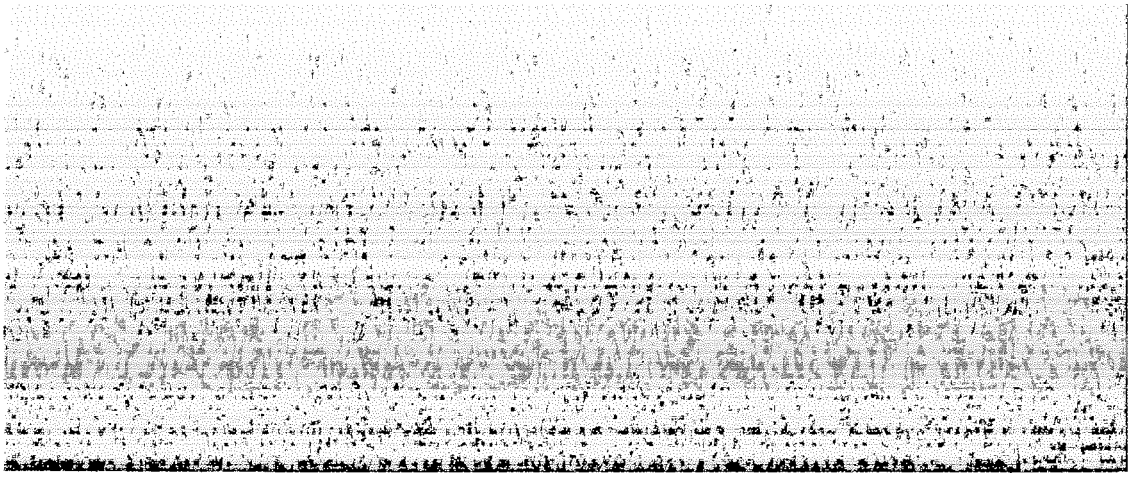
OUTCOME AT TWO YEARS OF AGE IN VERY PRETERM AND VERY LOW BIRTHWEIGHT INFANTS IN THE NETHERLANDS

D.M.C.B. VAN ZEBEN - VAN DER AA



STELLINGEN

1. De idee bestaat dat samenwerking van universitair en niet-universitair werkzame kinderartsen een follow-up onderzoek ten goede zou komen (Dev. Med. Child Neurol. 1983; 25: 415-416). In de nauwgezetheid waarmee ook deze laatstgenoemde groep aan dit onderzoek heeft meegewerkt, ziet men dit bevestigd.

2. Het is mogelijk met een gedecentraliseerd opgezette follow-up studie bij een follow-up percentage van 90% een betrouwbare uitkomst te krijgen.

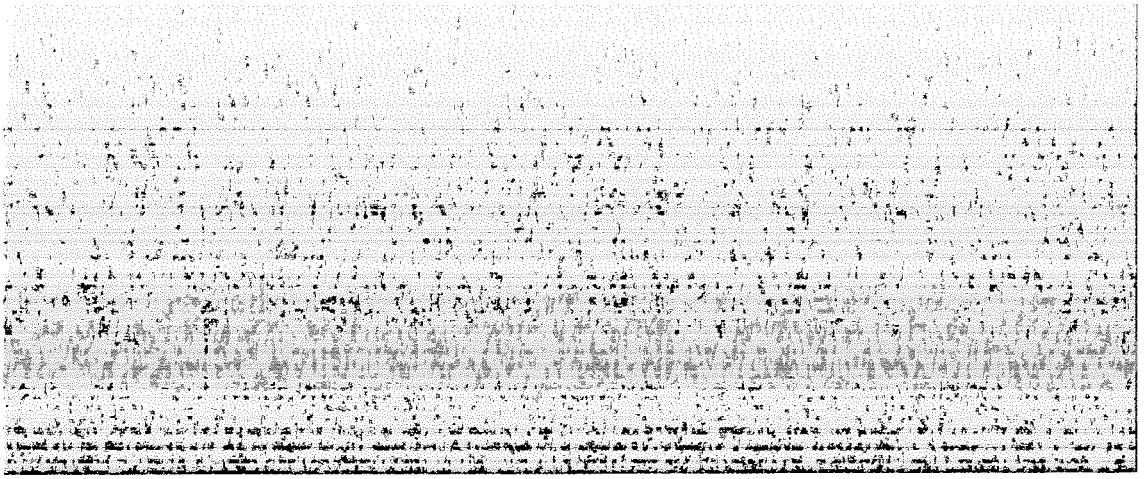
3. De "major adverse outcome" van zeer preterm geborenen in Nederland is gunstig vergeleken met in het buitenland gevonden resultaten. Dit is niet alleen de resultante van de in ons land voor iedere zwangere en pasgeborene goed toegankelijke medische zorg, maar evenzeer van maatschappelijke aspecten zoals een laag aantal tiener-zwangerschappen en gunstige economische omstandigheden zoals het niveau van bijstandsuitkering en minimumloon.

4. Het feit dat in deze studie de Apgar Score gemeten 5 minuten na de geboorte een zo duidelijke correlatie toont met een negatieve uitkomst van de levend geboren en van de overlevende kinderen, pleit voor een opnieuw beoordelen van de waarde van deze zeer eenvoudige scoringsmethode.

5. De bevinding dat elke verhoging van de maximale bilirubine concentratie in het serum boven 100 μmol/L bij zeer preterm geborenen het risico op een handicap vergroot, mag pas aanleiding zijn tot een drastische verandering van het hyperbilirubinaemie beleid, nadat dit via een interventie-trial is aangetoond.

6. In het tweede levensjaar vertoont 80% van de overlevende kinderen in onze studie eenzelfde patroon van medische consumptie als kinderen uit de doorsnee bevolking. In het kader van een gesystematiseerd nazorgprogramma mag men er vanuit gaan dat bij deze kinderen in die periode, een éénmalig gespecialiseerd onderzoek voldoende is.

7. In het algemeen vormt de intensiteit, de duur en het niveau van de zorg, die in de neonatale periode aan het kind wordt verleend de maatstaf voor de intensiteit, de duur en het niveau van de noodzakelijke názorg. Ook de omvang van de prenataal aan moeder en foetus verleende zorg zou in deze beslissing betrokken moeten worden.



8. Gezien de consequenties van de opvang en behandeling van pasgeborenen in NICU's en op kinderafdelingen met high-care faciliteiten op de lange termijn, lijkt het gerechtvaardigd een gedeelte van de in die periode gemaakte kosten aan te wenden voor de evaluatie van de verleende zorg. Tenslotte zou dit kunnen leiden tot een betere beheersing van de kosten in de toekomst.

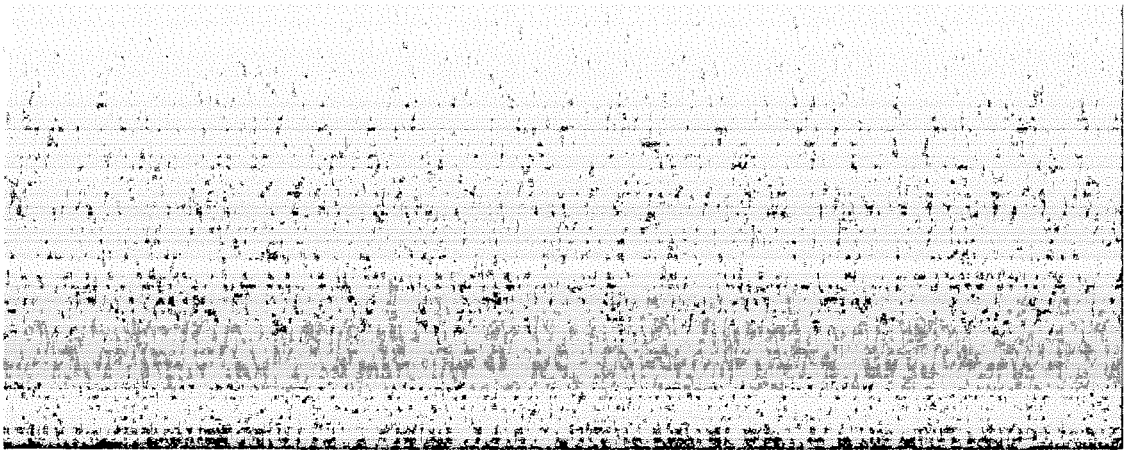
9. De sinds jaar en dag door (kinder)artsen en ouders gerespecteerde uitspraak: "melk is goed voor elk", is er waarschijnlijk mede schuldig aan dat het nog in 1988 nodig was een klinische les te publiceren onder de titel: "Koemelk-eiwit allergie, een nieuw ziektebeeld?
   (Nederlands Tijdschrift voor Geneeskunde 1988; 132: 1377-1379)

10. Het frequent voorkomen van aandoeningen van de bovenste luchtwegen bij zeer jonge kinderen, moet ook voor keel-neus-oorartsen vaker aanleiding zijn de mogelijkheid van een voedselallergie als predisponerende factor in overweging te nemen.

11. De stelling: "De verpleging van zieke kinderen, ook indien zij niet lijden aan een interne ziekte, dient te geschieden in een kinderziekenhuis", is nog steeds van kracht.
   (proefschrift Willem van Zeben, Utrecht 2 october 1945).

12. Het feit dat de vertragingen die optreden in het treinverkeer niet dagelijks via de media bekend worden gemaakt, zou tot de onjuiste conclusie kunnen leiden dat dit probleem zich alleen bij het wegverkeer voordoet.

Leiden, 12 oktober 1989 D.M.C.B. van Zeben-van der Aa



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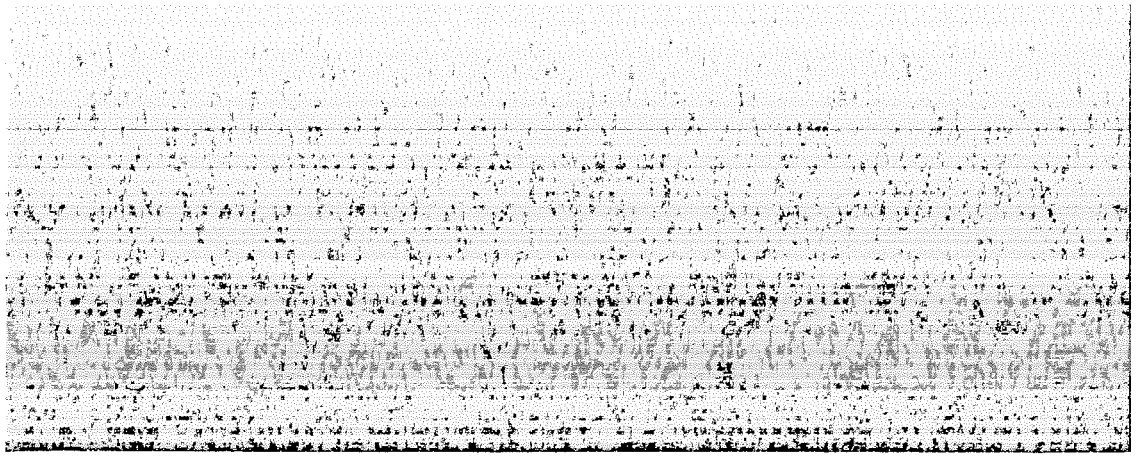

