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# Multimodal Outcome at 7 Years of Age after Neonatal Arterial Ischemic Stroke

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Sylvie Nguyen The Tich, MD, PhD<sup>6,12</sup>, on behalf of the  
Accident Vasculaire Cérébral du nouveau-né (AVCnn; [Neonatal Stroke]) Study Group\*

**Objectives** To evaluate the epileptic, academic, and developmental status at age 7 years in a large population of term-born children who sustained neonatal arterial ischemic stroke (NAIS), and to assess the co-occurrence of these outcomes.

**Study design** A cohort study including 100 term newborns with NAIS was designed. Two infants died during the neonatal period, 13 families were lost to follow-up, and 5 families declined to participate in this evaluation. Thus, 80 families completed the 7-year clinical assessment. Epileptic status, schooling, motor abilities, global intellectual functioning, spoken language, and parental opinions were recorded. Principal component analysis was applied.

**Results** Rates of impaired language, cerebral palsy, low academic skills, active epilepsy, and global intellectual deficiency were 49%, 32%, 28%, 11%, and 8%, respectively. All were highly correlated. Eventually, 59% of children were affected by at least 1 of the aforementioned conditions. In 30% of cases, the viewpoints of health practitioners and parents did not match.

**Conclusion** The prevalence of severe disabilities at 7 years after NAIS is low, but most children exhibit some impairment in developmental profile. (*J Pediatr* 2016;172:156-61).

**Trial registration** [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT02511249), Programme Hospitalier de Recherche Clinique Régional (0308052), Programme Hospitalier de Recherche Clinique Interrégional (1008026), and EudraCT (2010-A00329-30).

Although perinatal ischemic stroke (PIS) is common,<sup>1,2</sup> its long-term outcomes remain poorly understood. Two main biases limit the accuracy of most studies: heterogeneity/small size of the sample and too short or informal follow-up.

The first consideration is that PIS encompasses several disease states that differ in pathophysiology, timing of occurrence, and clinical presentation.<sup>1,3</sup> Thus, it is not surprising that outcome depends primarily on the subtype of stroke. For example, nearly all children who suffer an arterial presumed PIS or a fetal periventricular venous infarction have motor impairment, compared with one-third of those with a neonatal arterial ischemic stroke (NAIS; ie, arterial PIS with clinical manifestations before the 29th postnatal day).

Age at evaluation also plays a major role. Indeed, even though the original lesion in NAIS is focal and nonprogressive, its consequences within the maturing brain as a whole are amplified over time, compounded by environmental impacts, and thus affecting all dynamic and multidimensional fields of development.<sup>4</sup>

The AVCnn (Accident Vasculaire Cérébral du nouveau-né [neonatal stroke]) Study gives us the opportunity to monitor a cohort of term-born children having

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AVCnn	Accident Vasculaire Cérébral du nouveau-né (neonatal stroke)	PCA	Principal component analysis
BFMF	Bimanual Fine Motor Function	PIS	Perinatal ischemic stroke
CP	Cerebral palsy	PRI	Perceptual Reasoning Index
FSIQ	Full-scale IQ	PSI	Processing Speed Index
GMFCS	Gross Motor Function Classification Scale	VCI	Verbal Comprehension Index
NAIS	Neonatal arterial ischemic stroke	WISC-IV	Wechsler Intelligence Scale for Children-Fourth Edition
		WMI	Working Memory Index

suffered an NAIS. Here we present the clinical evaluation of these children at age 7 years. As observed in multiple situations with early brain insult, our hypothesis was that developmental disabilities co-occur, along with epilepsy.<sup>2,5-12</sup>

## Methods

The objective of the AVCnn study was to better delineate the risk factors, clinical and imaging presentation, mechanisms, and outcomes of NAIS, while avoiding the confounders described above. The study was conducted in accordance with international ethical standards and the Declaration of Helsinki. The current evaluation at age 7 years was approved by the Regional Ethics Committee in May 2010. Informed consent was obtained from each participant. The reporting of results follows the general guidelines for observational studies.<sup>13</sup>

