Title

Brain weight in sudden unexpected death in infancy: experience from a large single centre cohort

Authors

*[1,2]Bamber AR, *[1,2]Paine SML, [1]Ridout DA, Pryce JW,[1,2] #[1,2]Jacques TS, #[1,2]Sebire NJ

*These authors contributed equally

#These authors shared senior authorship

Affiliations

[1]UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH

[2]Department of Histopathology, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London WC1N 3JH

Corresponding author:

Professor Neil J Sebire

UCL Institute of Child Health

30 Guilford Street

London WC1N 1EH

neil.sebire@gosh.nhs.uk

Tel: 44(0)2078298663

Fax: 44(0)2078314366

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Abstract

Aims Published reports of brain weight in sudden infant death syndrome (SIDS) are contradictory, though several have concluded that brain weight is increased in SIDS compared to controls or reference data. This is important since, if brain weight is significantly different, it may be of diagnostic use or provide insights into the aetiology of SIDS. The aim of this study is to use a large series of well-characterised sudden unexpected infant deaths from a single centre to provide definitive data regarding this issue.

Methods A retrospective review identified 1,100 infants who had died suddenly and undergone a comprehensive post-mortem examination at Great Ormond Street Hospital between 1996 and 2011. These infants were split into two groups: those in whom death could be explained and those whose deaths remained unexplained despite full investigation (SIDS / unexplained SUDI). The brain weight, brain weight:head circumference ratio and brain weight:body weight ratio in the groups were compared.

Results There were 1,100 cases of whom 573 (52%) were unexplained and 527 (48%) explained. Multiple regression analysis, which adjusted for sex, age and post-mortem interval, showed no difference in the ratio of brain weight:body weight between those infants dying of explained causes and those in whom no cause could be found. This finding remained true when restricting analysis to those with macroscopically normal brains at autopsy.

Conclusions In this large series of infants dying of both explained and unexplained causes, brain weight, once corrected for body weight, did not vary consistently with the cause of death. Brain weight cannot be used as a diagnostic indicator of the cause of death or to inform hypothetical models of the pathogenesis of SIDS.

Abbreviations

SIDS Sudden infant death syndrome

SUDI Sudden unexpected death in infancy

Introduction

Sudden unexpected death in infancy (SUDI) is the largest category of death in post-neonatal infants in the UK (1), and describes the death of an infant aged between seven days and one year, whose death is sudden and unexpected on the basis of the clinical history. In some, a definite cause of death may be identified at autopsy (explained SUDI), but in many cases no specific cause of death will be found (unexplained SUDI). Some of these unexplained infant deaths may fulfill the criteria for SIDS (sudden infant death syndrome (2)), which is defined as “the sudden unexpected death of an infant <1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history” (3). It should be noted that the definitions and terms used to describe these deaths have varied significantly between jurisdictions and over time, which creates difficulty when comparing cases in the literature (4).

The underlying cause of SIDS / unexplained SUDI is unknown but a number of theories have been proposed, many of which are linked by the triple risk hypothesis, in which it is suggested that SIDS results from the effects of an external stressor in an intrinsically susceptible infant at a vulnerable stage of development (5). A wide range of neuropathological features have been investigated in these infants, particularly with reference to the ‘intrinsically susceptible infant’ aspect of the triple risk model, with a view to improving understanding of pathogenesis and diagnosis (6). An early report described increased brain weight in infants dying of SIDS when compared to reference 'normal' data (7). Since then, several groups have applied a range of methods to the issue and, perhaps not surprisingly given the disparate definitions of SIDS and statistical approaches adopted, reported conflicting results (Table 1). Prompted by these reports, the importance of the subject and the difficulties presented in interpreting the published data, this study tested the hypothesis that brain weight differs in infants dying of unexplained SUDI when compared to infants dying of known causes by examining the records of all infant autopsies conducted at a specialist centre for paediatric pathology over

a sixteen year period.

