Brain Mass Estimation by Head Circumference and Body Mass Methods in Neonatal Glycaemic Modelling and Control

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Abstract

Introduction: Hyperglycaemia is a common complication of stress and prematurity in extremely-low-birth-weight infants. Model-based insulin therapy protocols have the ability to safely improve glycaemic control for this group. Estimating non-insulin-mediated brain glucose uptake by the central nervous system in these models is typically done using population-based body weight models, which may not be ideal.

Method: A head circumference–based model that separately treats small-for-gestational-age (SGA) and appropriate-for-gestational-age (AGA) infants is compared to a body weight model in a retrospective analysis of 48 patients with a median birth weight of 750 g and median gestational age of 25 weeks. Estimated brain mass, model-based insulin sensitivity (S_I) profiles, and projected glycaemic control outcomes are investigated. SGA infants (5) are also analyzed as a separate cohort.

Results: Across the entire cohort, estimated brain mass deviated by a median 10% between models, with a per-patient median difference in S_I of 3.5%. For the SGA group, brain mass deviation was 42%, and per-patient S_I deviation 13.7%. In virtual trials, 87–93% of recommended insulin rates were equal or slightly reduced ($\Delta < 0.16$ mU/hr) under the head circumference method, while glycaemic control outcomes showed little change.

Conclusion: The results suggest that body weight methods are not as accurate as head circumference methods. Head circumference–based estimates may offer improved modelling accuracy and a small reduction in insulin administration, particularly for SGA infants.

1.0 Introduction

Hyperglycaemia, the elevation of blood glucose (BG) concentration, is common in extremely preterm infants, typically of 27 weeks gestation or less and is closely correlated with morbidity and mortality [1-3]. Hyperglycaemia in neonates is frequently treated with insulin to lower BG concentrations [4]. However, reported insulin protocols have increased the risk of hypoglycaemia in this cohort [5, 6], which is associated with neurological complications [7]. Hypoglycaemia is overrepresented in preterm infants, most severely in small-for-gestational-age (SGA) infants [8]. STAR (Stochastic TARgeted) is a model-based glycaemic control framework for critically-ill patients [9, 10]. In the neonatal intensive care unit (NICU) setting, STAR has delivered tight glycaemic control and reduced hypoglycaemia [11]. Its main attribute is a stochastic forecast of possible BG outcomes enabling a quantified level of risk of hypoglycaemia [12]. Hence, it directly mitigates the risk of inter- and intra-patient variability when using insulin.

STAR utilizes the NICING model [13] to simulate insulin therapy. The NICING model is a pharmacokinetic description of insulin–glucose dynamics in the preterm infant that uses the same fundamental dynamics as a clinically well-validated adult model of acute care hyperglcaemia [14-16]. This model is similar in fundamental dynamics to well-known type-1 diabetes models [17, 18]. Patients are fit to this model to create treatment-independent insulin sensitivity profiles, which serve as the basis for describing patient condition. The glucose compartment of this model, with parameters given in Table 1, is defined:

$$\dot{G} = -p_G G(t) - S_I G(t) \frac{Q(t)}{1+ \alpha_G Q(t)} + \frac{P(t) + EGP \times m_{body} - CNS \times m_{brain}}{V_{g,frac}(t) \times m_{body}} \qquad (1)$$

Non-insulin-mediated glucose uptake by the central nervous system (CNS) is the rate at which glucose is removed from the blood for use in the brain. This rate is relatively constant [19], irrespective of the body's plasma insulin concentrations [20]. CNS uptake is a required parameter in the NICING model, as [13] notes that in contrast to the adult case, the brain represents a major source of glucose uptake in infants, due to their larger brain-to-body weight ratio. Hence, given significant variability between preterm infants and no clinically practical ability to measure it directly, this parameter should be modeled as accurately as feasibly possible.

Table 1: Parameters and variables in Equation (1) of the NICING model.

