006)

New data by Malloy¹ further substantiate fetal growth restriction or being small for gestational age (SGA) as a risk factor for sudden infant death syndrome (SIDS). The similar odds ratios for sudden unexpected death in infancy (SUDI) excluding SIDS and for SIDS may reflect at least in part diagnostic shifts based on custom and preference of the medical examiner in classifying infant deaths consistent with SIDS not as SIDS but rather as, for example, "accidental suffocation" or "other ill-defined and unspecified causes". These new confirmatory data are important, but they provide no new insights regarding potential causal mechanisms for this association between SGA and SIDS. Does being SGA directly increase the risk for SIDS, or is this an

indirect association because of an underlying causal biological or environmental risk factor common to both conditions?

Low birth weight is defined as a birth weight <2500 g and can be due to prematurity (<38 weeks' postmenstrual age) and/or to fetal growth restriction (SGA). SGA, typically defined as a birth weight <10th percentile for gestational age, can be due to a variety of pathophysiological conditions or diseases.² The growth restriction in SGA infants can be either symmetrical (weight, length and brain size affected) or asymmetrical (brain growth preserved), the former often associated with factors intrinsic to the fetus and the latter often associated with external factors. In addition to chromosomal anomalies and other syndromic conditions, symmetrical SGA can also be caused by intrauterine infection (toxoplasmosis, rubella, cytomegalovirus and herpes infections), inborn errors of metabolism and fetal drug (or toxin) exposure, such as to alcohol, cigarette smoke and drugs of misuse (eg, cocaine or opiates). Of note, all of these

exposures causally linked to SGA are also risk factors for SIDS whether SGA or not³ (table 1). Asymmetrical SGA typically has its onset in the second and third trimesters, when fetal nutrition increasingly contributes to energy storage. SGA infants are more likely to have problems with perinatal asphyxia or other perinatal disturbances, and are at increased risk for long-term deficits in growth, neurodevelopmental handicaps, and higher rates of early infant mortality in addition to SIDS.^{2–3} Immunological function in SGA infants may be depressed at birth and can persist at least into childhood.

Table 1 Shared maternal characteristics and fetal exposures, and putative genetic causal mechanisms shared by sudden infant death syndrome (SIDS) and low birthweight infants*

	SGA Preterm	
Maternal characteristics		
Including inadequate prenatal care, low socioeconomic status, race/ethnicity, young age, unmarried, increased parity	+	+
Fetal exposures		
Alcohol and cigarette smoke	+	+
Drugs of misuse, including cocaine and opiates	+	+
Genetic polymorphisms		
Infection and inflammation		
Interleukin-6	+	+
Interleukin-10	+	+
Glucokinase	+	

SGA, small for gestational age.
+ Characteristic shared with SIDS.
*See text for references.

Many of the maternal conditions associated with low birth weight are common both to SGA (whether term or preterm) and to appropriate for gestational age (AGA) preterm infants^{3,4} (table 1). These factors include low maternal prepregnancy weight, prior preterm delivery, fetal exposure to cigarette smoke, indirect effects of very young or advanced maternal age, lower maternal socioeconomic status and multiple gestation. Although not readily discernible from the epidemiological studies of SIDS infants, SGA can co-occur with prematurity, and SGA incidence progressively increases as gestational age decreases. Compared with a 10% risk for being SGA in infants born at 38–42 weeks' gestation, for example, 30–40% of infants born at <28–30 weeks' gestation are SGA.⁵

Fetal growth is regulated by maternal, placental and fetal factors representing interactions between genetic mechanisms and environmental influences through which genetic growth potential is expressed and modulated.^{2,6} Many genes contribute to fetal growth. Although genetic factors are estimated to account for up to half of the risk for SGA with the balance determined by environmental factors, the extent to which SGA is due to gene–environment interactions rather than genetic or environmental causes is unclear.⁶ Fetal genes are estimated to account for about 80% of the genetic risk for SGA. Maternal genotype is more important than fetal genotype in overall normal regulation of fetal growth, but paternal genotype is also important.²