The study design is a birth closed-cohort study.<sup>14</sup> NAIS was defined as “a focal disruption of arterial cerebral blood flow, causing neurological symptoms and confirmed by neuroimaging (computed tomography and/or magnetic resonance imaging, centrally reviewed for all cases) after birth and before the 29th postnatal day.”<sup>3</sup> A total of 100 newborns (62 boys) were enrolled between November 2003 and October 2006 in 39 units distributed throughout France. To eliminate the consequences of prematurity, only term newborns were included. Patients with fetal stroke, cerebral sinovenous thrombosis, presumed PIS, or diffuse ischemic lesions were excluded. Clinical and imaging neonatal findings and outcomes at ages 2 and 3.5 years have been reported previously.<sup>14-16</sup>

### Assessment at age 7 Years

Regular contacts with the families and local physicians have been maintained since enrollment. Formal encounters took place during the systematic visits at ages 1, 2, and 3.5 years. Annual newsletters were sent to keep the families informed of the results of the ongoing study and the planned evaluations.

In 2010, families were asked via mailed letters to participate in the 7-year assessment. Those who accepted were contacted by phone by the study coordinators in the months before the child's seventh birthday and invited to attend a presentation on the current project. The encounter took place over an entire day in a medical setting close to the family residence. The evaluation team included a neuropsychologist, a speech therapist, and either a pediatric neurologist or a pediatric physical and rehabilitation medicine practitioner. All expenses were supported by the AVCnn study.

Three main categories of data were recorded: (1) history since the neonatal period; (2) developmental profile; and (3) parent opinions regarding the child's present function. The following items were documented: (1) medical history, notably the occurrence of seizures; (2) schooling; (3) gross and fine motor abilities; (4) global intellectual functioning; (5) spoken language; and (6) a single closed question to the family: “Do you consider that your child suffers any sequelae of his/her neonatal event?”

### Variables and Endpoints

Epilepsy was defined as the occurrence of 2 or more afebrile unprovoked seizures after the neonatal period or, in the case of a single afebrile unprovoked seizure, the initiation of anti-epileptic treatment. Epilepsy and seizures were classified according to the current International League Against Epilepsy terminology and classification scheme.<sup>17</sup> Seizure-free at age 7 years was defined as the absence of seizures and treatment for >1 year. Otherwise, epilepsy was classified as active.

Depending on the date of assessment, the child's expected level was either first or second grade. Grade retention, the need for specific and individualized support in a mainstream school, and inclusion in a special school were considered to represent low academic skills.

Three main domains were assessed for the developmental profile. Motor evaluation was focused on the presence of cerebral palsy (CP). The definition given by the Surveillance for CP in Europe was used: permanent abnormal tone or decreased strength as a consequence of a nonprogressive early brain insult, and associated with a patent functional deficit.<sup>18</sup> Motor impairment was further classified with the Gross Motor Function Classification Scale (GMFCS), according to the child's level of gross motor abilities. In the GMFCS schematic, level I subjects walk without limitations, and level V subjects need a manual wheelchair.<sup>19</sup> The Bimanual Fine Motor Function (BFMF) tool was used to assess the ability to grasp, manipulate, and hold objects for each hand separately (level 0, no impairment; level 5, only ability to hold or worse with both hands).<sup>20</sup>

Global intellectual ability was evaluated using the 4 indices of the Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV): Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), and Processing Speed Index (PSI). Global intellectual deficiency was defined as a full-scale IQ (FSIQ) <70. As recommended in WISC-IV Administration and Scoring Manual, when excessive discrepancies between indices precluded the composite FSIQ score validity, only subscores were provided. Global intellectual deficiency was then considered when both VCI and PRI were <70.

Finally, the standardized spoken language assessment *Nouvelles Epreuves pour l'Examen du Langage* was performed.<sup>21</sup> This battery was validated to test the language profile of 3.5- to 8.5-year-old French-speaking children, including speech and sound abilities as well as expressive and receptive lexicosemantic and morphosyntactic skills. Children with a score >2 SD below the mean for 1 of the 4 linguistic components (ie, not including isolated speech and sound delay) were considered to have impaired language.