Variable	Description	Value
$\boldsymbol{G(t)}$	BG concentration	mg/dL
$\boldsymbol{p_G}$	Non-insulin-mediated endogenous glucose clearance	0.0030 /min
$\boldsymbol{S_I}$	Insulin sensitivity	litre/mU/min
$\boldsymbol{Q(t)}$	Interstitial insulin concentration	mU/litre
$\boldsymbol{\alpha_G}$	Saturation parameter for insulin mediated glucose removal	0 litre/mU
$\boldsymbol{P(t)}$	Total glucose appearance in plasma from enteral and parenteral sources	mg/min
$\boldsymbol{EGP}$	Endogenous glucose production	5.112 mg/min
$\boldsymbol{m_{body}}$	Body mass	kg
$\boldsymbol{CNS}$	Central nervous system glucose uptake	15.84 mg/min
$\boldsymbol{m_{brain}}$	Brain mass	kg
$\boldsymbol{V_{g,frac}}$	Plasma glucose distribution volume	0.5961 L/kg

In Equation (1), CNS is weighted by a patient-specific brain mass m_{brain}. Currently, m_{brain} is calculated as 14% of body mass m_{body} [13]:

$$m_{brain} = 0.14\, m_{body} \qquad (2)$$

This calculation assumes that brain mass is directly proportional to body mass (m_{body}). Equation (2) is clinically convenient, as it requires only m_{body} data, which is easily available. However, it may not be accurate. Dobbing and Sands [21] showed a trend between m_{body} and brain mass, but with notable variance. A more precise measure for estimating brain mass may be head circumference (HC) [22].

Improving the estimation of the patient-specific CNS term in the NICING model is projected to have three potential benefits for patients and clincians: **1)** it may improve glycaemic control and outcomes of patients; **2)** it will improve the physiological accuracy of the model; and **3)** it will provide a method of brain mass estimation that is better justified by the existing literature. This work serves as a feasibility study as to whether growth metrics, such as head circumference [22], which are also readily measured in infants, should be used in model-based glycaemic control methods to better account for and manage the inter-patient variability that can make control difficult for preterm infants [11, 23]. Ultimately, improvements in glycaemic control that may come by this investigation could reduce the incidence of hyper- and hypo-glycaemia in this fragile cohort.

This work attempts to mitigate a limitation of STAR's model-based stochastic forecasting technique by improving physiological parameter estimation. Methods are not only limited by parameter estimation and modelling constraints, but also on the quality of the stochastic forecasting. A key component of improving stochastic models is understanding inter-patient variability [24]. Accounting for head circumference in the physiological model can reduce variability in stochastic modelling and forecasting.

2.0 Methods

2.1 Values for Brain Mass

Equation (2) is estimated using data from Ho et al. [25]. This paper reports the mean and standard deviation body and brain mass for a range of preterm infants, divided into sub-cohorts by sex and ethnicity. Ethnicity was defined by 'black' or 'white', with no further detail provided.

The ratio of these group means was taken for black female and black male cohorts, which had the lowest mean gestational ages (mean GA = 27.3 wk and 28.4 wk, respectively), and then averaged to give $m_{brain} = 0.140\, m_{body}$. White cohorts were neglected due to the larger mean body mass (1367 g for the white cohort versus 1058 g for the black cohort) and greater gestational age (30.0 wk vs. 27.9 wk), which do not reflect the weight of infants who typically require glycaemic control [5, 11]. If the same method was applied to the white cohort, it would give $m_{brain} = 0.131\, m_{body}$, and if the entire cohort was used, then $m_{brain} = 0.136\, m_{body}$. The calculated ratio for each cohort is summarized in Table 2.

Table 2: Mean statistics on body and brain mass from Ho et al. [25].

Cohort	Gestational Age (wk)	m_{body} (g)	m_{brain} (g)	m_{brain}/m_{body} (g/g)
Black Female	27.3	958	139	0.145
Black Male	28.4	1151	157	0.136
White Female	29.2	1258	165	0.131
White Male	30.4	1434	190	0.132

While Equation (2) captures a ratio that may be applicable to a patient around the median mass of 1055 g, it assumes a linear relationship with no offset between m_{brain} and m_{body}, which is not realistic far from this value. Because the cohort this method will be applied to is typically much smaller than 1055 g [11], the errors from this assumption will be amplified. Finally, the apparent choice of ethnic cohort may not best reflect the population of patients in New Zealand, where patients are predominantly of New Zealand European, Māori, Pacific Island, and Asian descent.