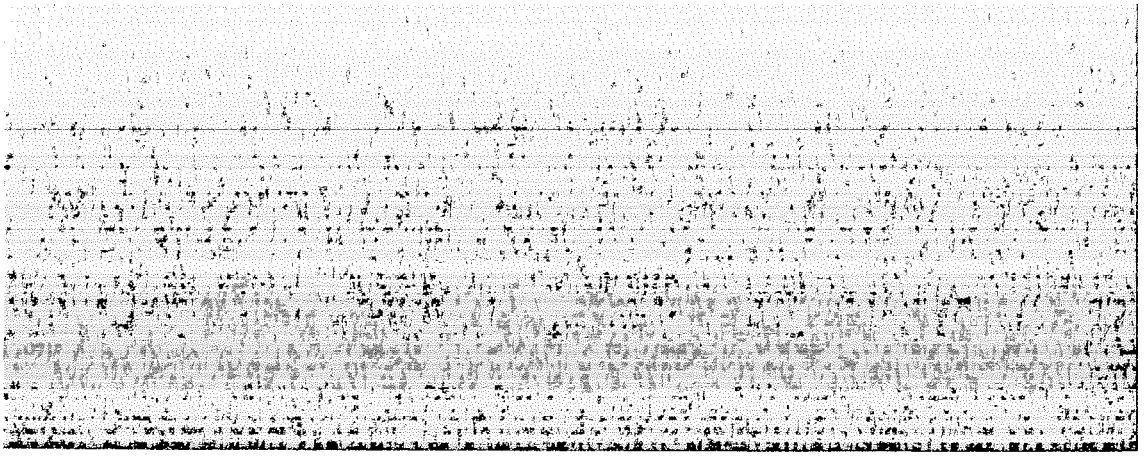

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PROEFSCHRIFT

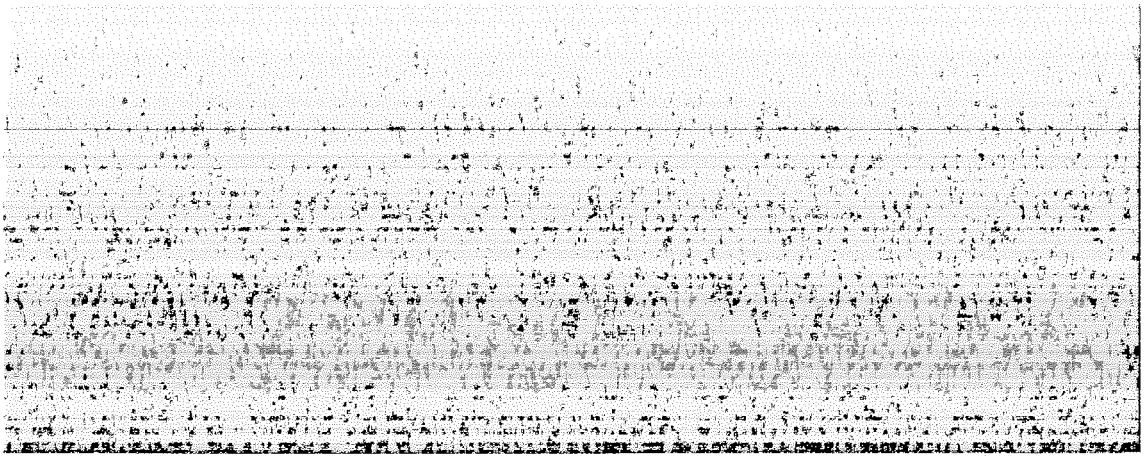
TER VERKRIJGING VAN DE GRAAD VAN DOCTOR AAN DE RIJKSUNIVERSITEIT TE LEIDEN, OP GEZAG VAN DE RECTOR MAGNIFICUS DR. J.J.M. BEENAKKER, HOOGLERAAR IN DE FACULTEIT DER WISKUNDE EN NATUURWETENSCHAPPEN, VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN TE VERDEDIGEN OP DONDERDAG 12 OKTOBER 1989 TE KLOKKE 14.15 UUR

DOOR

DOROTHEA MARIA CORNELIA BARTHOLOMEA VAN ZEBEN-VAN DER AA

GEBOREN TE LEIDEN IN 1953

1989
PASMANS OFFSETDRUKKERIJ B.V., 's-GRAVENHAGE



PROMOTIECOMMISSIE

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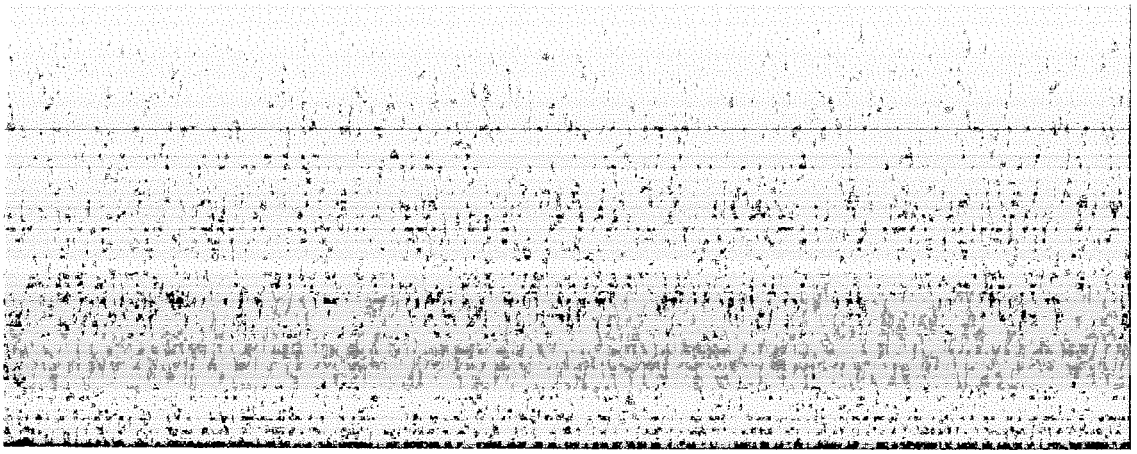
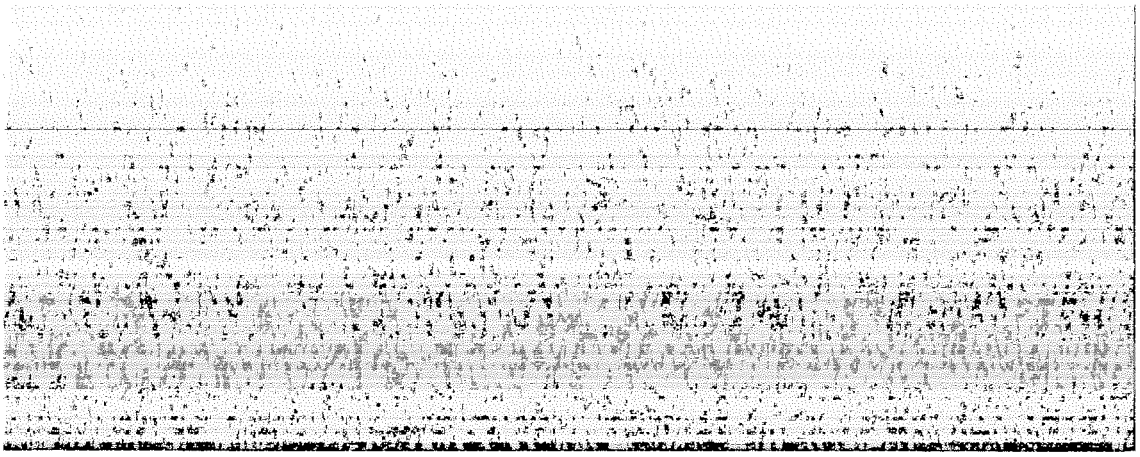
Referent:	Dr. L.A.A. Kollée, Katholieke Universiteit Nijmegen
Overige leden:	Prof. dr. J. Bennebroek Gravenhorst Prof. dr. L.J. Dooren

The Project On Preterm and Small for gestational age is supported by the Praeventiefonds, the Hague (grant 28-766)



ter nagedachtenis aan
mijn vader en schoonvader

aan Gert Jan
Josefien en Pieter



Cover: Dominique, geboren 18-2-1987, 30^{+1} weken, 1350 gram
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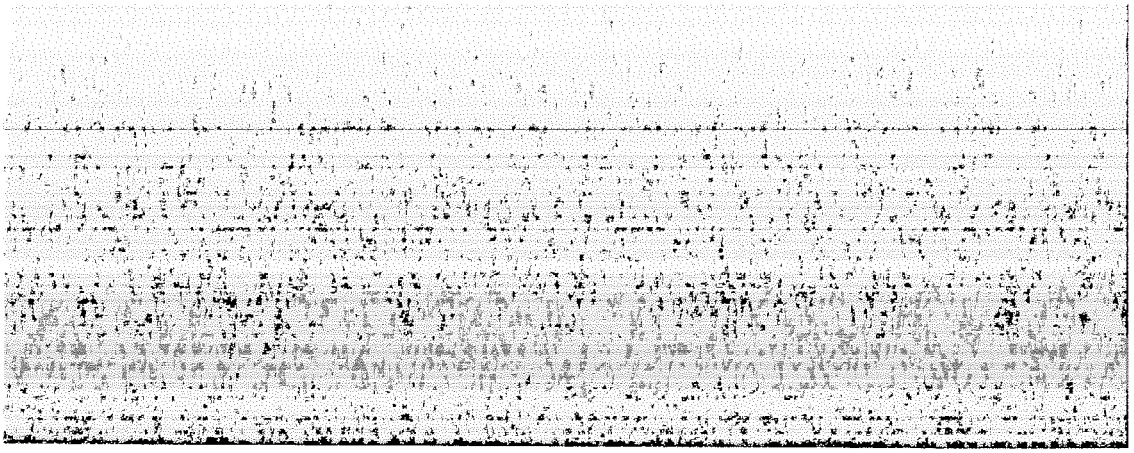