Materials and Methods

This was a retrospective review of a research autopsy database derived from unselected, consecutive paediatric autopsies performed at a single specialist centre. The database contained all autopsies performed between January 1996 and December 2011.

Case selection

Great Ormond Street Hospital, London, is a tertiary referral centre for paediatric investigation, including autopsies. An autopsy database containing detailed non-identifiable data from autopsies performed at the centre (including information regarding the circumstances of death and ancillary investigations), was searched according to the search strategy with strict inclusion and exclusion criteria (Figure 1). This was a retrospective study using routinely collected clinical data.

In addition to the brain and body weights, potential confounding factors were recorded, including: age at death, sex, post-mortem interval (the period between death and post-mortem) and the presence or absence of documented subjective brain swelling at the time of autopsy. Like many of the previous studies examining brain weight in SUDI (8-11), since the gestational age at birth was not provided in a large number of the cases, it was decided to use a ratio of brain weight to body weight in order to minimize any skew caused by effect of gestational age. The deaths were categorized as either explained or unexplained on the basis of the cause of death given by the pathologist following autopsy. Deaths were categorized as explained if the cause of death was completed with a defined clinical entity, such as infection or metabolic disease. Cases given causes of death such as “Sudden Unexpected Death in Infancy”, “Sudden Infant Death Syndrome” and “Unascertained” were included in the unexplained group, unless they were qualified with a defined clinical entity. This strategy for classifying infant deaths, using the same database, has been previously used with success to

study other aspects of sudden unexpected death in infancy, such as infection (12).

Statistical analyses

Skewed data, which included age and post-mortem interval, were logarithmically transformed. Univariate comparisons between the explained and unexplained cause of death groups were made using a 2-sample t test and a Mann Whitney U test for skewed data. Multiple regression analysis was used to compare the difference in brain:body ratio and brain weight; head circumference ratio between the groups adjusting for age, sex, PM interval and presence of macroscopic brain swelling.

For the provision of brain weight centiles, cases were separated by gender. Cases with macroscopic abnormalities and/or brain swelling were excluded. Linear regression analysis, accounting for age was performed. Cases which were more than two standard deviations from the mean were excluded, to avoid the influence of outliers, a recognized method of case selection (WHO, 2006). Analysis of the remaining brain weights was performed using the LMS Method (Cole, 1990) with LMS Chartmaker Light (Version 2.54, Medical Research Council, UK), as previously described (Pryce et al, 2014), with the creation of 5^{th}, 25^{th}, 50^{th}, 75^{th} and 95^{th} centiles.

Ethics approval

The study was approved by the local LREC (London (Bloomsbury) National Research Ethics Service Committee; formerly Great Ormond Street and Institute of Child Health Research Ethics Committee) as part of a larger retrospective review of paediatric autopsy findings.

Results

One thousand one hundred infants met the inclusion criteria, of whom 573 (52%) were unexplained and 527 (48%) explained. A summary of the causes of death in the explained group is provided (Figure 2). The characteristics of the two groups in terms of age, sex, and post mortem interval are given in Table 2.

The age distribution was similar between the groups, median (IQR) age = 68 days (40, 119) in the unexplained cause of death group and 76 days (28, 176) in the explained group (P = 0.49); there was no difference in the proportion of males to females (P = 0.72). The median post-mortem interval was three days for both groups, although there was a tendency for slightly longer intervals for the unexplained death group. A greater proportion of the deaths in the explained group displayed macroscopic subjective evidence of brain swelling at autopsy (12.9% vs 7.3%, P = 0.002).

There was no difference in the ratio of brain weight : body weight between infants dying of explained and unexplained causes of death (mean (sd) 12.1% (3.0) vs 12.2% (2.5), P = 0.43, Table 2 and Figure 3). This remained true after adjusting for age, sex, post-mortem interval and the subjective presence of brain swelling (P = 0.37).