The size of the placenta and placental nutrient transport functions are also important regulators of nutrient supply to the fetus, and hence of the rate of fetal growth.² Multiple placental growth factors and growth-regulating hormones are important in regulating placental growth and thus fetal growth, including insulin, insulin-like growth factors and their binding proteins, vasoactive intestinal peptide, thyroid and growth hormones, and glucocorticoids. Gene polymorphisms leading to loss of function of any of these growth factors and hormones would increase risk for SGA, but no relevant studies are presently available. Genotype data are available in SGA infants, however, that associate risk for SGA with polymorphisms in the fetal glucokinase and the β 3-adrenergic receptor genes^{7,8}; at present, these genotypes cannot be linked to antemortem phenotypes that would confer increased risk for SUDI. Of interest, however, there are some data in SIDS infants identifying novel polymorphisms in the glucokinase and glucose 6-phosphatase genes in infants dying suddenly and unexpectedly⁹ (table 1). Proinflammatory cytokine polymorphisms have been linked to increased risk for preterm birth, and polymorphisms leading to decreased

anti-inflammatory cytokines have been linked to increased risk for SGA.^{10,11} As discussed later, polymorphisms associated with increased proinflammatory cytokines have been linked with increased risk for SIDS^{3,4,12–14} (table 1).

The pathophysiology, epidemiology, genetic polymorphisms and gene–environment interactions pertinent to SIDS have recently been reviewed.^{3,12} Low birth weight due both to prematurity and to SGA are important risk factors for SIDS. Existing datasets do not permit assessment of any potential additive effect from being both preterm and SGA. To what extent, for example, might risk for SIDS be increased in preterm SGA compared with term SGA?

Polymorphisms have now been reported for 16 genes that occur in greater frequency in SIDS infants than in matched control infants.^{3,12} These include five sodium and potassium cardiac ion channelopathies, the serotonin transporter gene (5-HTT), and five genes affecting autonomic nervous system development. Although the corresponding antemortem phenotypes are largely unknown, fetal growth restriction has not emerged as a putative phenotypical characteristic of any of these polymorphisms or of any associated gene–gene or gene–environmental interactions. The remaining five of these 16 gene polymorphisms are complement factors C4A and C4B, interleukin (IL) 6 and IL10, and vascular endothelial growth factor, all of which affect infection and inflammation. Polymorphisms leading to increased proinflammatory cytokines or decreased anti-inflammatory cytokines have therefore now been linked with risk for SIDS and as already mentioned, risk for low birth weight^{3,12–14} (table 1). Although much remains to be elucidated, inflammation and immune responsiveness do appear to be a putative shared causal mechanism contributing to increased risk for SIDS and for SGA.¹

In summary, these new data provide additional “proof of concept” that SGA is a risk factor for SIDS.¹ It is speculated that the reduction in risk for SIDS following socioeconomic adjustment is consistent with environmental and behavioural conditions being the explanation for this association, and that SGA is not indicative of increased biological vulnerability to SIDS (or SUDI). On the basis of emerging genetic data and increasing knowledge of the importance of gene–gene and gene–environment interactions, and as summarised in this commentary, causation for the association between low birth weight and SIDS is probably much more complicated and multifactorial. Nevertheless, using this “proof of concept” as the stimulus, and using state-of-the-art

genomic and proteomic knowledge and expertise, investigators from the disparate research worlds of fetal growth, low birth weight and SUDI need to collaborate. The interdisciplinary partnerships so established could be a useful next step in testing new hypotheses regarding mechanisms contributing to increased risk of SIDS in low birthweight infants, which may enhance our understanding of causal mechanisms for SIDS and for SGA and for prematurity. Effective prevention strategies will hopefully become a more realistic goal as shared causal mechanisms are progressively better defined.

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