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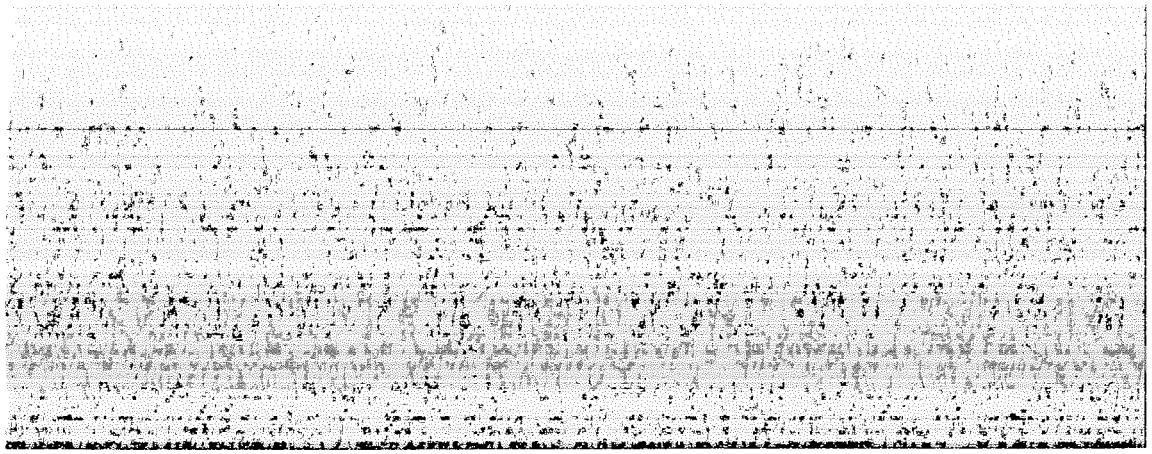
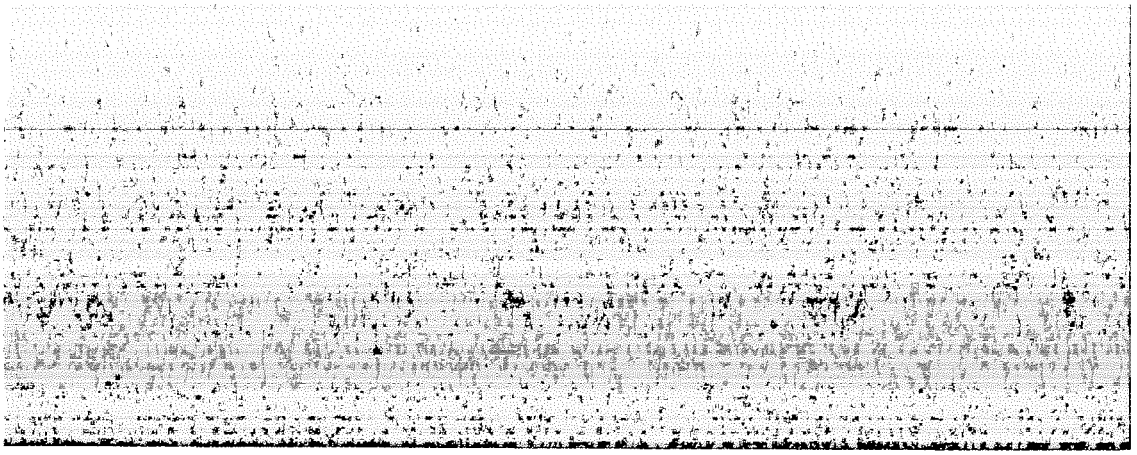




DEFINITIONS

The following definitions and recommendations have been given by the World Health Organization[1] and have been adopted by FIGO:[2,3]

Live birth

Live birth is the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached; each product of such a birth is considered live born.

Gestational age

The duration of gestation is measured from the first day of the last normal menstrual period. Gestational age is expressed in completed days or completed weeks (e.g. events occurring 280 to 286 days after the onset of the last normal menstrual period are considered to have occurred at 40 weeks of gestation).

Birthweight

The first weight of the newborn obtained after birth. This weight should be measured preferably within the first hour of life before significant postnatal weight loss has occurred.

Preterm

Less than 37 completed weeks (less than 259 days).

Low birthweight

Less than 2500 g (up to, and including 2499 g).

Early neonatal death

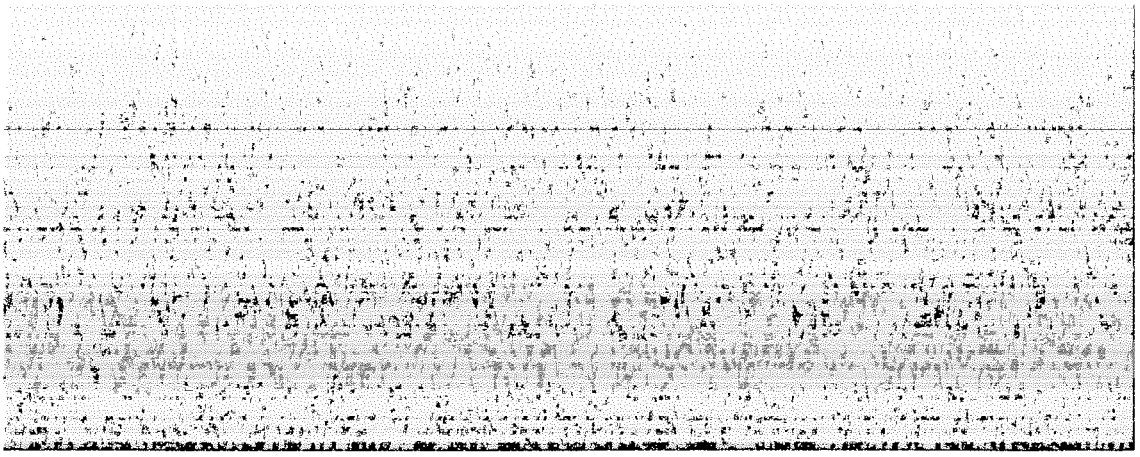
Death of a liveborn infant during the first seven completed days (168 hours) of life.

Late neonatal death

Death of a liveborn infant after seven completed days but before 28 completed days of life (WHO-Approved by FIGO with the modification of "completed days").

Neonatal death

Death of a liveborn infant before 28 completed days of life.



In addition to these, FIGO[3,4] issued the following recommendations:

Low birthweight (LBW)
500 g to less than 2500 g (up to and including 2499 g).

Very low birthweight (VLBW)
500 g to less than 1500 g (up to and including 1499 g).

Extremely low birthweight (ELBW)
500 g to less than 1000 g (up to and including 999 g).

The above mentioned definitions do not adequately cover all circumstances. In the absence of recommendations by WHO or FIGO, we use the following additional definitions:

Postneonatal death
Death from 28 completed days to less than 1 year from birth (i.e. up to and including 364 days).[5,6,7]

In-hospital death
Death of a liveborn infant during the hospital stay following birth and before discharge home, irrespective of transferral between hospitals within this period.

Very preterm
Less than 32 completed weeks of gestation (less than 224 days).

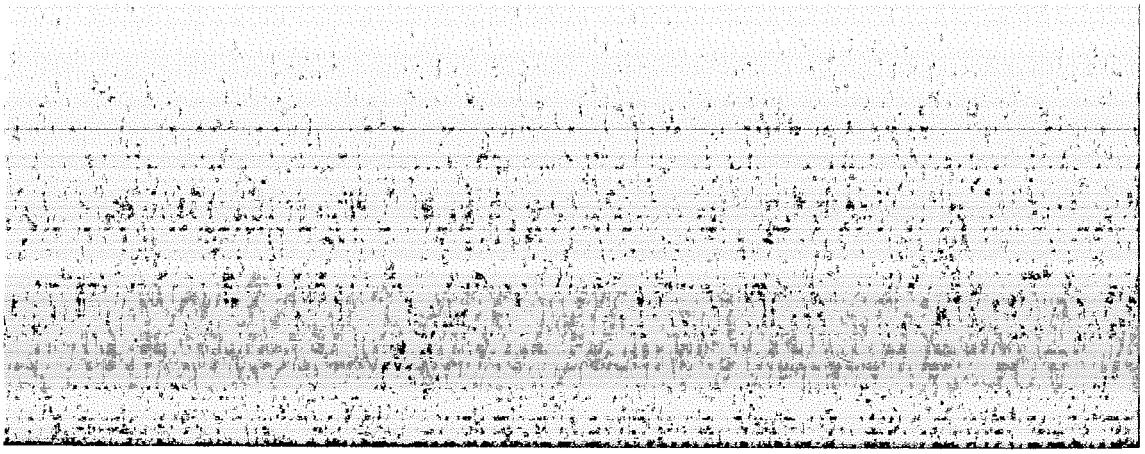
For the follow-up phase, we use the following definitions:

Chronological age = postnatal age
Age calculated from the date of birth.

Corrected age = postconceptual age
Age corrected for preterm birth i.e age from the expected date of birth = age calculated by substracting the difference between term birth (40 weeks) and actual gestational age from the chronological age.

Major adverse outcome
Total deaths plus major handicaps assessed at the age of two years corrected for preterm birth.

Total adverse outcome
Total deaths plus major and minor handicaps assessed at the age of two years corrected for preterm birth.



Total handicaps in survivors

Major and minor handicaps assessed in the surviving children at the age of two years corrected for preterm birth.

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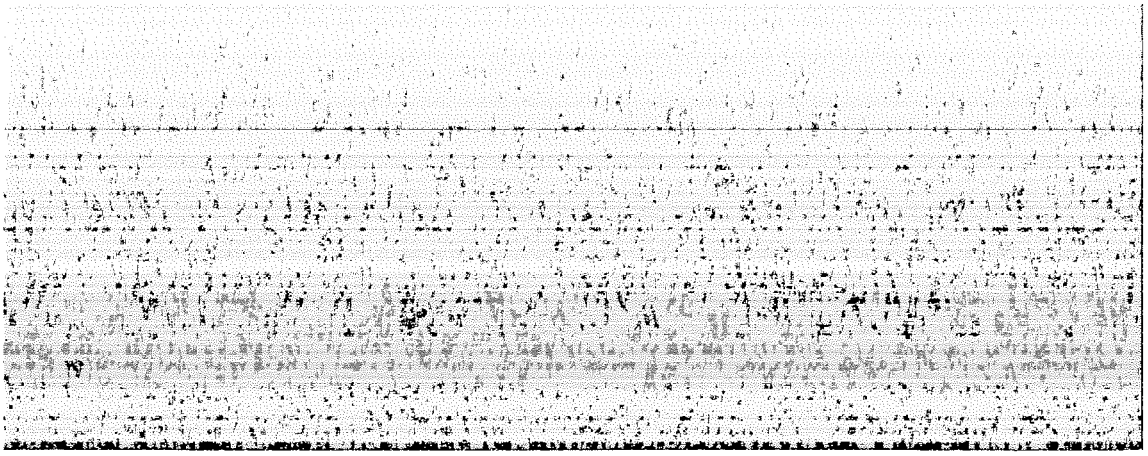
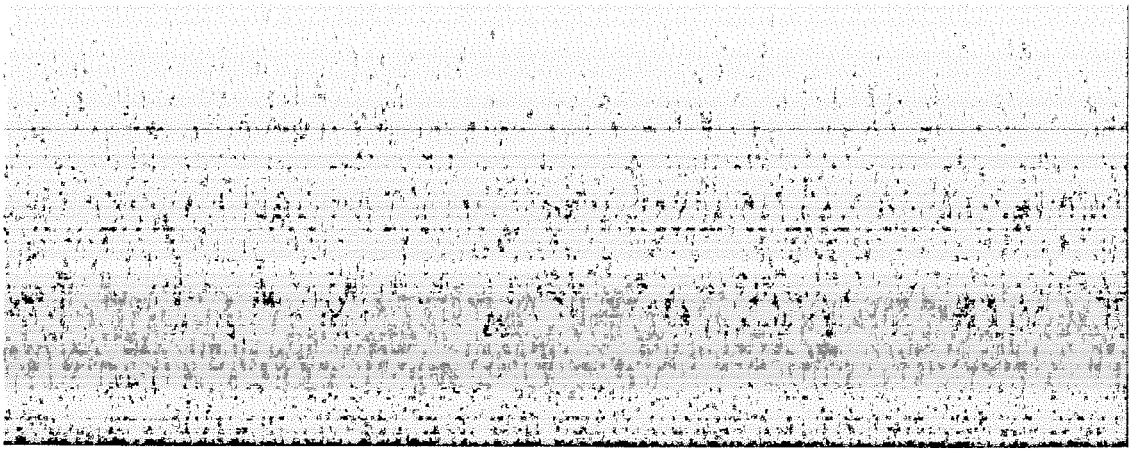