The brains of infants dying of explained causes were lighter than those dying of unexplained causes by an average of 38.2g, (P < 0.01); this difference remained after adjusting for confounding factors (age, sex, post mortem interval and the presence of brain swelling; P < 0.001).

In order to address possible confounders using another method, we also analysed the data including only those cases from both groups with macroscopically normal brains. There were now 811 cases in total, 491 of which were unexplained and 320 explained causes of death. Similarly, there was also no difference in the brain weight : body weight ratio between the groups 12.2% (sd 2.5) vs 12.3% (sd 2.8; P=0.54). This furthermore remained true after adjusting for age and sex as above (P=0.30).

The brain weights for the explained group were lighter on average by 40.8g, (P< 0.01), which remained after adjustment for age and sex (P<0.001). All other variables we considered showed similar findings to those from the complete dataset.

There was a difference in head circumference (hc) between the explained and unexplained groups, with the unexplained group being slightly larger on average. ($P<0.01$) This remained after adjustment for age, sex, pm interval and subjective brain swelling ($P<0.001$). The Brain:hc ratio was therefore greater in the unexplained group compared with the explained group ($P<0.001$).

Following exclusion of macroscopic abnormalities and brain swelling, 414 female and 576 male infants were available for analysis. 392 female and 541 male infants were within 2 standard deviations and were subsequently used for the creation of centiles using the LMS method. The penalized deviance and LMS values were 4550.4, 3, 4 and 3 for females, and 6496.0, 3, 4 and 3 for males. The subsequent centiles are provided (Figure 4 and 5).

Discussion

Several groups have examined brain weight in SIDS (7-11,13-17). The majority of these investigators have reported that the brain (either in isolation, or expressed as a ratio of brain weight:body weight) is heavier in SIDS than either a control population or published 'normal' data (7-10,13,14,16).

There are, however, significant limitations to published normal weight ranges, which limit their utility for reliable comparison. Firstly, the data for the published normal ranges which are commonly used were collected between 1933 and 1964 (17), and since then, average organ weights have increased (10). Secondly, the demographic characteristics of the study populations and the populations from which the normal ranges were created may vary.

Where brain weight in SIDS has been directly compared with measured control populations, brain weight has been reported to be both greater in SIDS (14), or not different (9,11,15,17,18). Using a combination of approaches, a German study compared organ weights in SIDS to both a control group and recently collected normative data and also reported that brain weight in SIDS was no different to controls (17).

Whilst there are plausible reasons for the different results reported, such as geographic or ethnic variation and the possibility that multiple pathologies underlie SIDS and only some of these result in a pathological state in which brain weight is increased, there are common limitations to many of these studies that hamper attempts to interpret their findings. SIDS is a diagnosis of exclusion. Therefore, the variable use of ancillary investigations, particularly death scene investigation, coupled with the different definitions of SIDS that have been used, lead to inconsistencies between the 'SIDS' populations in the different studies. A second problem is in the selection of a suitable control group, which ought to be matched for demographic variables, but often is not.

Mindful of these limitations, we investigated brain weight in a very large cohort of uniformly well-characterized infants who have undergone post-mortem examination at a single centre using a standard autopsy protocol. It includes

infants who have died of a wide range of explained causes as well as those in whom no cause was found after extensive clinical and pathological investigation. These two groups are similar in age and sex, and although the ethnicity of each infant is not available, it is likely that it is similar between the two groups since the geographic population served is identical. We found no difference in the ratio of brain weight:body weight between these two groups.

Comparison of brain weight alone between the two groups showed a small but statistically significant increase in brain weight in unexplained infant deaths. However, as discussed above, using brain weight alone allows no correction for other factors such as gestational age at birth and age at death between individuals, introducing a degree of uncertainty. Even if this brain weight increase were genuine, it is small and therefore unlikely to be useful in determining the pathogenesis of unexpected infant death on a population or individual case basis.

