Supplemental Digital Content 1: Additional definitions and methods of the study

Contents

Cardiac surgery procedures amenable for inclusion

Cardiac surgery procedures which were considered amenable for inclusion are reported below:

- Norwood procedure
- Glenn procedure
- Damus–Kaye–Stansel procedure
- Systemic-to-pulmonary artery shunt
- Pulmonary artery banding
- Atrial Septal Defect closure
- Patent Foramen Ovale repair or closure
- Widening of the supravalvular aorta
- Arterial switch operation
- Tricuspid valve repair
- Mitral Valve Repair
- Patch closure of sinus venosus
- Coarctatio of the aorta
- Surgical correction for congenital heart defects such as: vascular ring, ventricular septal defect, pulmonary venous connection, double-chambered right ventricle, troncus arteriosus type 1, total anomalous pulmonary venous return, tetralogy of Fallot, interrupted aortic arch, univentricular heart, Fontan procedure, Subaortic stenosis

Definition of educational level of parents

The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level.

Definition of syndrome

The presence of a syndrome was defined as an a priori clinical condition that could affect neurocognitive development (1). It included all adverse clinical conditions that fall under the following categories:

- Genetically confirmed syndrome or pathogenic chromosomal abnormality
- Clearly defined syndrome, association or malformation without (identified) genetic aberration
- Polymalformative syndrome of unknown etiology
- Clear auditory or visual impairment without specified syndrome
- Congenital hypothyroidism due to thyroid agenesis
- Brain tumour or tumour with intracranial metastatic disease
- Pedopsychiatric disorder (e.g. autism spectrum disorder, (treatment for) attention deficit hyperactivity disorder)
- Severe medical disorder, not primarily neurologic, but suspected to alter psychomotor and/or mental performance
- Severe neonatal problem (e.g. severe asphyxia)
- Severe craniocerebral trauma or near-drowning
- Severe infectious encephalitis or drug-induced encephalopathy
- Infectious meningitis, encephalitis or Guillain-Barré
- Resuscitation and/or need for extracorporeal membrane oxygenation prior to inclusion
- Severe convulsions or stroke prior to inclusion

Definition of early and late parenteral nutrition

Early parenteral nutrition implied initiation of supplemental parenteral nutrition within the first 24 hours after admission to the pediatric intensive care unit (PICU) when enteral nutrition alone was insufficient to reach the caloric target. Late parenteral nutrition is defined as the withholding of parenteral nutrition in the first week of intensive care when enteral nutrition was insufficient to reach the caloric target. Although late parenteral nutrition might imply lower caloric intake, it has been shown to be clinically superior as compared with early parenteral nutrition in terms of incidence of new infections, time to recovery and long-term neurocognitive outcomes (1, 2).

Description of the medical assessment

Neurocognitive outcomes of part of the included children were assessed in the context of the PEPaNIC study. In the PEPaNIC study, a follow-up visit was performed by trained clinicians and psychologists and scheduled 2 years after the admission of the child at the PICU.

For this study, only the total IQ was analysed as indicator of long-term neurocognitive outcomes. The remaining children (children that were not originally part of the PEPaNIC study) were contacted by phone to schedule the follow-up specifically for this study. Follow-up protocol strictly followed the neurocognitive assessment protocol of the PEPaNIC study.

Description of the total IQ tests

General intellectual abilities were assessed with use of age-appropriate versions of the Wechsler Intelligence Quotient (IQ) tests. In detail, the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III-NL)(3) was used for children aged 2·5 years – 5 years 11 months (one version for age range 2 years 6 months – 3 years 11 months, and another version for age range 4 years – 5 years 11 months), the Wechsler Intelligence Scale for Children (WISC-III-NL) (4) was used for older children.

Brief description of Bayesian linear regression

The use of Bayesian statistics in clinical studies has already been described extensively (5, 6). We will provide a brief and simplified overview of the principles of Bayesian linear regression.

Bayesian models describe the regression coefficients between variables (β estimates) within the context of Bayesian inference. In contrast with frequentist statistics (traditional statistical method), the β estimates of the linear regression model are formulated using probability distributions rather than point estimates. In other words, the β estimates that link dependent variables (total IQ) with the independent variables (mean $SctO_2$, presence of syndrome, PIM3 etc..) are expressed in terms of the probability that the β estimates of the population have certain values, see Figure 1. The use of a probability distribution allows to model the uncertainty derived from a limited number of observations.

In Bayesian analysis, the final β estimates of the linear regression model (posterior β estimates), integrate prior knowledge (results of previous studies or common knowledge) with the information provided by the analyzed data. Prior knowledge is provided through the "priors", which, in this case, represent the predictions about the probability of β estimates values before additional information (the analyzed data) becomes available. For example, in this study we are investigating the association between $SctO_2$ desaturation and long-term total IQ in pediatric patients with congenital heart disease. We analyze this association with a Bayesian model, which was adjusted for the co-factors: age, nutrition strategy, presence of syndrome, presence of cyanotic cardiopathy after surgery and PIM3 score. From previous studies, we know that the presence of a syndromic condition (genetic disorder, brain tumor, severe neonatal problem etc.) is associated with lower total IQ. This represents "prior knowledge" or, in other words, validated information that can be added to the model before the model is applied to the analyzed data. On the contrary, it is unclear whether the age of the patient at PICU admission affects the patient's long-term total IQ. In this case, there is no validated knowledge to provide to the model, hence we will set a "non-informative prior". A non-informative prior allows the analyzed data to steer the direction and strength of the association, if any. The inclusion of prior knowledge is important in analyses with small-size datasets, where outliers have a bigger influence on the results and one data point can minimize or maximize the strength of an association.