ABBREVIATIONS

AGA = appropriate for gestational age
BPD = bronchopulmonary dysplasia
CBS = Netherlands Central Bureau of Statistics
CI = confidence interval
CNS = central nervous system
CPAP = continuous positive airway pressure
CT = computerized tomography
CTG = cardiotocography
DQ = developmental quotient
ELBW = extremely low birthweight
FIGO = Fédération Internationale de Gynécologie et d'Obstétrie
IC = intensive care
ICH = intracranial haemorrhage
IPPV = intermittent positive pressure ventilation
IRDS = idiopathic respiratory distress syndrome
IUGR = intrauterine growth retardation
LBW = low birthweight
LGA = large for gestational age
MR = mental retardation
ND = neurological dysfunction
NEC = necrotising enterocolitis
NICU = neonatal intensive care unit
OR = odds ratio
PFC = persistent fetal circulation
POPS = Project On Preterm and Small for gestational age
ROP = retinopathy of prematurity
SGA = small for gestational age
TBmax = maximal serum total bilirubin concentration
TPN = total parenteral nutrition
VLBW = very low birthweight
WBC = white blood cell count
WHO = World Health Organization



CHAPTER 1

GENERAL INTRODUCTION

SCOPE OF THE FOLLOW-UP STUDY
OUTLINE OF THIS THESIS
STUDY DESIGN AND METHODOLOGY

GENERAL INTRODUCTION

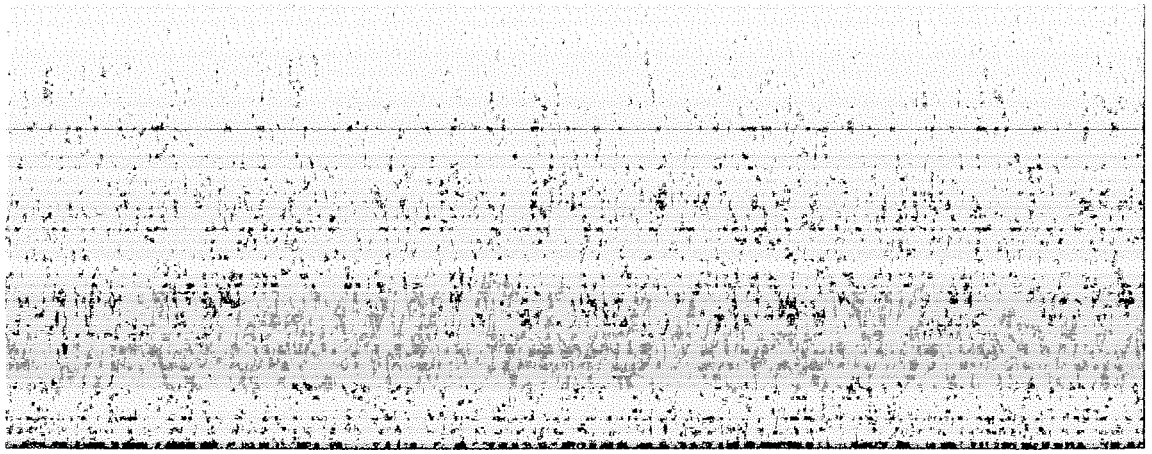
In the absence of a national registration system of birthweight and gestational age of liveborn infants in the Netherlands, no data were available on incidence, morbidity or mortality by gestational age or birthweight. It became a necessity to record pre-, peri-, and neonatal data for two main reasons: collecting information on the incidence of high-risk infants i.e. very low birthweight and very preterm infants, and evaluating the perinatal care offered to them.

Therefore, in the beginning of the 1980's members of the "Sectie Perinatologie van de Nederlandse Vereniging voor Kindergeneeskunde" (Division of Perinatology of the Dutch Paediatric Association) decided to collaborate on collecting information on very low birthweight and very preterm infants in their departments.

With the above mentioned aims in mind a study centre was established in the perinatal centre of the Paediatric and Obstetric Departments, Leiden University Hospital, to initiate and coordinate a nationwide prospective survey. Thus, with Prof. dr. J.H. Ruys, head of the neonatal centre, as supervisor, and S.P. Verloove-Vanhorick, neonatologist, as projectmanager, the "Project On Preterm and Small for gestational age infants " (POPS) was started in 1983. Financial support was given by the Praeventiefonds, the Hague.

The obstetric and neonatal features of the study population have been described previously in the thesis by Verloove-Vanhorick and Verwey, Leiden 1987,[1] and in various other publications, [2-14] as far as pregnancy, delivery, birth and hospital stay after birth were concerned.

For the assessment of care offered to these infants evaluation of neonatal mortality and morbidity, however, is not sufficient. Postneonatal mortality and outcome in terms of later morbidity and handicap should be reported. Therefore, from the outset of the project, a follow-up programme was prepared for all surviving children up to the age of two years corrected for preterm birth. The results deriving from this second phase of this nationwide survey are presented here as a continuation of the thesis by Verloove-Vanhorick and Verwey.



SCOPE OF THE FOLLOW-UP STUDY

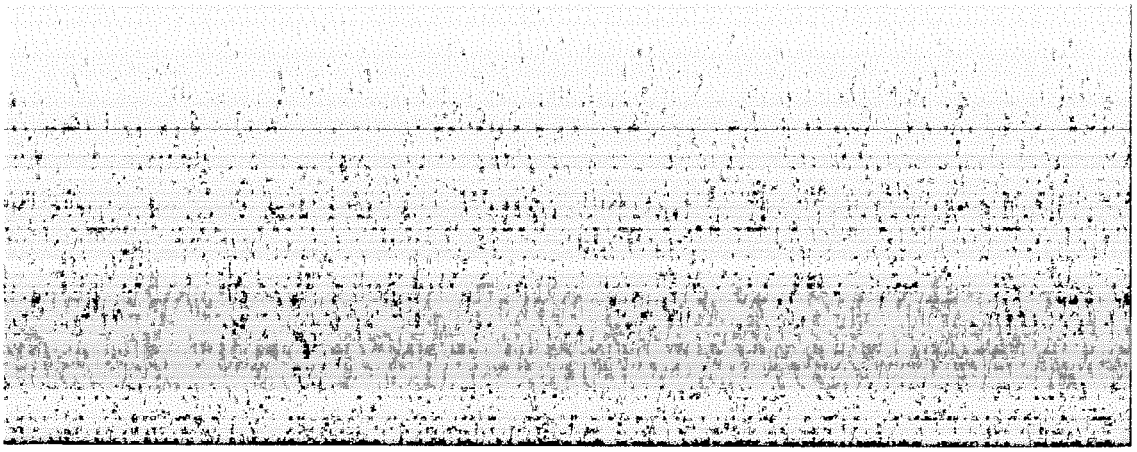
From the beginning of the study, evaluation of neonatal mortality and morbidity alone was considered insufficient to assess the care offered to the high risk infants enrolled in the study: "Project On Preterm and Small for gestational age infants" (POPS).[1] Postneonatal mortality and outcome in terms of later morbidity and handicaps must be reported, based on data recorded during a follow-up period.[15] Initially, a follow-up period was decided on up to the age of two years corrected for preterm birth. The main considerations leading to this decision were the financial feasibility and the readiness of the participating paediatricians to cooperate throughout such a follow-up period. This first phase of the follow-up programme turned out according to plan. From the 1338 infants originally entered in the POPS-survey, 969 were alive at the age of two years. A compliance rate of 97.4% (944 children) was accomplished and within the Netherlands as well as elsewhere interest was taken in the results.

While the two year follow-up programme was carried through, a scheme was worked out for a second follow-up programme to be executed at the age of five years. By now, this second phase of the follow-up study has been carried out successfully. The results are still to come; they will enable us to reveal the consistency between the outcome of the follow-up programmes at two and five years of age as far as the number and severity of handicaps is concerned.[16,17]

OUTLINE OF THIS THESIS

In this thesis the main results deriving from data of the two year follow-up programme are described. The final outcome of the study population i.e. the total mortality, morbidity and handicaps at the age of two years corrected for preterm birth, in association with various perinatal factors is reported. Obviously not all data collected during that period could be incorporated. Some of the information is used in separate publications,[18,19,20,21] or is still being evaluated.

In chapter 2 the handicaps at the corrected age of two years are presented in a descriptive way. In the following chapters the outcome is related to a maternal disorder, i.e. hypertensive disorders during pregnancy (chapter 3), to gender (chapter 4) and to neonatal disorders, such as central nervous system disorders (chapter 5), seizures (chapter 6) and hyperbilirubinemia (chapter 7). The use of health services, such as rehospitalization and outpatient care, is discussed in the chapters 8 and 9. In a descriptive way the frequency of and reasons for using these services are stated. In chapter 10 the separate risk factors are discussed in the context of multivariate analyses, followed in chapter 11 by a general discussion.



STUDY DESIGN AND METHODOLOGY

Infants born between January 1 and December 31, 1983, after a gestational age of less than 32 completed weeks or with a birthweight of less than 1500 g were enrolled in the survey: "Project On Preterm and Small for gestational age infants" (POPS).[1] With the cooperation of paediatricians at the 8 neonatal intensive-care units in university hospitals, 22 neonatal units in teaching hospitals, and 71 neonatal wards in general hospitals, data on infants, born in 133 obstetric departments in the Netherlands were entered prospectively. The study ultimately comprised 1338 infants, i.e. 94% of all such infants born alive in 1983 in our country, and is representative of the total population at risk.

To evaluate the care offered to these infants during the pre-, peri-, and neonatal period, data on neonatal and postneonatal mortality and on outcome in terms of later morbidity and handicaps should be available.[22] Therefore, in continuation of the intake phase of the study, a follow-up programme was planned up to the age of two years corrected for preterm birth. All infants surviving the initial hospital stay were incorporated in this programme. The decentralized study design installed during the intake phase of the study was continued.

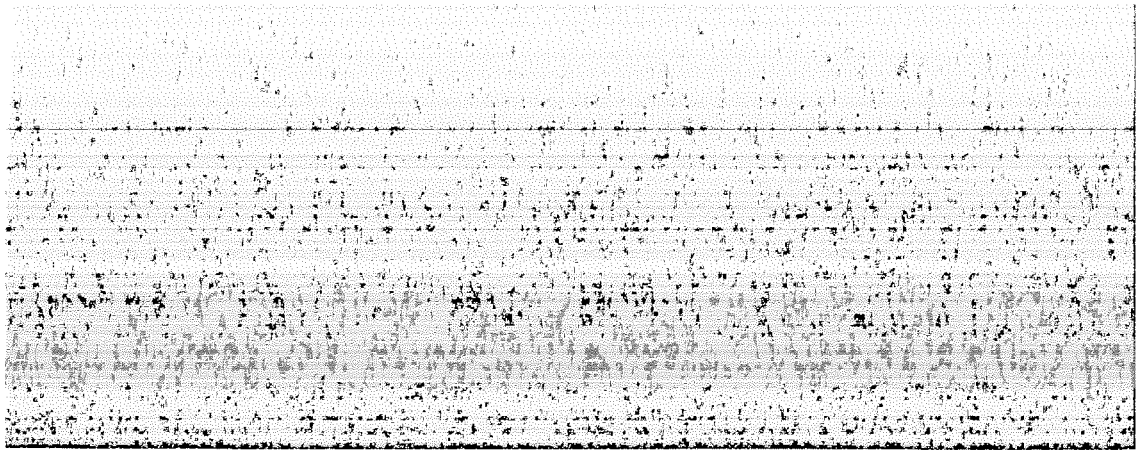
In theory the choice existed between either a follow-up programme on a nationwide scale for all infants discharged after the neonatal hospital admission or a technically highly qualified follow-up programme for a smaller part of the population under study.