### Biases

Some families could not be contacted or declined to participate in the present evaluation, and thus the final rate of disabilities could have been misestimated. This incomplete follow-up did not alter the relationship between variables, however, because hypotheses were applied only to those

who fully completed the current study. One child did not complete the WMI of the WISC-IV, and another 2 children did not complete the PSI. Their VCI and PRI values were used to assess their global intellectual abilities. One child was not assessed for language. Because principal component analysis (PCA) cannot take missing data into consideration, this patient was not included in PCA.

### Statistical Analyses

Descriptive statistics are summarized as percentages of children for each of the 5 variables and as median and IQR for continuous data. PCA was used to evaluate the relationships between variables. In brief, the original data were plotted in a 5-dimensional data space in which each orthogonal axis represented a variable. This space was thereafter projected through the PCA transformation on the plan of maximal contribution, that is, the cross-sectional plan whose axes (the 2 principal components) ensured the best total variance of the dataset. The relative contribution of each variable to these components was graphically represented as a vector. The correlation matrix between each pair of variables was represented by a heat map. Factor analyses were carried out using the R package FactoMineR.<sup>22,23</sup> The criteria used for the PCA was the default in FactoMineR.

## Results

Of the 100 patients (Figure 1; available at [www.jpeds.com](http://www.jpeds.com)), 2 died in the neonatal period, and 13 families were lost to follow-up. Of the 85 families contacted for the 7-year assessment, 5 declined to participate and 73 accepted. Seven other families refused to participate in the encounter but agreed to complete part of the evaluation by phone. In these families, data on epilepsy, schooling, and parental opinions were recorded.

Data were available for 80 families (82% of the survivors). The assessments requiring a face-to-face encounter (motor examination, language assessment, and WISC-IV) were available for 73 children (74%); of these, 1 child did not complete the language assessment. The median age at evaluation was 7 years, 1 month (IQR, 7 years, 0 month to 7 years, 2 months).

### Epilepsy (n = 80)

Sixteen children (20%) experienced at least 1 seizure after the neonatal period, including 3 with seizure with fever at age 11, 15, and 36 months. One child had a single untreated afebrile focal seizure at age 5 years. Among the 12 children (15%) with epilepsy, 10 had multiple seizures and 2 had a single focal afebrile seizure before the initiation of antiepileptic treatment. Four children had epileptic spasms (all before 1 year of age), and the remainder had epilepsy with focal seizures (all after 1 year of age). At the time of assessment, 3 children were seizure-free for >1 year without treatment. Thus, the prevalence of active epilepsy at 7 years of age was 11% (Figure 2; available at [www.jpeds.com](http://www.jpeds.com)).

### Schooling (n = 80)

Sixty children attended their ordinary school grade, 2 at a higher grade than expected. Four of these 60 children received individual educational support through a school assistant individually assigned to the child. Ten children were held back by 1 (n = 10) or 2 (n = 1) grade levels within the regular school program, and 7 children were attending a special school. Altogether, 22 children (28%) had low academic skills.

### Developmental Profile

**Motor (n = 73).** Fifty children had a normal examination, and 23 (32%) had unilateral CP. Ten were classified as GMFCS I, and 13 were classified as GMFCS II (ie, walk with limitations). Eight children were classified as BFMF1 (limitations of more advanced fine motor skills in the impaired hand), 12 were classified as BFMF2 (ability to grasp or hold in the impaired hand), and 2 were classified as BFMF3 (no functional ability in the impaired hand). One child had motor symptoms only in the lower limb (BFMF0).

