

Chapter 2

Study population, MRI studies & neuropsychological evaluation



STUDY POPULATION

For the current studies we included children born SGA and AGA. The group of SGA children was further divided into a subgroup of SGA children with persistent short stature (SGA-) and a subgroup with postnatal catch up growth (SGA+). Following the International Small for Gestational Age Advisory Board Consensus Development Conference Statement (Lee *et al.*, 2003), SGA was defined as a birth weight and/ or birth length \leq -2SD, adjusted for gender and gestational age; SGA+ was defined as postnatal catch-up growth with an actual height of less than 2 SD below the Dutch population reference mean and SGA- as persistent postnatal growth failure based on an actual height below -2.5 SD (Fredriks *et al.*, 2000). AGA was defined as birth weight and length above -2 SD, without known history of prenatal growth restriction. Inclusion was (mainly) based on birth weight because data on birth length were not available in a substantial part of the children. Each group included 15-20 children.

Inclusion criteria (AGA, SGA+ and SGA-):

- Gestational age \geq 34 weeks
- Single birth
- History without complicated neonatal period with signs of severe asphyxia, defined as an Apgar score \geq 7 after 5 min
- No growth failure due to other somatic or chromosomal disorders or syndromes (except for Silver Russell syndrome)
- No previous or present use of medication that could interfere with growth or GH treatment
- When MRI/ MEG investigation: body containing irremovable metal parts (bracelet, pacemaker etc)
- No severe learning disability (No IQ < 70)

Additional inclusion criteria of short statured SGA (SGA-):

- Actual length below -2.5 SD and at least 1 SD below target height-SDS
- No evidence of catch-up growth during the preceding year
- Calendar age between 4 and 7 years at time of inclusion

Additional inclusion criteria SGA with catch-up growth (SGA+):

- Actual length above -2 SD
- Calendar age between 4 and 7 years at time of inclusion
- For optimal comparability, the group of AGA children was matched for age, gender and gestational age with the SGA group.

Recruitment

After approval by the ethics committee of the VU University Medical Center, Amsterdam, The Netherlands, inclusion period was between 1st of April 2007 and 1st of August 2010.

SGA children

We recruited SGA children with three different strategies.

1. Selection from birth registration databases of the department of obstetrics and gynecology of mainly three hospitals (Medical Center Alkmaar (Alkmaar), Kennemer Gasthuis Hospital (Haarlem) and Zuwe Hofpoort Hospital (Woerden))
2. Selection and referral by pediatricians of the VU University medical Center or one of the participating hospitals (Appendix).
3. Referral via the Dutch growth Foundation after indication and approval for GH therapy.

Children who were selected via one of the birth registration databases were subsequently sent an invitation to visit the outpatient department of that particular hospital. During the first visit, children underwent a routine check-up and were asked to participate in the study. Children and their parents were informed about the study during the visit by the pediatrician who participated in the study (HMA de Bie). Additional written and audiovisual information including a child-friendly video/ DVD was provided for home use. Parents could announce their participation in the follow-up telephone call which took place shortly after the visit.

AGA children

Most of the AGA children were friends or classmates of the SGA children, some were siblings. The remainder were not at all related to the SGA children and were recruited via friends or acquaintances of one of the staff members of the study project.

Written informed consent was obtained from the parents or guardians of each child and obtained according to the Declaration of Helsinki (BMJ 1991; 302: 1194). Figure 2.1 displays the derivation of the study population. 71 children participated in the study. A subgroup of 58 underwent both NPT and MRI investigations, the remainder 13 children participated the NPT part only. Baseline characteristics of the total group and subgroup are listed in Table 2.1 and Table 2.2.

MRI STUDIES

To investigate brain anatomy, children underwent s-MRI lasting approximately 5 minutes. Furthermore, f-MRI (both task-related and rs-fc) was included in the MRI