Generally, assessment of care takes place in follow-up studies based on small populations derived from one level of care, i.e. from neonatal intensive care units (NICU's) or from paediatric wards in general hospitals. However, to assess trends in morbidity, without any bias, prospective follow-up studies in geographically defined areas are indispensable.[23,24] Till now not many of these have been undertaken for various reasons, such as high costs and the impossibility to cover large areas. After succeeding in incorporating 94% of the infants meeting the original intake criteria, we were encouraged to continue with the total study population in the follow-up phase. In that way, no bias would be introduced in the second phase of the study.

A follow-up period up to the age of two years was decided on for various reasons. Estimation of the influence of perinatal factors on the outcome is possible, relatively free of the effects of intervening events and environmental conditions, known to be important, such as maternal education and social class.[25,26] Subsequent disorders are given sufficient time to surface.[15,27] Moreover, a two year follow-up period was financially feasible, and the cooperation of the participating paediatrians could be relied on throughout the follow-up period.

The decentralized way of recording data was maintained during the second phase of the study. The paediatrician responsible for the infant during the neonatal period was asked to perform the follow-up examinations. This could be the local paediatrician or the paediatrician at the referral hospital in accordance to the parents' preference and local practice.

The danger of inter-observer variability is the main problem in such a de-



centralized study design. Therefore, it was necessary to restrict the information to be collected to unequivocal conditions, diseases and treatments that were generally accepted and used. All items had to be defined as precisely as possible.

The lower financial burden was considered as an important positive aspect. Follow-up examinations in the local hospital can prevent long, expensive trips of the parents and child to a specialized neonatal follow-up clinic and loss to follow-up for this reason. Furthermore, a higher participation rate by the parents was to be expected.

In general, the parents' motivation for follow-up visits to the perinatal clinic or outpatient department lessens markedly when the infant looks healthy and performs well. Also, when the infant does not develop in accordance to the parents' expectations, further cooperation is easily refused, in order to avoid confrontation with negative judgements about their child.[23,28] Familiar, and often frequent, contacts with the local paediatrician may prevent refusal to cooperate for the above mentioned reasons. Infants mostly come from young families who are apt to move frequently.[29] In case the family changes their residence the paediatrician is usually informed and can recommend another paediatrician to perform the follow-up examinations or inform the study centre on the removal. Finally, local paediatricians are often strongly motivated to follow up their own infants.[17]

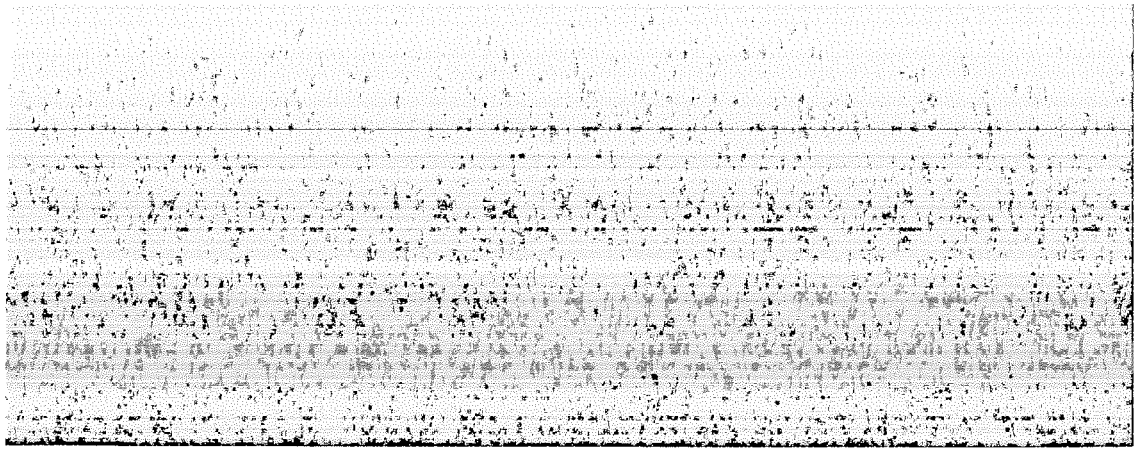
Data collecting

In the months preceding the start of the data collecting, many discussions took place with interested paediatricians, obstetricians and statisticians to agree upon data to be collected. After an agreement was reached on this point a pilot-study was performed, to test the feasibility of the planned scheme of data collecting and processing.

Evaluation of the many discussions and the pilot-study resulted in an oral and written instruction for all participating paediatricians, previous to the phase of data collecting. Furthermore, during the intake as well as follow-up phase of the study, frequent individual contact with the participants took place to minimize possible mistakes in recording the data and to prevent irretrievable loss to follow-up. Every few months summaries and overviews of the collected data were produced for individual clinics and for the total population separately. Finally, at the meetings of the "Sectie Perinatologie van de Nederlandse Vereniging voor Kindergeneeskunde (Division of Perinatology of the Dutch Paediatric Association) progress reports were presented every few months.

To assess the physical status and developmental progress of each child, health examinations were planned in accordance with international literature, at the age of 3, 6, 12 and 24 months corrected for preterm birth. Information was recorded on health, growth, psychomotor development, use of medical services, rehospitalization and psychosocial problems.

For each individual (anonymous) child the name of the paediatrician performing



the follow-up examinations was known to the study centre; in the course of the follow-up study this paediatrician acted as an intermediary between the parents and the study centre. This way anonymity was maintained during this follow-up period.

As soon as the name of the paediatrician performing the follow-up examinations was known to the study centre, precoded forms already completed with the patient identification number, date of birth and future control dates were sent out. These precoded forms were used for data collection and were returned to the study centre after each examination.

At regular intervals the number of forms returned to the study-centre was checked and missing forms were traced. In most cases of missing forms, follow-up examinations had taken place according to the scheme, but the form had not been sent to the study centre yet. Should appointments for follow-up examinations have been forgotten by the parents or further cooperation refused for psychological, financial or religious reasons, the participating paediatrician and study centre personnel decided by mutual agreement, how to obtain further attendance of the family in question. Renewal of the contact with the own paediatrician was strived for; if not feasible, contact with another paediatrician, the family-doctor or the community child health centre was established. Death, emigration or return to the native country were considered as reasons for "unavoidable" loss to follow-up; all other reasons for withdrawal from the study i.e. removal within the Netherlands, financial or religious motives, were considered as "avoidable" loss to follow-up.[30] The efforts to limit the "avoidable" loss to a minimum were in most cases succesfull; in some, however, the anonymity of the survey interfered.

The forms used during the follow-up period were methodologically designed in accordance with the forms used during the perinatal period (appendix A + F). At the corrected age of three months form b (appendix B), at six months form c (appendix C), at 12 months form d (appendix D) and at 24 months form e (appendix E) was used.

The data recorded contained information on impairments and disabilities diagnosed during the follow-up examinations. At the age of 2 years some additional information was collected on various particulars such as congenital malformations detected at a later age (form e, page 3). Furthermore, on this same page, the paediatricians performing the follow-up examinations were asked to allocate each child to one of three categories: major handicapped, minor handicapped and not handicapped. The term handicap was introduced deliberately. According to the International Classification of Impairments, Disabilities and Handicaps[31] and to current practice[32] a handicap implies a disturbance of normal life and as such it places the impairment or disability in a social context. The presence of a handicap was, in most cases, not deducible from the information provided on one of the previous forms. Therefore, the opinion of the paediatrician performing the follow-up examinations was necessary to indicate whether a disability had caused a handicap. A description of some disabilities probably

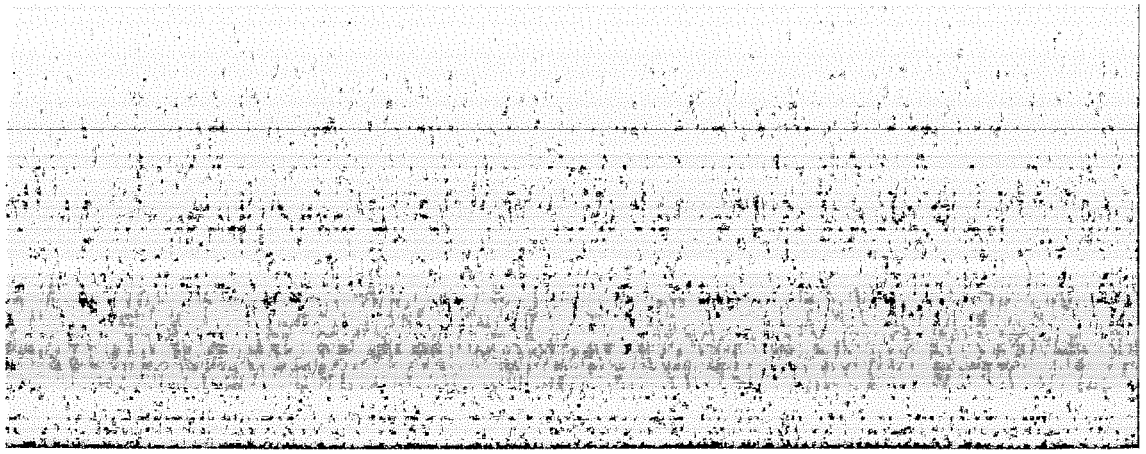


Table 1: Collected data concerning perinatal period (the numbers correspond to those on the registration forms used)

Mother

1. registration number POPS
2. date of birth
3. maiden name (first 3 letters)
4. postal code (place of residence)
5. education and occupation (mother and father) health insurance: national health /private
6. ethnic origin: caucasian, mediterranean, asian, negroid or other (of either parent)
7. marital status

Obstetric history

8. first day of last menstrual period
9. number of previous pregnancies
10. number of previous abortions
11. number of previous preterm deliveries
12. number of children alive
13. pre-existing maternal disease: heart disease, epilepsy, diabetes mellitus, renal disease, hypertension
14. diseases during pregnancy: diabetes mellitus of pregnancy, isoimmunization, hypertension
15. toxic agents during pregnancy: smoking, alcohol abuse, soft drugs, hard drugs, methadon
16. hospital admission during and because of the index pregnancy
17. cardiotocographic tracings before labour (Fischer score < 5 or late decelerations)
18. drug treatment: diuretics, antihypertensives, tranquilizers, antiepileptics, antibiotics, progestatives, asthma-therapeutics, others