To conclude, in our large series of infants dying of both explained and unexplained causes, brain weight corrected for body weight did not vary with the cause of death. Therefore, brain weight cannot be used as a diagnostic indicator, nor should it feature or be used to infer the aetiology or pathogenesis in a plausible model of SIDS.

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Reference	Total number of cases	Number of SIDS cases	Number of control cases	Brain weight:body weight ratio	Brain weight
7	79 & reference data	79	Reference data	-	SIDS heavier
13	261 & reference data	208	53 & reference data	-	SIDS heavier
14	150	61	89	-	SIDS heavier
8	227 & reference data	227	Reference data	No difference	SIDS heavier
9	163 & reference data	125	38	No difference	SIDS heavier than reference data but not heavier than control infants
15	77	46	31	-	No difference
10	267	152	115	SIDS heavier	No difference
16	120 & reference data	97	23 & reference data	-	SIDS heavier
17	231 & reference data	231	Reference data	-	No difference
11	67	42	25	No difference	-

Table 1. A summary of the previous reports considering brain weight in Sudden Infant Death

	Unexplained cause of death (n=573)	Explained cause of death (n=527)	P value
Age[$]	68 (40, 119)	76 (28, 176)	0.49
Males	331 (57.8)	310 (58.8)	0.72
PM Interval[$]	3 (2, 5)	3 (2, 4)	0.02
Brain Swelling	42 (7.3)	68 (12.9)	0.002
Brain weight:body weight ratio (%)	12.2 (2.5)	12.1 (3.0)	0.43
Brain weight (g)	619.7 (176.0)	581.5 (241.8)	< 0.01
Body weight (g)	5363.1 (2096.0)	5147.7 (2562.7)	0.13

$ skewed variables median (IQR) presented

Table 2. Characteristics of the two cohorts of infants dying suddenly and unexpectedly and undergoing autopsy at one specialist centre over a 16-year period (Unexplained deaths and Explained deaths).