The results of the Bayesian models are presented as the most likely values of the posterior β estimates and credible interval. The credible interval of the posterior distributions indicates the range of values to which the regression coefficients belong with a certain probability. In this study, an 80% credible interval was used.

After the concerns on the limitations and misuse of the p-value in clinical studies, Bayesian models were listed by the American Statistical Association (ASA) Board as one of the alternative statistical methods that can supplement or even replace the statistical measures resulting from the classical frequentists approach (7).

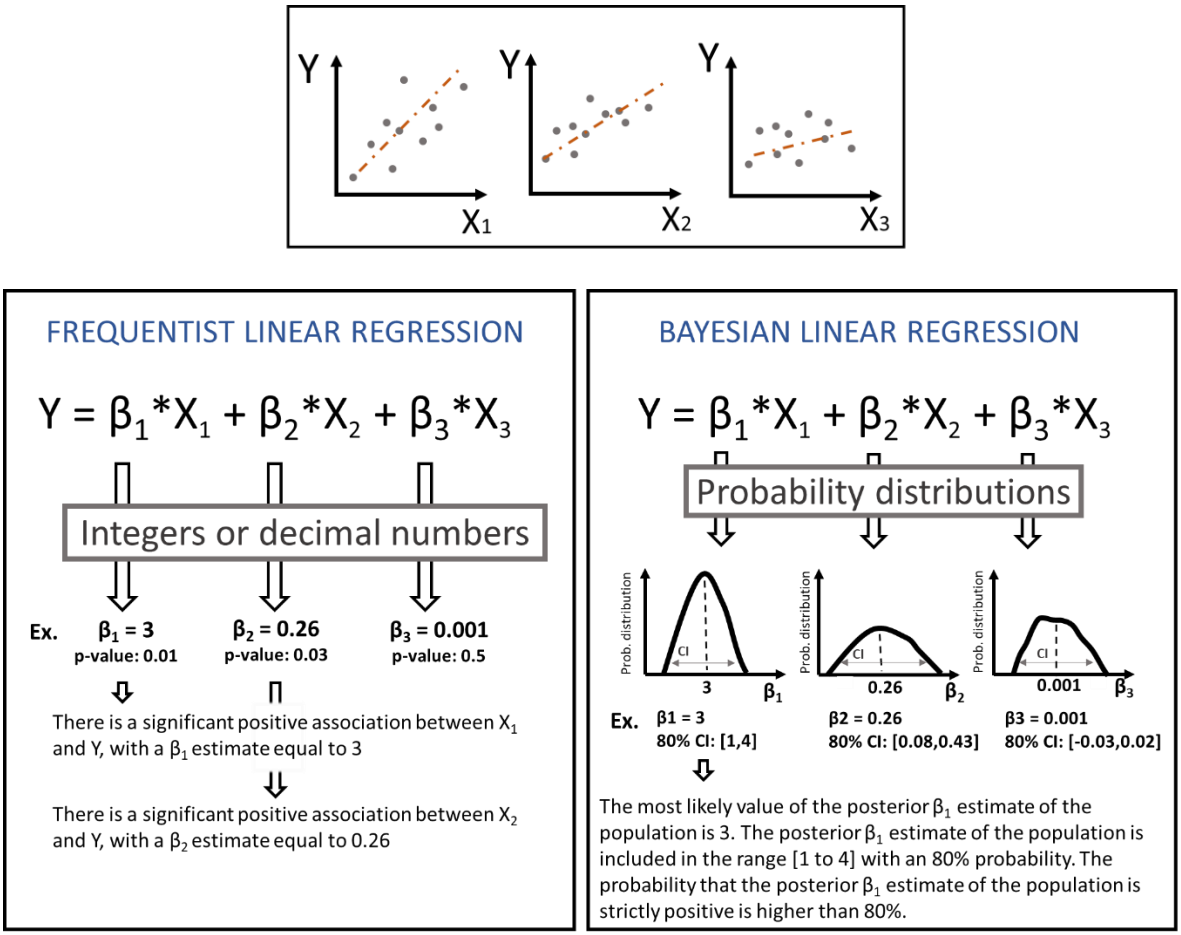

Figure 1 Visualization of correlation between a dependent variable Y and three independent variables X_1, X_2 and X_3 as conceptualized by the Frequentist statistics and the Bayesian statistics. In the frequentist approach, the β estimates of the linear regression model are expressed as numbers (point-estimates), uncertainty in the estimates is modeled with the p-value. In the Bayesian approach, the β estimates are expressed as probability distributions. Each probability distribution is characterized by the most likely value of the posterior β estimate and credible interval. In Bayesian statistics, the credible interval of the posterior distributions indicates the range of values to which the regression coefficients belong with a certain probability. In this study, an 80% credible interval was used.

Construction of the Bayesian model

The Bayesian model was built by using the No-U-Turn Sampler (NUTS). All non-informative priors were given a normal distribution, with a mean equal to 0 and a SD equal to 2 times the SD of the variable.

Informative priors were set for the variables syndrome and cyanotic cardiopathy. In detail, we assumed that the presence of syndrome would worsen the neurocognitive outcomes of the child by 5% (8–14). Similarly, we assumed that the presence of cyanotic cardiopathy would worsen the neurocognitive outcomes of the child by 1% (15, 16). Given that the mean total IQ at 2-years follow-up of children admitted in the PICU is 90.6 (1), the mean value and standard deviation of the priors set for of the syndrome and cyanotic cardiopathy are reported in Table 1.

Table 1 Parameters of the prior distributions for syndrome and cyanotic cardiopathy.

Covariate	Mean value	SD
Syndrome	-4.53	10
Cyanotic cardiopathy	-0.91	10

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