Delivery/Birth of infant

19. date of birth
20. time of birth
21. gestational age (best obstetrical estimate)
22. degree of reliability of gestational age
23. sex
24. fetal presentation
25. tocolysis (beta-mimetics, prostaglandin synthesis inhibitors, others), together with glucocorticoid administration
26. use of oxytocic drugs during labour
27. induction of labour
28. mode of delivery: vaginal (vertex, vacuum, forceps, spontaneous breech, breech extraction, version and extraction), caesarean section (with or without labour and /or ruptured membranes)
29. cardiotocographic tracings during labour
30. sedatives and /or analgesic drugs
31. anaesthesia during labour and delivery
32. prolonged duration of ruptured membranes
33. chorioamnionitis
34. staining of amniotic fluid (clear, fetid, meconium or bloodstained)

Infant

35. birthweight
36. length at birth
37. head circumference at birth
38. paediatric maturity score (Dubowitz, Ballard, Finnström, other)
39. Apgar scores

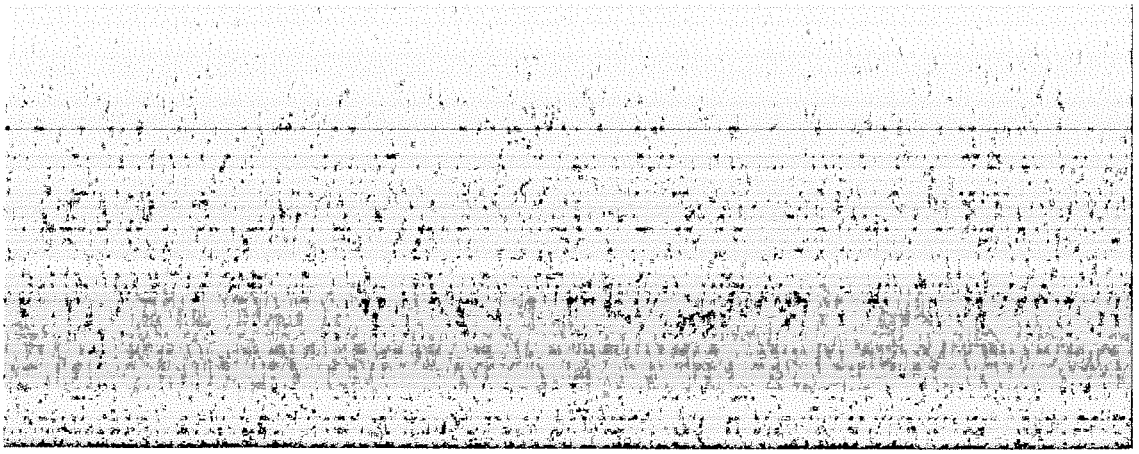
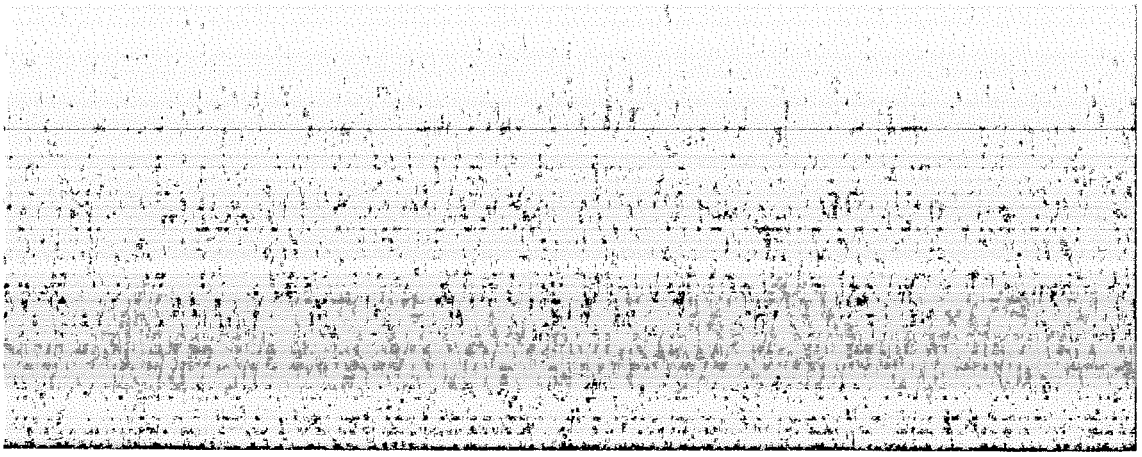


Table 1 continued

40. pH (umbilical artery, umbilical vein, capillary), PCO2 (umbilical artery, umbilical vein, capillary)
43. singleton or multiple pregnancy; number of infants; birthing order
44. place of birth (perinatal intensive care centre in university hospital, perinatal unit in general hospital, other obstetrical ward with or without paediatric service, elsewhere)
45. transport (antenatal and neonatal)
46. infant transport service used
47. hypothermia
48. respiratory tract disorders (idiopathic respiratory distress syndrome; wet lung; (congenital) pneumonia; atelectasis; air leaks; interstitial emphysema; meconium aspiration; milk aspiration; bronchopulmonary dysplasia; Mikity Wilson's disease)
49. persistent fetal circulation
50. persistent ductus arteriosus Botalli (treated by fluid restriction and diuretics; indomethacin; surgical closure)
51. apneic spells (treated with caffein /theophylline; continuous positive airway pressure; intermittent positive pressure ventilation)
52. bradycardia
53. continuous positive airway pressure (days)
54. intermittent positive pressure ventilation (days)
55. intrauterine infection (haemolytic streptococcus Group B; hepatitis B; herpes; cytomegalovirus; listeriosis; rubella; toxoplasmosis; syphilis)
56. septicaemia
57. causative bacteria
58. meningitis
59. maximal serum bilirubin concentration
60. day of highest value
61. phototherapy
62. exchange transfusions (for hyperbilirubinaemia, septicaemia, metabolic disorder, intoxication)
64. total parenteral nutrition; duration
65. transpyloric nutrition
66. necrotising enterocolitis
67. intracranial haemorrhage (diagnosed by lumbar puncture; ultrasound; computerized tomography scan; pulsatility index; postmortem)
69. localization (subependymal, parenchymal, subarachnoidal, intraventricular, cerebellar, subdural)
70. seizures
71. hydrocephaly, (ventricular dilatation, increased headcircumference; treatment)
72. central nervous system disorders
73. peripheral nervous system disorders
74. retinopathy of prematurity
75. drug treatment (antibiotics, diuretics, digoxin, corticosteroids, anticonvulsives, other)
76. congenital malformations (lethal, non-lethal)
77. description of congenital malformation
78. causes of death (congenital malformation; idiopathic respiratory distress syndrome; intracranial haemorrhage; intrauterine infection;septicaemia; necrotising enterocolitis; other)
79. date of death
80. time of death
81. special features of death (spontaneous; intensive care withheld or withdrawn; error or accident)
82. date of discharge from neonatal intensive care unit in university hospital
83. date of discharge home
84. condition at discharge home
85. weight at discharge home
86. mental and psychomotor development at discharge home



causing a major or minor handicap was given on the e form, page 3, as an example.

A major handicap was diagnosed when severe retardation was present (5 or more months retarded or developmental quotient (DQ) less than 80) and/or a severe neurological disorder existed such as hemi- or quadriparesis and/or severe visual or hearing defects and/or serious psychosocial problems were present. Such disabilities are likely to prevent the child from going to a normal school, or (will) cause serious interference with normal function in society. A child was categorized as having a minor handicap when some retardation was present (3-4 months retarded or DQ between 80 and 90) and/or a mild neurological disorder existed such as a slight hemi- or quadriparesis and/or mild visual or hearing defects and/or moderate psychosocial problems appeared. Such disabilities are unlikely to prevent the child from going to a normal school, or to interfere seriously with normal life.[33] *All other children were considered "non-handicapped".*

A translation of the collected items is presented in table 1 (perinatal period, form a) and table 2 (follow-up: forms b, c, d and e). The items 8-29 on each follow-up form examine the psychomotor development of the child, following the Van Wiechen examination (appendix G), based on the Gesell test but adapted to Dutch standards.[34]

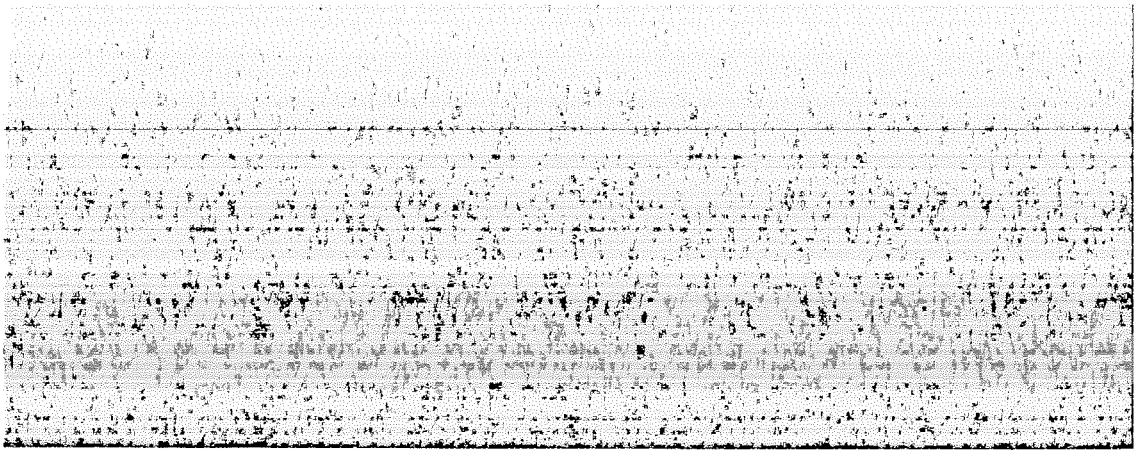
Table 2: Collected data concerning follow-up period (the numbers correspond to those on the registration forms used)

3. date of visit to outpatient department
4. cause of loss to follow-up (death, family move, other)
5. length
6. weight
7. headcircumference
8. psychomotor development (according to Dutch standards, appendix G)

29. central nervous system disorders
30. peripheral nervous system disorders
31. seizures
32. physical therapy
33. respiratory tract disorders (bronchopulmonary dysplasia, Mikity Wilson's disease; other chronical disorders; repeated infections of upper respiratory tract; repeated (broncho) pulmonary infections)
34. digestive tract disorders (feeding difficulties; infections)
35. inguinal and umbilical hernias
36. hearing disorder
37. visual disorder (retinopathy of prematurity, squint; other)
38. rehospitalization
39. consultation of other specialists (e.g. ophthalmology, ear-nose-throat surgery, paediatric neurology, orthopedic surgery, physical rehabilitation, paediatric cardiology)
40. psychosocial problems (crying, sleeping disorder, restlessness, eating disorder, battering)
41. mother's height
42. father's height

At age 2 years (additional)

- further particulars (congenital malformations detected at a later age; disease presumably without relation to preterm /VLBW birth; details of central nervous system disorder if present)
- conclusion of attending paediatrician concerning handicap: none, minor, major



Data processing

Upon arrival at the secretarial office all forms were checked manually for obvious mistakes. The data were then entered into the computer (IBM-3083 mainframe). A plausibility-control system, written in PL/I, traced improbable values or impossible combinations prior to entrance into the database. All questions resulting from these checks were discussed again with the paediatrician concerned, who then provided the definite answer. No data were changed without consultation of the participating paediatrician. After correction of the data had taken place, they were entered into the data base system. Data management was performed with the Statistical Package for the Social Sciences (SPSS-X 2.1).