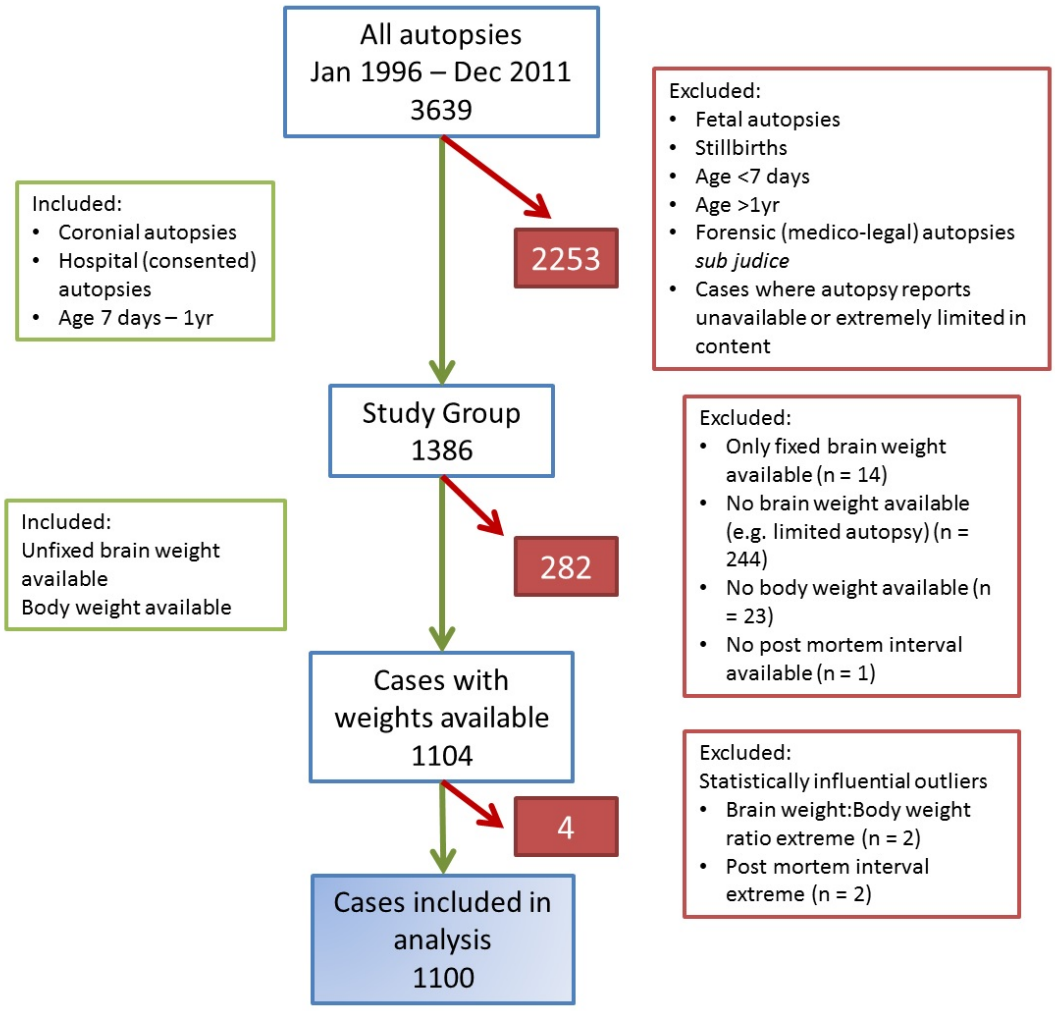

Figure 1. Inclusion & exclusion criteria

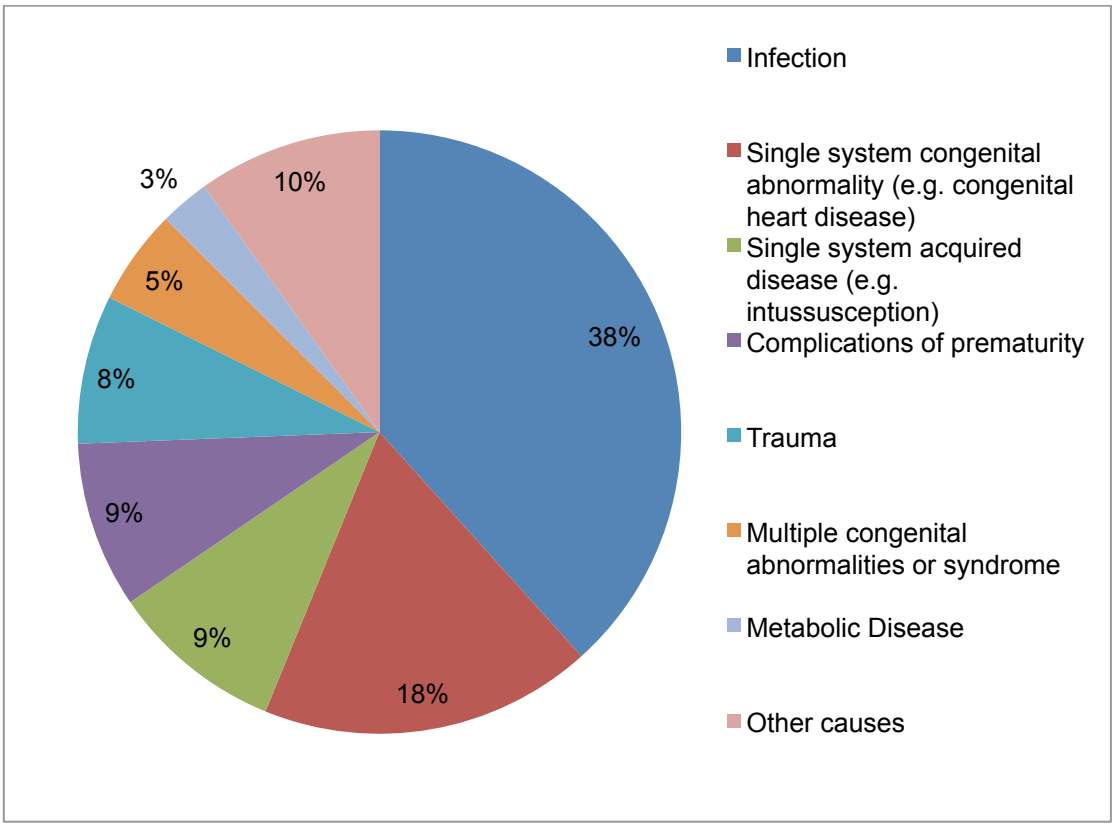

Figure 2. Cause of death categories in explained death group, with percentages.