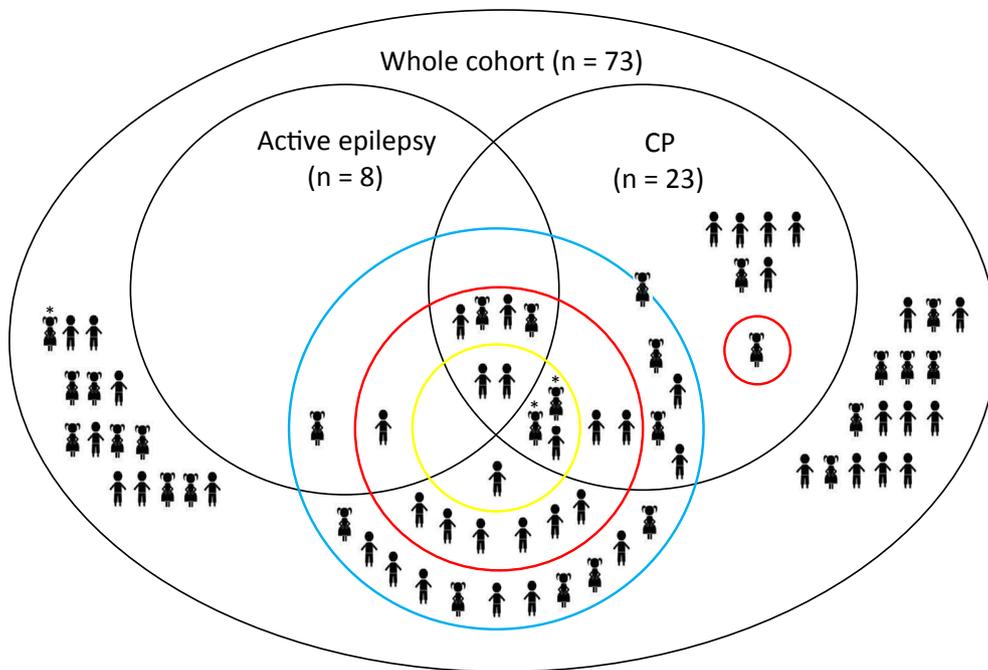
In 4 children, motor status changed between the previous assessment (at ages 2 or 3.5 years) and the current assessment. Two of them have now mild spastic features (GMFCS I, BFMF1/2), and the other 2 have predominant dyskinetic features. None of those who had been diagnosed with CP earlier had recovered normal motor functions at age 7 years.

**Global Intellectual (n = 73).** Median overall results were as follows: VCI, 98 (IQR, 83-108); PRI, 94 (IQR, 76-108); WMI, 87 (IQR, 76-100); PSI, 100 (IQR, 83-111). FSIQ was calculated in only 15 children owing to significant discrepancies between indices that precluded a valid calculation in the 58 other children. Three children had an FSIQ <70. Among those with a nonvalid total FSIQ calculation, 3 had both a VCI and a PRI <70. A total of 6 children (8%) exhibited global intellectual deficiency (Figure 3; available at [www.jpeds.com](http://www.jpeds.com)).

**Spoken Language (n = 72).** Thirty-five children (49%) had impaired language. Numbers of left, right, and bilateral lesions were similar between children with impaired vs normal profiles: 24/9/2 vs 22/12/3, respectively. The morpho-syntactic expressive component was most frequently affected. 26/35 (74%) children had both expressive and receptive language impairments, and 7 children (20%) had isolated expressive deficiency, and 2 children (6%) had isolated receptive deficiency. Twenty-six children (74%) had deficiency in at least 2 of the following components: speech and sound abilities, lexicosemantic, or morphosyntactic. Six children (17%) had isolated morphosyntactic deficiency and 3 children (8%) had isolated lexicosemantic deficiency.

### Co-Occurrence (n = 72)

Figure 4 shows a high co-occurrence between all variables. This was confirmed by PCA, showing that all endpoints were positively correlated (Figures 5 and 6; Figure 5; available at [www.jpeds.com](http://www.jpeds.com)). The principal component was



**Figure 4.** Girls and boys belonging to each of the following categories at 7 years of age: active epilepsy, CP, impaired language (blue circle), low academic skills (red circle), and global intellectual deficiency (yellow circle). One girl with CP was not tested for language. An asterisk indicates children who were epileptic earlier but who were seizure-free for >1 year without treatment at 7 years.

particularly linked to schooling. The second axis was more prone to characterize clinical assessment, with 2 sets: language/epilepsy and motor/global intellectual. Although these sets of variables are located in opposite quarters, they contribute roughly equally to the academic dimension. Finally, the factorial plan (Figure 5) can be divided into 3 parts: children with (1) good academic skills and no neurologic signs and those with low academic skills; and either (2) impaired language and active epilepsy; or (3) global intellectual deficiency and CP.