Data analysis

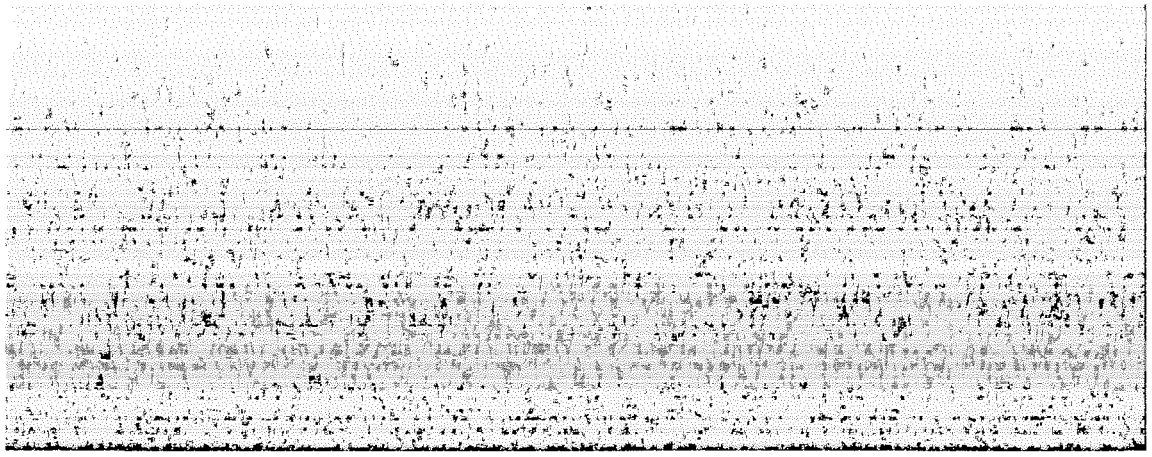
The same line of thought regarding descriptive and inferential statistics used to process the data from the perinatal period, was maintained for the follow-up study. As descriptive statistics, frequencies and rates were computed from the database system. In cross tabulations differences in distribution were expressed, only to be interpreted for clinical relevance. The crude odds ratio was calculated as a measure comparing risks in exposed and non-exposed groups. No routine statistics, such as chi squares, were applied since the underlying clinical research questions should be addressed in a multivariate way to avoid bias.

A multivariate analysis is especially suited for the study of the relationship between two (or more) variables while controlling for one or more other variables. The advantages of a multivariate over univariate analysis can be summarized as follows:

1. Controlling for more "confounding" factors at the same time
2. Quantification of the prognostic influence of more than one factor simultaneously
3. Assessment of "interaction" between factors

The choice of which factors to include in a multivariate analysis can be made in several ways. The practice of using only the "significant" factors of a number of univariate procedures in a subsequent multivariate analysis,[35,36,37] has a distinct disadvantage: factors not significantly associated with the outcome in the univariate analysis, due to positive or negative associations with other factors, may be wrongly omitted from the multivariate analysis, which could lead to highly biased estimates and misleading conclusions. It is far better to select perinatal factors in advance. With the available literature and present knowledge as a basis, a deliberate choice can be made.

If the number of factors to be studied simultaneously in relation to the outcome is small, stratification into subgroups can be a good solution. However, in our study population we wanted to consider many perinatal factors in relation to several different measures of outcome. We deliberately refrained from univariate



statistical testing to estimate associations between factors and outcome. The crude odds ratios gave an impression of the relationship between the exposures and a certain outcome. These crude odds ratios were not yet adjusted for differences in the distribution of other perinatal factors, that may influence the outcome-exposure relationship. Therefore, multivariate modeling techniques (such as logistic regression) were used to obtain information on adjusted odds ratios, confounding effects, and interaction effects. These methods can be applied very well to cohorts such as our study population.[38] The logistic regression technique is well suited to obtain valid and precise estimates of exposure-disease relationships, while controlling (adjusting) for the effects of many other factors.

For analytical purposes, the Statistical Package for the Social Sciences (SPSS-X 2.1) was used together with the Statistical Analysis System (SAS);[39] SPSS-X was used primarily for all descriptive statistics and for reporting to the participants. SAS was used for logistic regression analysis.

Thus, as decribed in the thesis by Verloove-Vanhorick and Verwey,[1] the relationship was analysed between 31 selected perinatal factors and mortality (both neonatal and in-hospital) as well as neonatal morbidity (idiopathic respiratory distress syndrome, intracranial haemorrhage and septicaemia). Applying logistic regression analysis, the association between several perinatal factors and the sequelae of very preterm birth was studied. As measures of outcome we used "major adverse outcome" (= total deaths plus major handicaps) and "total adverse outcome" (= total deaths plus major and minor handicaps), both in liveborn infants; and "total handicaps" (= major and minor handicaps) in surviving children.

The number of perinatal factors used in these analyses was limited to 22, because the number of cases with the outcome handicap was much lower than the number of cases with the outcome death. In chapter 10 these various analyses will be described more extensively.

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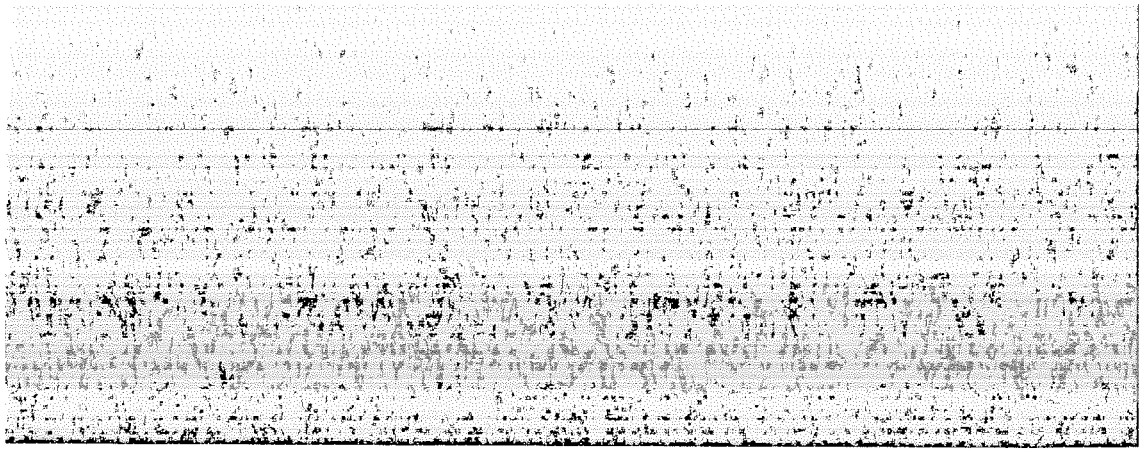

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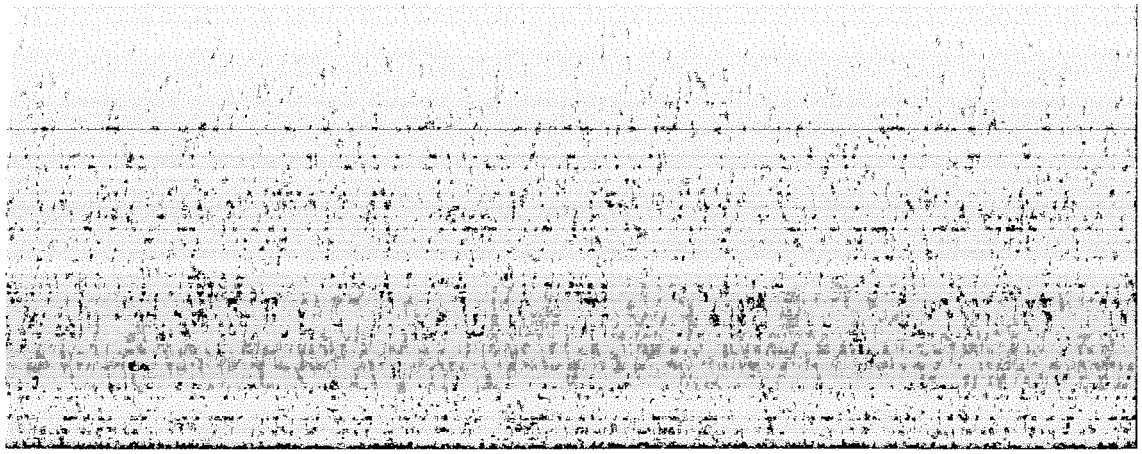

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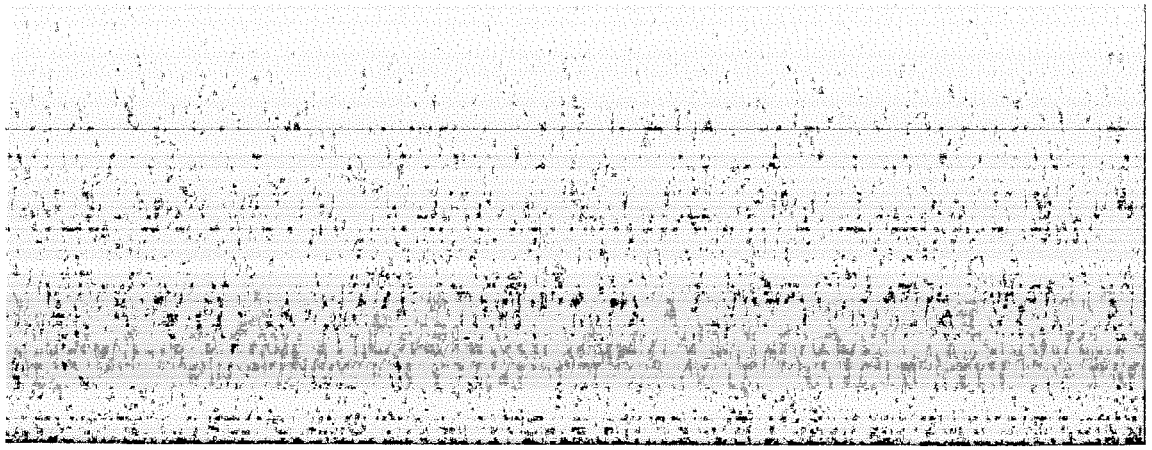

CHAPTER 2

MORBIDITY OF VERY LOW BIRTHWEIGHT INFANTS AT CORRECTED AGE OF TWO YEARS IN A GEOGRAPHICALLY DEFINED POPULATION

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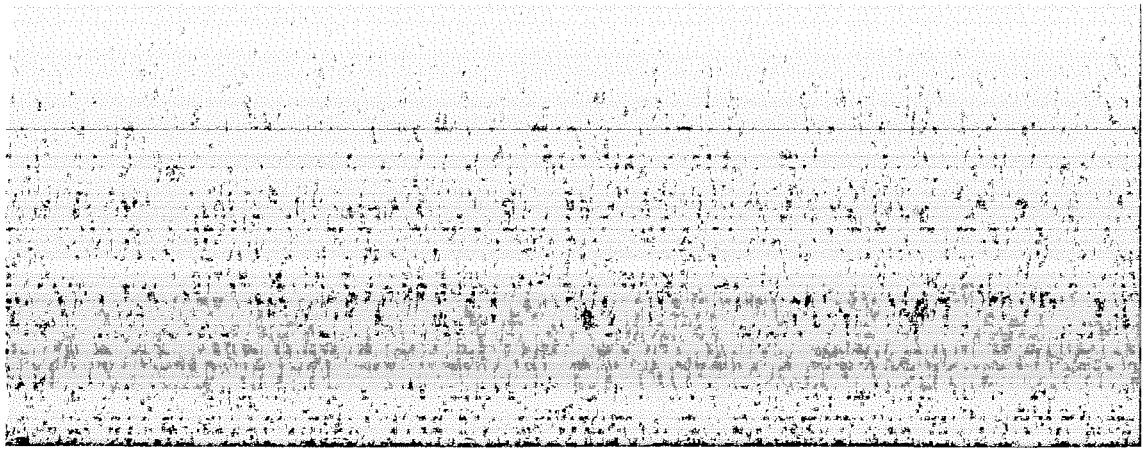


SUMMARY

In a nationwide prospective survey on very preterm and very-low-birthweight infants in the Netherlands, a neurodevelopmental assessment was made at the corrected age of two years in a virtually complete population. The study achieved a 97.4% follow-up rate. A major handicap was found in 59 children and a minor handicap in 111 children (4.4% and 8.3% of liveborn infants, respectively). Unlike mortality, handicap was apparently unrelated to gestational age or birthweight.