2.2 Head circumference and brain mass

A model relating HC to brain mass from Cooke et al. [22] is compared to the original NICING assumption that brain mass is 14% of m_{body}, based on Ho et al. [25] and in Equation (2).

Cooke et al. [22] provide a relationship between HC and brain mass following a post-mortem study of 485 premature infants with gestational ages (GA) between 18 and 43 weeks. Small-for-gestational-age (SGA) infants are accounted for using a different parameter set to those that were appropriate-for-gestational-age (AGA). This separation was the result of SGA infants having a statistically higher brain mass for their gestational age than AGA infants [22]. Such a distinction may also be necessary in the relationship between m_{body} and brain mass, which has not been investigated using the m_{body} model.

The HC model from Cooke et al. [22] is defined:

$$m_{brain} = C^b \times k \qquad (3)$$

where C is the head circumference in centimetres and m_{brain} is the brain mass in grams. The remaining parameters given are in Table 3.

Table 3: Parameters in HC model [22].

Cohort	b	k
Appropriate-for-Gestational-Age	3.001	0.0093
Small-for-Gestational-Age	3.225	0.0048

Head circumference and weight data for this feasibility analysis are taken from the HINT trial of 88 preterm infants undergoing tight glycaemic control, for which the population is described in [6]. Of this cohort, patients were included that had episodes of insulin therapy with five or more consecutive BG measurements that were recorded less than eight hours apart. Inclusion also required a head circumference measurement during, or 24 hours before the start of the episode. These criteria were necessary to fit patients to the NICING model, and to compare brain mass estimates. Multiple episodes were recorded per patient where applicable. A total of 48 patients were selected, totaling 82 episodes. None of the mothers of patients in the study experienced maternal diabetes. 17 of 48 patients experienced intraventricular haemorrhage (IVH), all of whom were AGA infants. IVH was rated on a scale of 1–5 in order of increasing severity; the 17 patients had a median [IQR] IVH score of 2 [1–3.5]. Table 4 has demographic data from the overall cohort with further details in [6].

Table 4: Median [IQR] cohort demographics.

Birth Weight (g)	750 [678–894]
GA at birth (weeks)	25.0 [24.0–26.5]
Age at start of trial (days)	4 [2–7]
Ethnicity (%)	
NZ European	28
Māori	35
Pacific Islander	6
Asian	10

The SGA cohort is investigated in greater detail in each analysis to discern the effect of separating this group in estimation, and whether they may be more at-risk. Of the entire cohort, 5 of 48 patients were SGA, corresponding to 7 of 82 patient episodes. SGA infants were defined as patients at or below the 10th percentile of weight for their GA using growth charts from New South Wales, Australia [26] that have been used in New Zealand hospitals. 4 of the 5 SGA patients were asymmetric SGA, as determined by the Ponderal index [27]. Due to the small SGA cohort, asymmetric and symmetric patients are not analysed separately.

2.3 Analyses

First, changes in the estimated value of m_{brain} were investigated. For each head circumference measurement, patient brain mass is estimated using both models of Equations (2)–(3).

Next, changes in glycaemic control were analyzed using clinically-validated virtual patients [11, 28]. In particular, both models for estimating brain mass were compared by fitting data to create virtual patients. Patients were fit for treatment-independent insulin sensitivity profiles (S_I) to create virtual patients [29] using the NICING model.

Finally, glycaemic control outcomes were simulated in clinically-validated virtual trials [29], to assess the effect on glycaemia and interventions.

Because it is not known which of the two brain mass estimation methods is most accurate or useful in control, S_I profiles from both are used to create virtual patients. Both models are also tested within the model-based control. Hence, four combinations are tested, shown in Table 5. Cases *B* and *C* in Table 5 give estimates of the worst-case effects of estimation where model-based control and physiology are mismatched, in relation to *A* and *D* respectively.

Control simulations used the STAR controller defined in [30], with four-hourly insulin interventions. Insulin infusions are given through an IV pump, with a minimum rate of 0.1 mL/hr and step size of 0.01 U/kg/hr.

Table 5: Combinations of assumed model and controller-perceived model used in virtual trials.