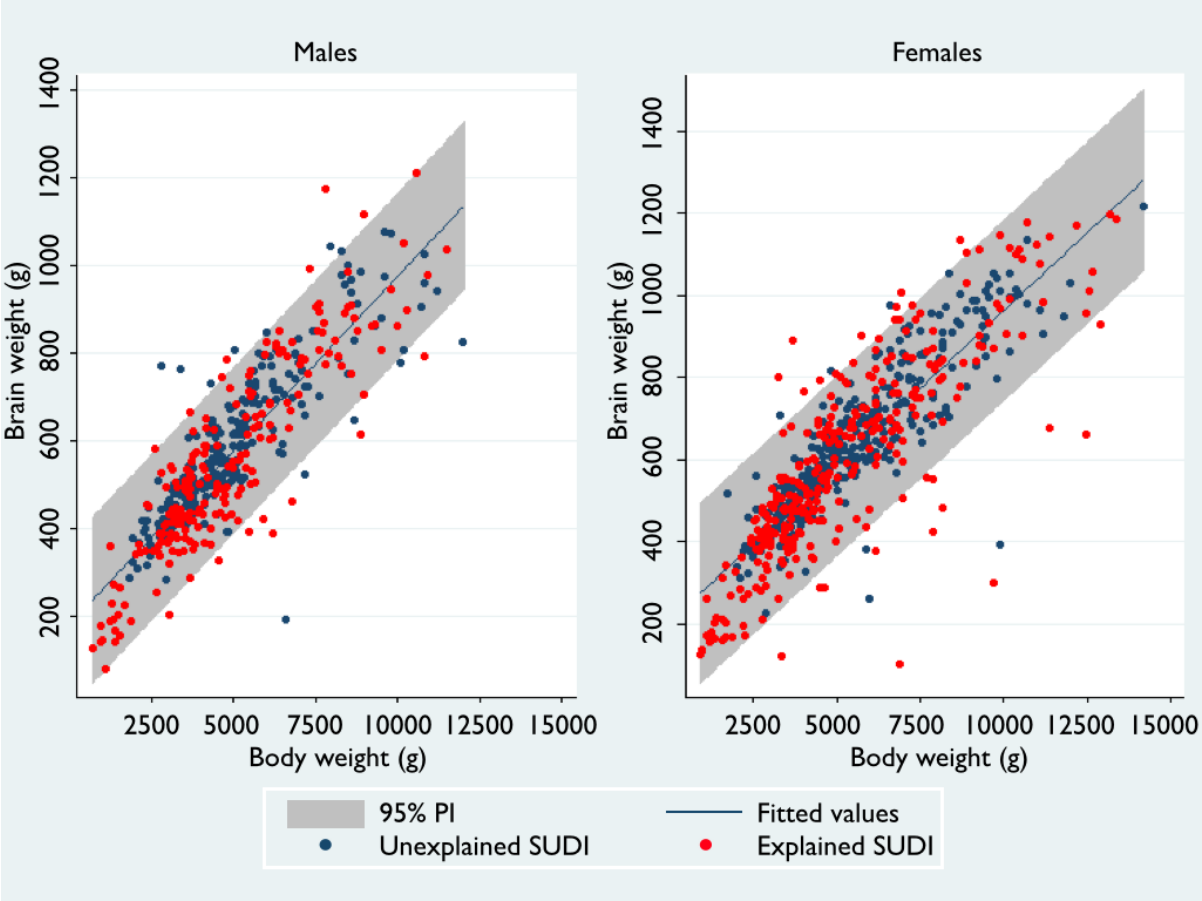

Figure 3. The ratio of brain weight:body weight for male and female infants dying of explained and unexplained causes of death

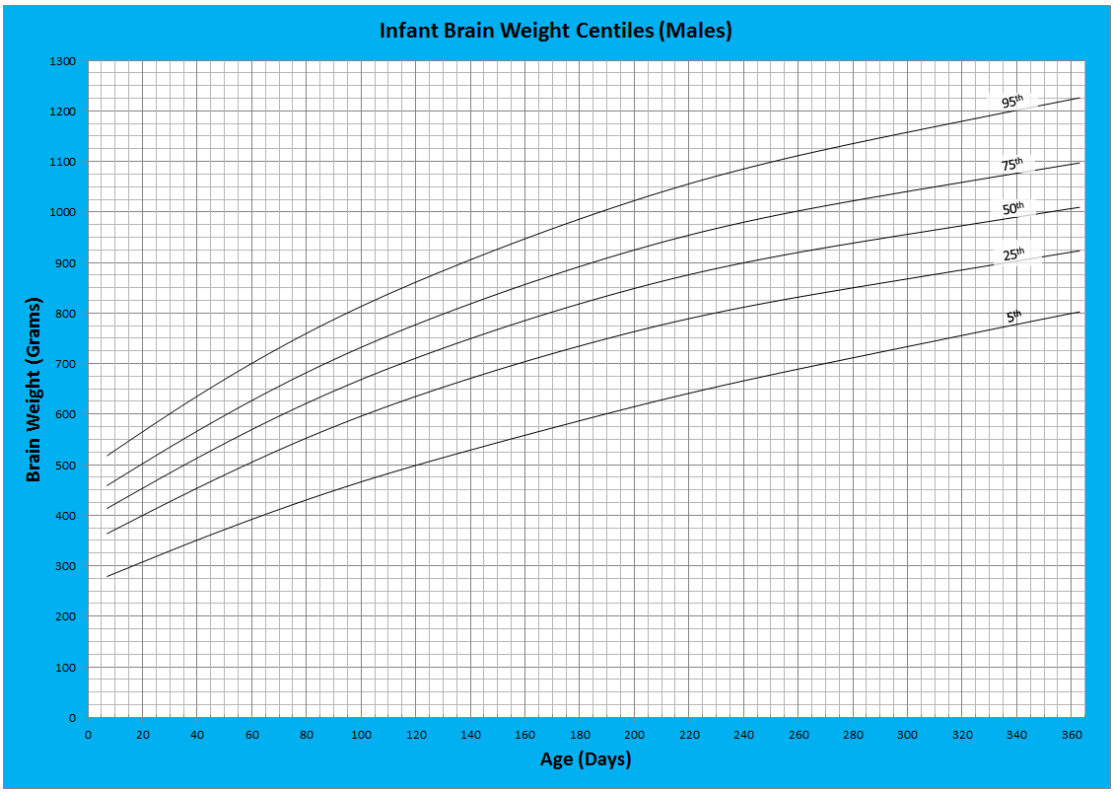

Figure 4. . Brain weight centiles for male infants (5^{th}, 25^{th}, 50^{th}, 75^{th} and 95^{th} centiles).

Figure 5. . Brain weight centiles for female infants (5^{th}, 25^{th}, 50^{th}, 75^{th} and 95^{th} centiles).