### Parental Opinion (n = 69)

Forty-three children were classified into at least 1 of the following categories: active epilepsy, low academic skills, CP, global intellectual deficiency, and impaired language (Figure 4). Thirty-one parents (42%) reported sequelae of the child's neonatal event, 38 (52%) reported no sequelae, and 3 did not answer. In 49 cases, the parental and medical views matched. In 6 cases, the family thought the child had sequelae but the medical team did not, and in 14 cases the opposite was found. In 1 family in which the parents disagreed, the child was medically evaluated with low academic skills and impaired language.

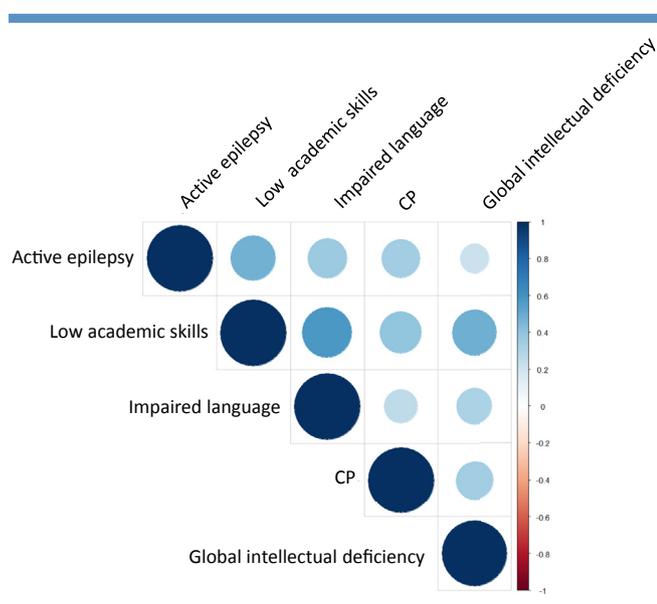
## Discussion

In this cohort of term newborns with NAIS, most children exhibited some sequelae 7 years later; however, severe disability, such as drug-resistant epilepsy, moderate/severe CP

(GMFCS  $\geq$ III or BFMF  $\geq$ 3), or global intellectual deficiency, is the exception: 6%, 3%, and 8%, respectively, with a major co-occurrence. In other words—and to answer to a common question of parents—all were able to walk independently and to talk. These results are in line with previously reported data, but our study has the advantage of longitudinally addressing multimodal outcomes of a large homogeneous population, thereby providing a more comprehensive view of the consequences of NAIS by school age.

Although early imaging determinants of motor outcome after NAIS are now well-accepted,<sup>1,16</sup> evidence concerning epilepsy is more controversial. Recent longitudinal studies of term and near-term NAIS populations have provided consistent data.<sup>2,9,24</sup> The risk of epilepsy is lower than initially presumed: 9% at 2 years of age in the Swiss Neuropaediatric Stroke Registry (n = 74),<sup>2</sup> 13% at 2.5 years of age in a US cohort (n = 46),<sup>9</sup> 15% at 7 years of age in our cohort (n = 80), and 15% at 8.5 years of age in an Italian cohort (n = 55).<sup>24</sup> Because epilepsy is not necessarily permanent, the prevalence of active epilepsy in any given period is lower than this cumulative incidence over time. Furthermore, epilepsy segregates with impaired development.

The proportion of global intellectual deficiency after NAIS appears to be low. Our 8% rate is in line with the 11% rate reported by Ricci et al<sup>25</sup> and the 7% rate reported by Westmacott et al<sup>26</sup> in their NAIS population assessed at ages 5.8 years (n = 28) and 9.6 years (n = 26), respectively. Reported results are inconsistent regarding whether these cognitive abilities are maintained at the same level over the course of development,<sup>6</sup>



**Figure 6.** Heat map obtained with PCA of the 5 variables. The color of the circles indicates the direction (*blue*, positive) of the correlation, and the diameter of the circles indicates its strength.

or whether the children are at increased risk for emerging deficits during school years, notably in nonverbal reasoning.<sup>7,26</sup>

Nonetheless, global intellectual abilities within normal limits do not preclude impaired development. This is particularly apparent in our population, in which 28% of children have low academic skills after 1 year of mandatory schooling. That this rate will rise steadily as grade level increases is a logical assumption. Even without IQ deficit and behavioral problems, perinatal/childhood stroke impairs social adjustment and participation, with consequences extending to a large range of life skills.<sup>27</sup>