		S_I profile in Control	
		HC-fit control	m_{body}-fit control
S_I profile in Simulation	HC-fit virtual profile	**A.** Assume HC gives the best estimate, and control with it.	**B.** Assume HC gives the best estimate, but control with m_{body}.
	m_{body}-fit virtual profile	**C.** Assume m_{body} gives the best estimate, but control with HC.	**D.** Assume m_{body} gives the best estimate, and control with it.

Nonparametric statistics were used in this analysis. Distributed data are compared using the Wilcoxon rank-sum (Mann–Whitney U test). Values of $p < 0.05$ are considered statistically significant.

3.0 Results

3.1 Model Comparison

Estimations of brain mass from the m_{body} model, $f(m_{body})$, based on body weight, and the HC model, $f(\mathrm{HC})$, based on head circumference are compared in a Bland–Altman plot in Figure 1. The figure shows a bias towards the m_{body} model estimating a significantly lower value for m_{brain} ($p < 0.005$). The median difference ($f(m_{body}) - f(\mathrm{HC})$) was -11.4 g, with an inter-quartile range (IQR) of $(-22.3, 0.8)$ g. The median brain mass estimated for the m_{body} model was 110 g, and was 121 g for the HC model. Hence, the HC model predicts a median increase in the brain mass of approximately 10%.

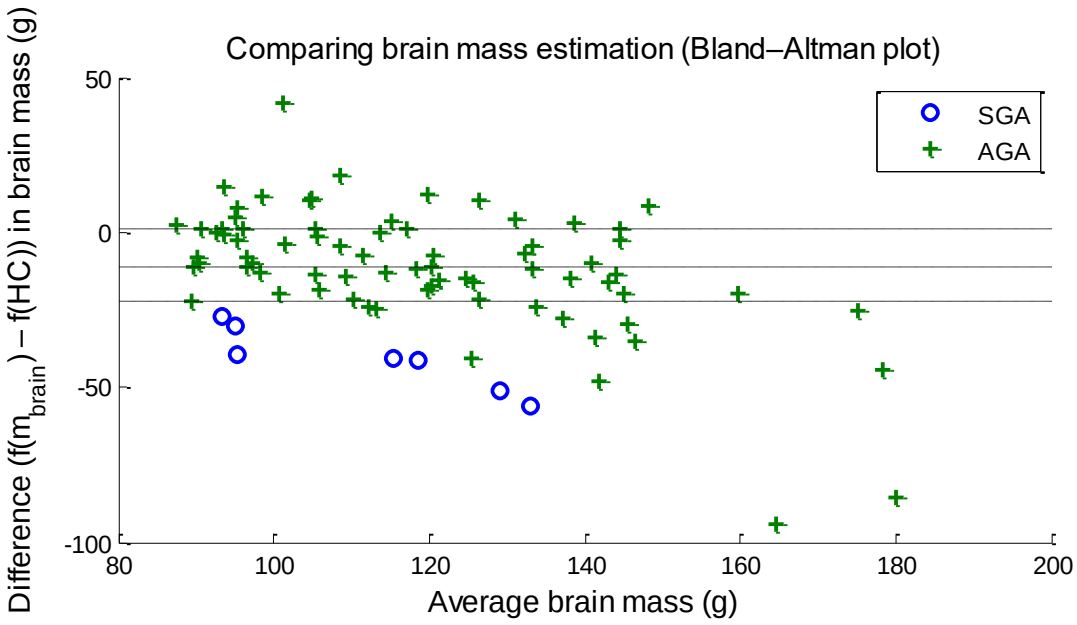

Figure 1: Comparison of m_{body} and HC estimations for brain mass, highlighting SGA infants.

SGA infants are discriminated in Figure 1. These patients are clearly biased, with a median difference of -40 g (42%), and inter-quartile range of $(-49, -33)$ g ($p \ll$

0.001). This result shows that the distinction between AGA and SGA infants that Cooke et al. [22] required for their HC model may also be necessary when using a body mass estimate, this highlighting difficulty with Equation (2).

Two infants in Figure 1 with average estimated brain mass greater than 150 g had a bias of over 80 g. This result suggests a further, nonlinear deviation between the two models at greater brain mass. However, the scarcity of data in this region is a reflection of the typical cohort and, as such, only a very small minority of patients undergoing insulin therapy might be expected to exist in this region.