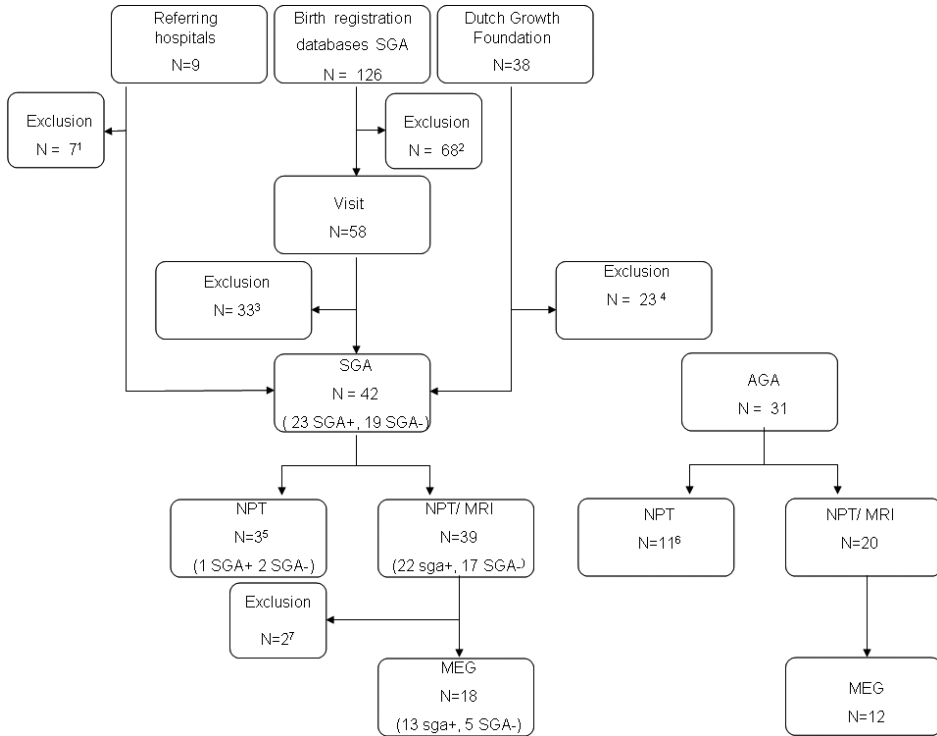


Figure 2.1 Study population.

- 1: 5 prematurity < 34 weeks, 1 twin, 1 severe learning disorder & eIQ<70 (Silver Russell Syndrome)
- 2: 1 AGA, 3 moved, 6 refused, 58 no response
- 3: 10 too busy, 2 syndrome evaluation, 4 school problems, 7 too stressful, 1 IQ <70, 9 no reason
- 4: 2 started GH, 6 prematurity, 1 twin, 2 distance, 3 too busy, 3 too stressful, 1 illness father, 5 no reason
- 5: 2 mock scanner failure (SGA-)
- 6: 6 mock scanner failure, 5 participation NPT only
- 7: 1 SGA- exclusion due to diagnosed IGF1 receptor mutation after inclusion, 1 SGA+ due to IQ <70

procedure. For this purpose, a picture learning task was developed (long-term memory task including 1. encoding phase lasting approximately 7 minutes; 2. recognition phase lasting approximately 14 minutes). Prior to scanning, a pilot study was performed at an elementary school to check whether children in this age range are capable of performing a long-term memory task and to assess the mean attention span of 4-7 year old children. Based on our observations, we concluded that in general, children in this age range will be capable of performing the encoding task in the scanner properly while paying attention. Unfortunately, we had to conclude that for a substantial proportion of the children it was too difficult to accomplish the recognition phase in the MRI scanner. Instead of performing the recognition phase of the memory task in the scanner, we decided to present the recognition test on a personal computer screen, set up in a stimulus-free room, outside the scanner. The rs-fc MRI lasted approximately 6 minutes.

Table 2.1 Baseline characteristics of total group of children (n=71)

	AGA (N=31)	SGA+ (N=22)	SGA- (N=18)	F value	p value
Gender (boys:girls)	17:14	12:10	11:7		ns
Gestational age in weeks	39.9 (1.2)	38.9 (2.0)	39.3 (2.2)	1.7	ns
primigravidae/ multigravidae	14/17	12/10	10/8		ns
Birth weight in SD	0.4 (0.9)	-2.6 (0.4)	-2.4 (0.5)	163	<0.0001***
Birth Length in SD ^a	0.5 (0.8)	-1.9 (1.2)	-2.7 (0.8)	66.5	<0.0001******
Head circumference in SD at birth ^a	0.0 (0.9)	-1.1 (0.5)	-1.1 (1.1)	8.1	0.001***
Paternal length in cm	183.3 (9.1)	181.5 (7.0)	179.4 (7.1)	1.2	ns
Paternal length in SD	-0.2 (1.3)	-0.4 (1.0)	-0.7 (1.0)	0.7	ns
Maternal length in cm	170.3 (6.1)	168.8 (6.4)	162.0 (4.4)	11.5	<0.0001***
Maternal length in SD	0.0 (1.0)	-0.3 (1.0)	-1.3 (0.6)	10.4	<0.0001***
Target height in SD	0.5 (0.9)	0.3 (0.8)	-0.3 (0.6)	5.8	0.005*
Target height in SD (2010)	0.0 (0.8)	-0.2 (0.6)	-0.7 (0.5)	6.5	0.003***
Parental education					
≥ upper-secondary education (fathers) in %	47	38	53		ns
≥ upper-secondary education (mothers) in %	50	43	59		ns