We found a higher prevalence of language impairment than previous reports suggesting that early expressive delays are usually resolved by school age, and that verbal abilities seem to be preserved after early brain insult.<sup>11</sup> In our cohort as well, VCIs are better maintained than PRIs (Figure 3). Yet, using assessments tools that probe detailed linguistic functions, subtle deficiencies become more apparent; for example, 29 children with PIS who were administered the Clinical Evaluation of Language Fundamentals–Revised at 10.5 years of age had a mean receptive score of 82, a mean expressive score of 78, and a mean total score of 79 (out of a theoretical mean 100), and a mean verbal IQ of 99.<sup>6</sup> Specific tests after perinatal/childhood stroke also have revealed that standard skills are preserved, but there is a reduction in more sophisticated language.<sup>28,29</sup>

Ultimately, all of these impairments may weaken schooling. This is particularly salient in our population, in which low academic skill is a subset of impaired language (Figure 4). The co-occurrence between impaired developmental issues and epilepsy is well documented.<sup>2,5-12,24</sup> This is a prominent point in our cohort as well. Furthermore, all of these issues

have been independently associated with low reported health status.<sup>30</sup> The strongest correlations were observed among schooling, language, and global intellectual abilities (Figure 4). These assessments may represent different approaches of the same field of intellectual dysfunctioning, and CP and epilepsy might be understood as associated or explicative medical variables of this aforementioned field of impairment (Figures 4-6).

It is often hypothesized that the larger the stroke lesion, the more diffuse the impact. Nevertheless, our imaging data at 7 years of age in the same population demonstrate that motor outcome is more strongly related to the localization of the ischemic insult along the motor pathway than to its size.<sup>19</sup> Impaired development due to motor deficiency itself is an additional, nonexclusive possibility. In a recent study of a large population of children with CP, the most reliable predictor of FSIQ was motor ability, and the second most common independent variable was epilepsy.<sup>31</sup> Thus, pervasive interactions between motor and other intellectual skills, which occur in normally developing children,<sup>32</sup> also might arise after early brain insult. The detrimental effect of epilepsy, its treatment, and its socio-familial burden on neuroplasticity and development will also benefit from further research.

The non–population-based design of the AVCnn cohort is a limitation. However, the great majority of participating units (which epitomize the range of neonatal units in France) declared that they had reported consecutively all cases satisfying the inclusion criteria.<sup>14</sup> According to more recent epidemiologic data, our cohort includes one-third of NAIS cases born during the inclusion period.<sup>2</sup> Furthermore, the neonatal clinical and imaging data were similar to those reported for other large hospitalized- or population-based studies.<sup>2,33,34</sup> Thus, the AVCnn cohort likely provides a good representation of NAIS.

Health practitioner–centered and familial perceptions certainly merit further study, given the remaining gaps between parental and medical approaches. The impact of a child’s longstanding impairment on the family’s day-to-day life and how parents adapt and cope with the child’s diagnosis are increasingly recognized as determinants of well-being and developmental and behavioral trajectories. Understanding these issues and improving family-centered care may serve to identify those who may benefit from specific guidance. A rapidly applied scale to assess the familial impact of perinatal stroke has recently been proposed.<sup>35</sup> This measure could have been relevant, but was not available at the time the 7-year assessment study was designed.

In conclusion, this report provides a cross-sectional snapshot at school age of a population of term-born children who sustained an NAIS. Furthermore, the AVCnn cohort is a unique tool providing a research opportunity and methodology to increase our knowledge of developmental issues following stroke in childhood.<sup>36</sup> The next steps will be dedicated to the early intrinsic (obstetrical characteristics, sex, lesion volume, and laterality) or extrinsic (sociodemographic variables) determinants

of outcome. This longitudinal approach will help clinicians predict and prevent adverse outcomes. ■