Figure 2 classifies the points in Figure 1 by the GA percentile bands. In general, infants in the lower GA percentiles, who are thus low weight for their GA, were underestimated by the m_{body} model, and those with higher percentiles were overestimated. This result indicates that the body weight and head circumference methods represent significantly different measures of brain mass.

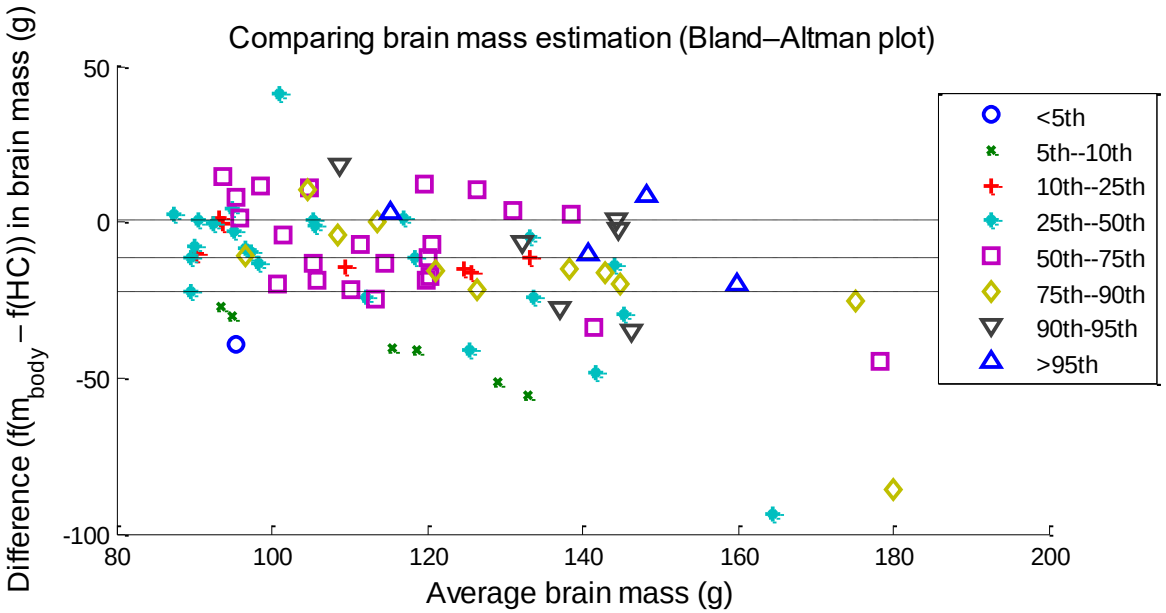

Figure 2: Comparison of m_{body} and HC estimations for brain mass at different expected weight percentile bands [26].

3.2 Effect on Model-Based Insulin Sensitivity

Patients are fit to the NICING model to generate S_I profiles for virtual patients using both methods of brain estimation. The resulting S_I profiles identified are summarized in Table 6.

Table 6: Deviations in S_I profiles under different models.

	Entire cohort	SGA only
$\boldsymbol{S_I}$ with m_{body} model (Med [IQR]) (mL/mU/min)	1.09 [0.70–1.49]	0.82 [0.66–1.35]
$\boldsymbol{S_I}$ with HC model (Med [IQR]) (mL/mU/min)	1.08 [0.68–1.43]	0.75 [0.59–1.22]
Per-patient $\%\boldsymbol{\Delta S_I}$ (Med)	**3.5**	**13.7**

The median [IQR] S_I for the cohort fit by the m_{body} model was 1.09 [0.70–1.49] mL/mU/min, and for the HC model, 1.08 [0.68–1.43] mL/mU/min. Per patient, the median change in S_I ($f(m_{body}) - f(\text{HC})$) was 3.5% ($p = 0.0048$). This result shows a small but significant reduction in model-based S_I under the Cooke model using HC.

For the SGA group, m_{body}-fit S_I was 0.82 [0.66–1.35] mL/mU/min while HC-fit S_I was 0.75 [0.59–1.22] mL/mU/min. Per-patient median change in S_I was much greater for this group at 13.7% ($p = 0.0015$). The results for this cohort are much more significant than for the wider cohort, indicating that this particular group may be particularly poorly modeled by the current m_{body} model. In particular, significantly different S_I may yield significantly different insulin interventions in model-based control.