Data (except gender and parental educational levels) are presented as mean (\pm standard deviation);

a: When birth length or head circumference were not available, measures from first visit at child health centre was taken; $p < 0.05$: *AGA vs SGA-, **AGA vs SGA+, ***SGA+ vs SGA-

NEUROPSYCHOLOGICAL EVALUATION

The assessment battery consisted of developmentally adequate tasks covering intelligence and major domains of cognition. The assessments lasted approximately 2 hours.

General Intelligence

- Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R, Dutch Version) (Wechsler 1989): Block Design, Comprehension, Picture Completion and Calculation (age < 6 years). Short form (LoBello SG. 1991)
- Wechsler Intelligence Scale for Children (WISC-III^{NL}): Vocabulary, Block Design, Similarities and Picture Completion (6 < age < 16 years) (Wechsler 2002). Short form (Kaufman *et al.*, 1996)
- Raven's Coloured Progressive Matrices (CPM, 1998 Edition, computerised version)

Memory and Learning

- Word Span (age < 6 years) (Schouten *et al.*, 2002) and Digit Span (age \geq 6 years) (Wechsler 2002)
- Learning Locations (computerized) (Schouten *et al.*, 2002)

Table 2.2 Baseline characteristics of subgroup of children undergoing both NPT and MRI investigations (n=58)

	AGA (N=20)	SGA+ (N=21)	SGA- (N=16)	F value	p value
Gender (boys:girls)	11:9	11:10	9:7		ns
Gestational age in weeks	39.4 (2.0)	38.8 (1.9)	39.2 (2.0)	0.5	ns
primigravidae/ multigravidae	8/12	12/9	9/7		ns
Birth weight in SD	0.3 (0.9)	-2.6 (0.4)	-2.3 (0.4)	127.8	<0.0001***
Birth Length in SD ^a	0.5 (0.9)	-1.9 (0.9)	-2.5 (0.8)	62.2	<0.0001***
Head circumference in SD at birth ^a	0.0 (0.7)	-1.0 (0.7)	-1.0 (1.0)	8.9	<0.0001***
Paternal length in cm	180.2 (9.0)	181.2 (7.0)	178.4 (6.7)	0.6	ns
Paternal length in SD	-0.5 (1.3)	-0.4 (1.0)	-0.8 (1.0)	0.6	ns
Maternal length in cm	170.5 (6.1)	168.5 (6.3)	162.0 (4.5)	9.2	<0.0001***
Maternal length in SD	0.0 (0.9)	-0.4 (1.0)	-1.3 (0.6)	8.8	0.001***
Target height in SD	0.4 (0.9)	0.3 (0.8)	-0.4 (0.6)	4.0	0.02*
Target height in SD (2010)	-0.2 (0.7)	-0.3 (0.6)	-0.8 (0.5)	4.3	0.02*
Parental education					
≥ upper-secondary education (fathers) in %	68	35	60		ns
≥ upper-secondary education (mothers) in %	63	41	47		ns

Data (except gender and parental educational levels) are presented as mean (\pm standard deviation);
a: When birth length or head circumference were not available, measures from first visit at child health centre was taken; p<0.05: *AGA vs SGA-, **AGA vs SGA+, ***SGA+ vs SGA-

Visual Constructive skills (and Visual Memory)

- Rey-Osterrieth Complex Figure Test (Bernstein and Waber D.P. 1996)
- Target Test (incorporated in the Reitan Neuropsychological Battery for Children, Dutch Version (Vieijra JPM *et al.*, 1994).
- Beery-Buktenica Developmental test of Visual –Motor Integration, with supplemental developmental tests of Motor Coordination and Visual Perception (Beery 2010).

Reaction Times

- Schuhfried Reaction Time measurement, Vienna Test System (computerized)

Behaviour

- Child Behaviour Checklist (Achenbach and Edelbrock 1991)
- Teacher's Report Form (Achenbach 1991)

Contextual information was gathered through self-formulated questionnaires on demographics and parental educational levels.