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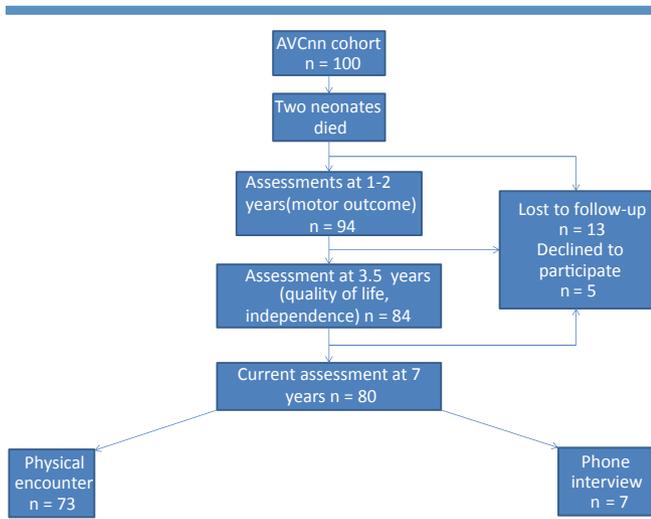
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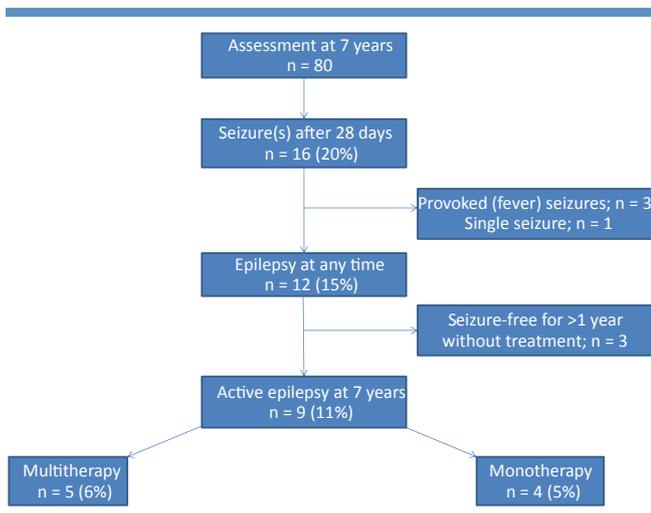
## Appendix

Additional members of the AVCnn Study Group include:

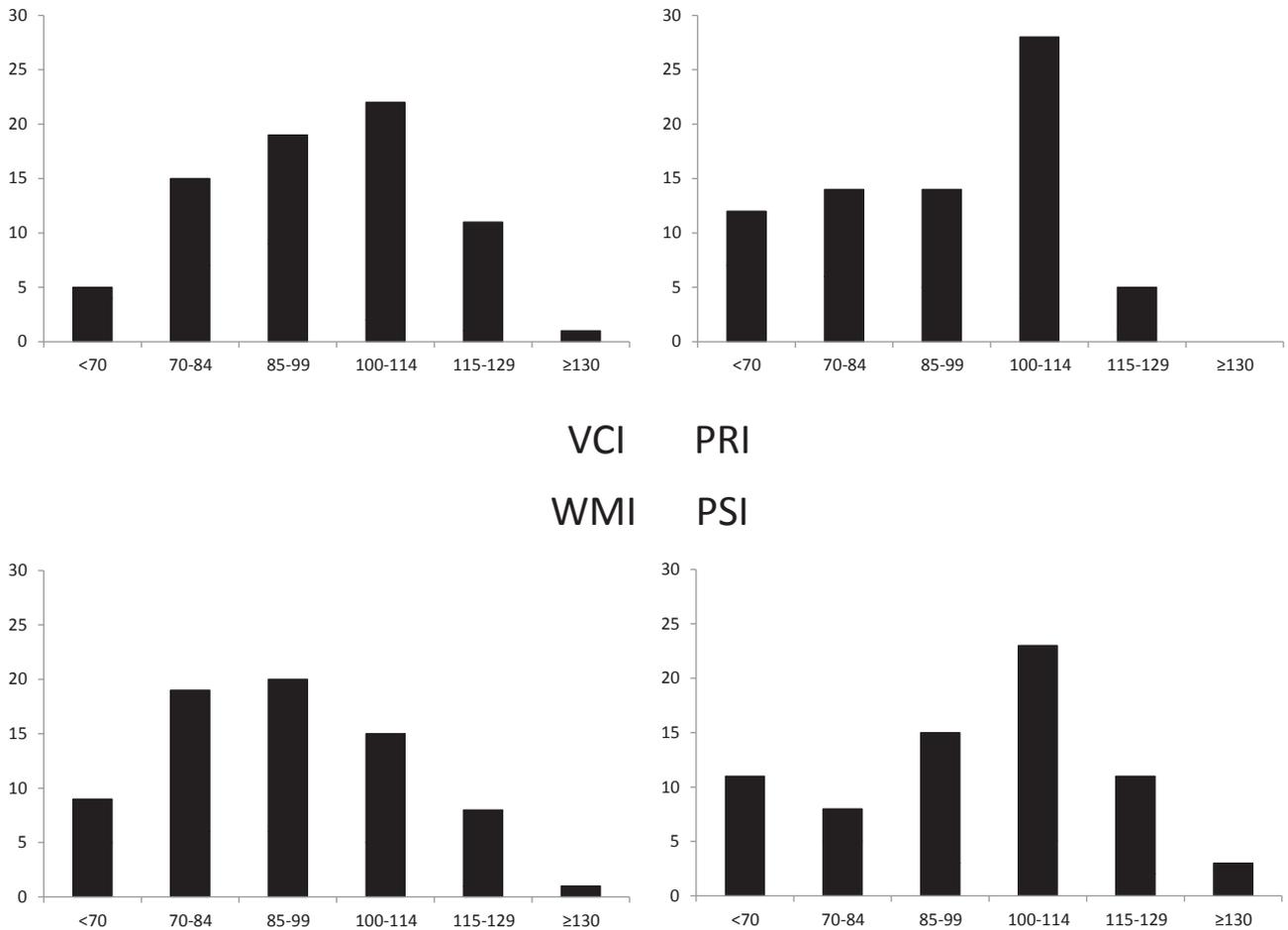
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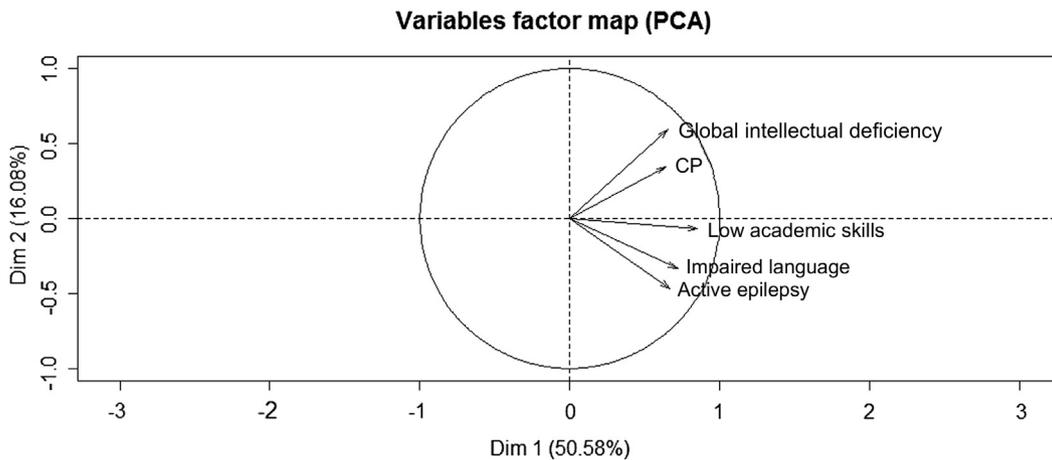
**Figure 1.** Follow-up until the age of 7 years of a cohort of 100 children with an NAIS.



**Figure 2.** Seizures and epilepsy from ages 29 days to 7 years in 80 children with an NAIS.



**Figure 3.** Overall results of the 4 indices of the WISC-IV at 7 years of age. VCI and PRI were assessed in all children (n = 73). WMI was assessed in 72 children; PSI, in 71 children.



**Figure 5.** Variable factorial plan obtained with PCA of the 5 variables. All vectors contribute positively to the principal axis. The value of the analysis is strengthened by the fact that the 2 principal dimensions represent two-thirds of the total variance of the dataset, and that all vectors are close to the circle of equilibrium contribution.