Despite changes in the absolute values of S_I, both the full cohort and the SGA subgroup displayed relatively similar IQRs across the two models. Variability is a much more important factor in glycaemic control and forecasting than absolute S_I [12, 23, 31],

particularly for safety from hypoglycaemia. Hence, glycaemic control outcomes for SGA patients may not be compromised by this discrepancy if, despite differing values of median S_I, profiles are only shifted, rather than altered with changed variability.

3.3 Effect on Control

Results for virtual trials across the entire cohort are shown in Table 7. The 82 episodes simulated constituted 7032 hours of care, with 1881 BG measurements (mean 3.7 hrs/intervention). Electing to use HC in control instead of body mass could potentially decrease insulin interventions by as much as a median of 0.03 U/kg/hr or 7.1% (compare *A–B* or *C–D* in Table 7). BG outcomes are not significantly altered, with a negligible change to the time in band (% of BG measurements 4.0–8.0 mmol/L) and hypoglycaemia (% of BG measurements < 2.6 mmol/L). For both simulation S_I profiles, controlling with HC gave a small decrease in excessive hyperglycaemia (% BG > 10 mmol/L).

Table 7: Control interventions and outcomes from virtual trials for entire cohort.

Whole cohort statistics	A. **Simulate HC Control HC**	B. **Simulate HC Control m_{body}**	C. **Simulate m_{body} Control HC**	D. **Simulate m_{body} Control m_{body}**
Median insulin rate [IQR] (U/kg/hr):	**0.042** [0.030–0.061]	**0.045** [0.032–0.062]	**0.040** [0.030– 0.061]	**0.042** [0.030– 0.061]
% BG within 4.0–8.0 mmol/L	**68.92**	**68.41**	**69.58**	**68.92**
% BG > 10 mmol/L	7.89	8.49	6.94	7.72
% BG < 4.0 mmol/L	1.50	1.48	1.66	1.52
% BG < 2.6 mmol/L	0.17	0.17	0.18	0.16

Control is also assessed for patients for the SGA cohort only. Results from just these virtual trials are shown in Table 8. Time in band is marginally improved by controlling using the HC model. This simulation of 7 patient episodes was 622 hours, with 166 BG measurements (9% of total hours).

The same trend for insulin interventions and glycaemic outcomes are seen in the SGA cohort simulation. However, the time in band for this group is significantly lower across all simulations, indicating another underlying reason for difficulty in control. It is worth noting that SGA infant data (N=7), contributing only 9% of total hours, is reasonably sparse and highly influenced by outlying patients.

Table 8: Control interventions and outcomes from virtual trials for SGA infants.

Whole cohort statistics	A. **Simulate HC Control HC**	B. **Simulate HC Control m_{body}**	C. **Simulate m_{body} Control HC**	D. **Simulate m_{body} Control m_{body}**
Median insulin rate [IQR] (U/kg/hr):	**0.046** [0.036–0.075]	**0.051** [0.039–0.085]	**0.041** [0.033–0.064]	**0.046** [0.037–0.073]
% BG within 4.0–8.0 mmol/L	**62.96**	**61.84**	**64.07**	**62.80**
% BG > 10 mmol/L	17.97	20.19	13.35	17.65
% BG < 4.0 mmol/L	2.70	2.38	3.18	2.70
% BG < 2.6 mmol/L	0.16	0.16	0.32	0.16

The matched difference in insulin interventions between Cases *A*–*B* and *A*–*D* are shown in Figure 3 and summarized in Table 9. Comparing *A*–*B* shows the difference between doses for either controller method, assuming that the HC model is a true in simulation, while using HC (Case *A*) or m_{body} (Case *B*) in model-based control. Comparing *A*–*D* shows the difference between best-case model selections, with no mismatch between virtual patient and controller model. For both comparisons, Case A is most likely to give the equal or slightly less insulin (87–93% of doses across comparisons and sub-cohorts). This result shows that changes in interventions are small, and that the majority of these changes reduce insulin and therefore associated

risk. Less than 1% of interventions would be increased by more than 0.16 U/hr, the standard step increase in insulin between STAR interventions.

Table 9: Changes in insulin dosing comparing Cases *A*–*B* and *A*–*D*.

	Cohort	**Percent change in insulin rates by using Case *A* (%)**				
		Large decrease (by > 0.16 U/hr)	Decrease within 0.00–0.16 U/hr	Equal	Increase within 0.00–0.16 U/hr	Large increase (by > 0.16 U/hr)
A*–*B	AGA	3.4	**37.0**	**50.8**	7.9	0.9
	SGA	7.5	**64.2**	**24.9**	2.9	0.6
A*–*D	AGA	1.7	**16.1**	**74.1**	7.1	0.9
	SGA	0.0	**34.7**	**57.8**	7.5	0.0

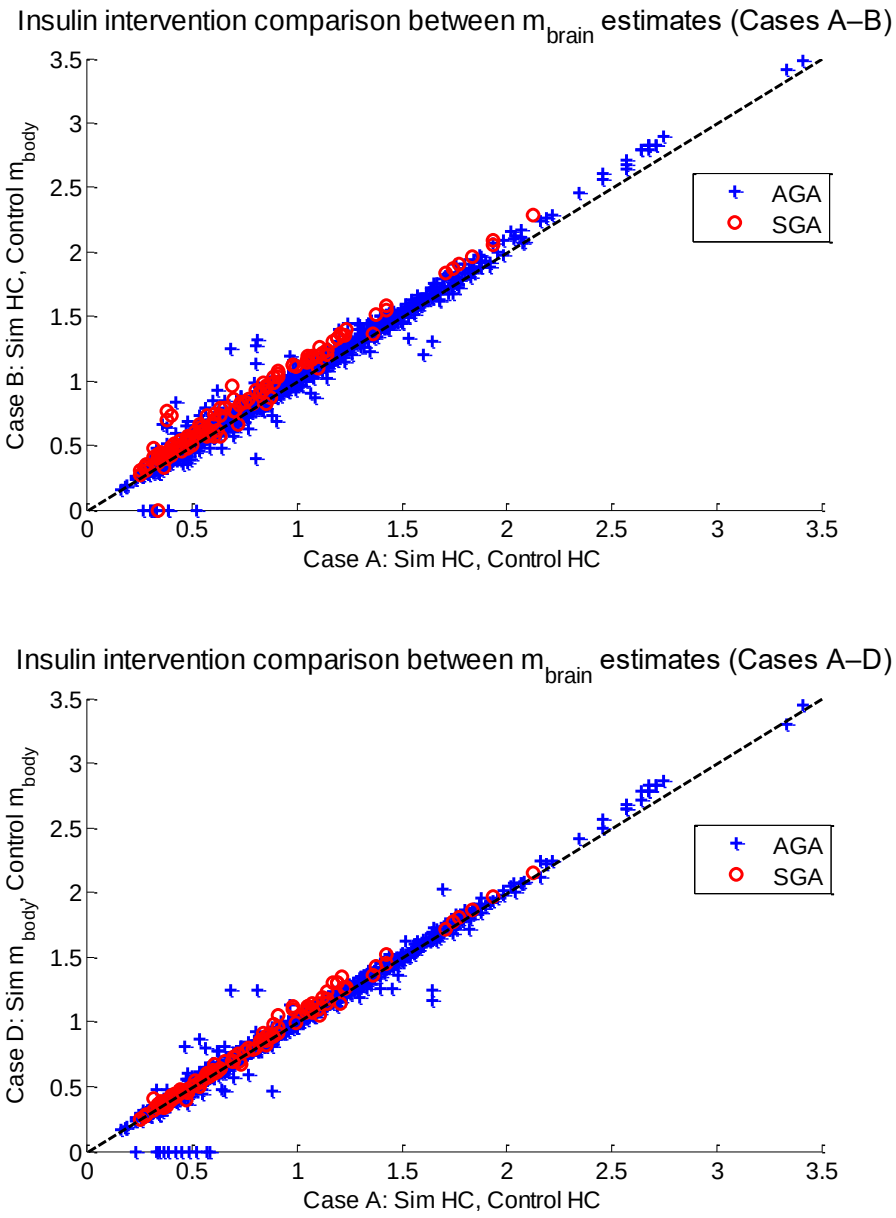

Figure 3: Changes in insulin interventions between Cases *A–B* (top) and Cases *A–D*

4.0 Discussion

Across the entire cohort, parameter changes in S_I were negligible. However, for SGA infants, m_{brain} fit under the HC model was notably larger, and the resulting S_I profiles fit were reduced. This indicates that insulin has less effect in BG changes observed, assuming this model. Hence, there is an indication that any discrepancies in between the two methods of estimation are exacerbated in SGA infants. This result may be attributed to the median mass of 1055 g of the cohort from which Equation (2) was derived [25], versus the median mass of 750 g used here and 760 g in Le Compte et al. [11].

Control performance negligibly improved by using the HC model for control decisions. This result was independent of which model was used in simulation. However, the using the HC model resulted in less insulin being recommended for the same glycaemic outcomes. Such a result indicates that insulin was used more effectively, and potentially improves the safety of care by reducing the risks associated with insulin intake.

It is worth noting that the data acquired from the HINT trial has some longer periods between interventions than those for which NICING was designed. This difference may have degraded some of the virtual trials by reducing some potential S_I variability [12]. However, in each case, these virtual trials are comparing the patients and cohort as their own control. Head circumference data has not yet been analysed for patients undergoing STAR at Christchurch Women's Hospital NICU, or any other cohort with more frequent BG measurement, which eliminated other sources of clinical data. Other than frequency of measurement, data from the HINT trial contains sufficient information that is of practical use in glycaemic modelling.

The introduction of the Cooke method using HC would require an additional input for clinical staff when starting glycaemic control. Additional complexity to clinical protocols may increase clinical burden and potential for error [32, 33]. However, HC is routinely measured, and thus should not require any additional effort at the point of care. Furthermore, if for computer-based protocols this input was left as optional in a graphical user interface (e.g. “Head circumference (if available):”), it would minimise clinical burden when inconvenient.

As the comparative accuracy of both the HC and body mass models is not known it would be beneficial to have an objective study compare the two models against a more accurate method. For example, both could be compared to PET scans of patients, using approaches such as in [34], which would provide a significantly better estimate, although is impractical at the bedside. HC and body mass methods could be compared against this baseline metric.

The discrepancies observed between SGA and AGA infants is of interest, however, more data on SGA infants is necessary to claim robust conclusions. In particular, this investigation was not able to distinguish differences in symmetric and asymmetric SGA infants due to lack of data. As SGA infants are the most affected by model choice, this distinction may be of clinical use. Future research should investigate these cohorts in greater detail. Additionally, further variables of interest could be investigated. These variables could include placental insufficiency, maternal anti-hyperintensive therapy, and enteral/parenteral, protein, calorie and lipid intake.

Although the HC model is much more likely to be physiologically accurate both due to the nature of the measurement [21] and because the method is derived from a cohort of the same demographics it will be used on, it may not necessarily affect clinical

outcomes. However, the authors suggest that it should be used in preference to body mass–based estimates for neonatal glycaemic modeling, particularly for SGA infants. The similarity in glycaemic control outcomes demonstrates the robustness of the model-based stochastic forecasting approach for glycaemic control that STAR utilizes.

5.0 Conclusions

An alternative model for estimating brain mass using head circumference in preterm infants has been investigated. This model is likely to have greater physiological accuracy than previous and better reflects the demographics of the cohort of patients that typically require glycaemic control. Cohort-wide, changes in brain mass were significant, but changes in resulting insulin sensitivity profiles were negligible. The SGA subgroup was estimated to have a median brain mass difference of 40 g, reducing median insulin sensitivity by 13.7%. These results were statistically significant. Simulated glycaemic control under the STAR protocol suggested that 87–93% of insulin interventions would be the same or slightly reduced (within 0.16 U/hr), for similar glycaemic outcomes. Further, prospective research with larger cohorts is necessary to better understand the implications of the discussed modelling differences. Due to the improved physiological accuracy and mildly reduced insulin intake, there are preliminary indications that head circumference–based models for glycaemic modeling and model-based control may be preferable, particularly for SGA infants.

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