INTRODUCTION

In the Netherlands, data on the birthweight or gestational age of liveborn infants are not collected routinely. The Project On Preterm and Small for gestational age infants (POPS) was designed to obtain epidemiological data on very preterm and/or very-low-birthweight infants, and to investigate the relations between perinatal factors and mortality and morbidity.

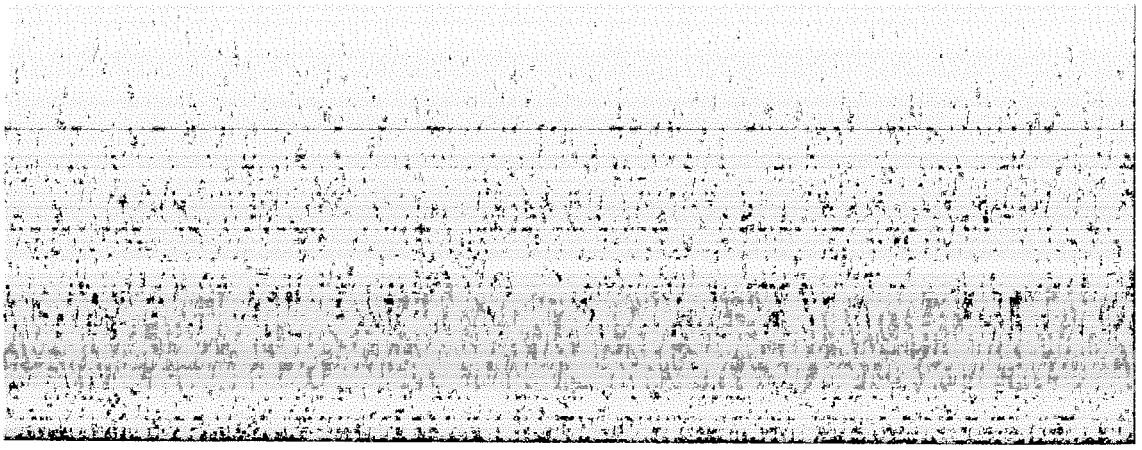
The results concerning the prenatal, perinatal and postnatal period have been published previously.[1-7] All surviving study infants up to the corrected age of 2 years have now been followed up in a decentralised nationwide programme. We report here the main findings.

MATERIALS AND METHODS

Data were collected on all liveborn infants delivered between Jan 1 and Dec 31, 1983, before 32 completed weeks of gestation and/or with a birthweight of less than 1500 g. Paediatricians in 8 neonatal intensive-care units in university hospitals, 22 neonatal units in teaching hospitals, and 71 neonatal wards in general hospitals prospectively entered data on infants born in 133 obstetric departments all over the Netherlands. The total study population was 1338 infants, which is 94% of all liveborn infants meeting the entry criteria. To avoid any bias due to an unintentional sample selection, the survey was conducted throughout the whole country (total population 14.3 millions).

All infants surviving the initial hospital stay were enlisted for the 2 year follow-up programme. Examinations at the outpatient department were scheduled at 3, 6, 12 and 24 months (corrected for gestational age) by the local paediatrician or in the referral hospital according to parental preference. Information on health, growth, development and psychosocial problems were recorded on precoded forms. Data management and processing was centralised at the study centre as previously described.[2]

Neurodevelopmental outcome was assessed in all surviving infants at the corrected age of 2 years by the participating paediatrician and, when necessary, by a multidisciplinary team. An overall developmental level was done with the Gesell test adapted for Dutch children[8] and by neurological, visual and hearing



examinations. In cases where paediatric follow-up was discontinued, the family doctor or doctor at the child health centre was asked to make an assessment instead. According to the outcome the children were divided into three groups: no handicap, minor handicap, or major handicap. The infant was considered to have no handicap when retardation was absent (developmental quotient [DQ] above 90) and there were no motor, visual, or hearing disabilities. A minor handicap was diagnosed when some retardation was present (3-4 months retarded or DQ between 80 and 90) and /or at least one of the following; a mild neurological disorder such as a slight hemiparesis or quadriparesis, mild visual or hearing defects, or moderate psychosocial problems. Such disabilities were unlikely to prevent the child from going to a normal school, or to interfere seriously with normal life. A major handicap was diagnosed when severe retardation was present (5 or more months retarded or DQ less than 80) and /or at least one of the following; a severe neurological disorder, severe visual or hearing defects, or serious psychosocial problems. Such disabilities would probably stop the child going to a normal school or cause serious interference with normal function in society.[9]

RESULTS

Of 1338 infants enrolled in the study, 998 were discharged home alive and were included in the follow-up programme. Up to the corrected age of 2 years, 29 infants died and 25 infants (2.5% of the infants under study) were lost to follow-up: 12 families moved abroad, 6 children were lost because further cooperation was refused, and 7 children could not be traced. During the follow-up period, 34 parents declined further examination by the paediatrician, either because of financial considerations or because they had decided that their child was healthy. In these cases the family doctor or the child health centre was asked for an assessment concerning the neurodevelopmental outcome at the corrected age of 2 years. Of these, 33 children were healthy and 1 had a minor handicap. These data were included in the results. At the corrected age of 2 years, data on 944 children (97.5% of the survivors) were available (table I).

MORTALITY (tables I and II)

In the first 2 years of life the mortality rate was 27.6%, ranging from 100% at a gestational age of <24 weeks to 8.2% at >32 weeks. 22 boys and 7 girls died after discharge. Causes of death were cot death (15), bronchopulmonary dysplasia (2), congenital malformations including heart and kidney abnormalities and bileduct atresia (5), and miscellaneous disorders (6) such as milk aspiration, ventriculoperitoneal drain dysfunction, severe neurological dysfunction, whooping cough, chicken pox, and non-accidental injury. In 1 case the cause of death was unknown.

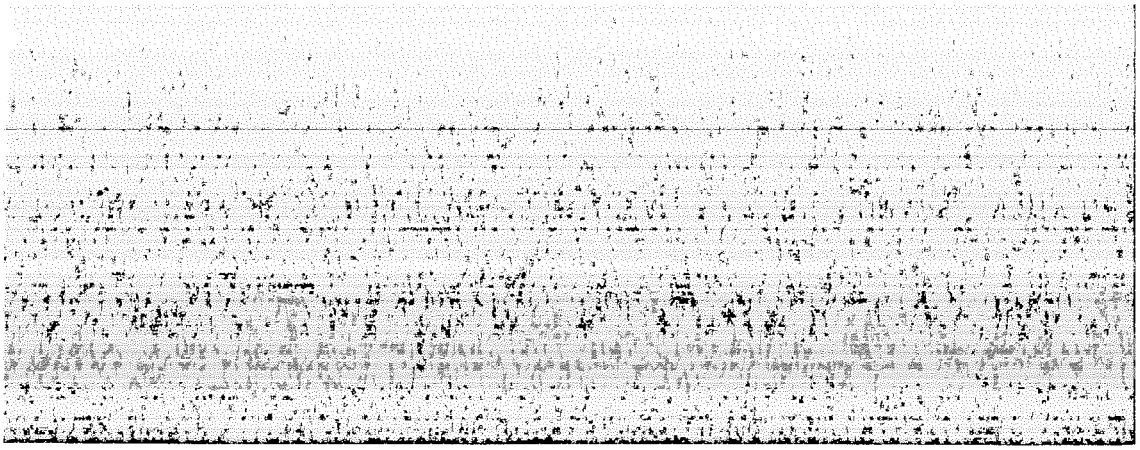


Table I - Outcome at the corrected age of 2 years

	No		(%)
Deaths	369		(27.6)
In-hospital	340		
Neonatal		312	
> 28 days		28	
After discharge	29		
Discharge-1 yr		23	
1-2 yr		6	
Lost to follow-up	25		(1.9)
Major handicap	59		(4.4)
Minor handicap	111		(8.3)
No handicap	774		(57.8)
Total liveborn, < 32 wks and /or < 1500 g	1338		(100.0)

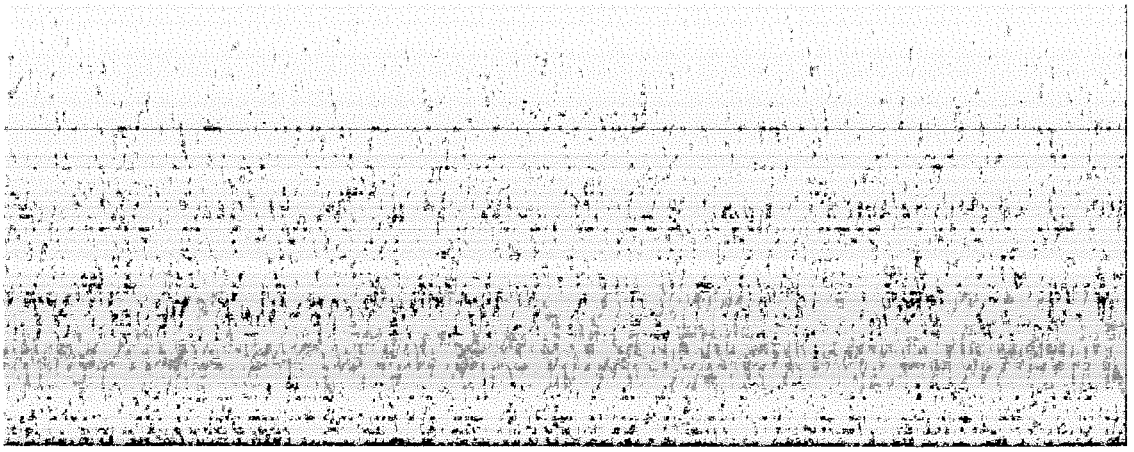
Table II - Mortality up to 2 years of corrected age in various gestational age categories

Gestational age (wk)	No of infants	Mortality			
		In-hospital No	After discharge No	Total No	(%)
<24	8	8	0	8	(100.0)
24	19	19	0	19	(100.0)
25	48	41	2	43	(89.6)
26	77	48	1	49	(63.6)
27	103	47	0	47	(45.6)
28	136	46	2	48	(35.3)
29	171	37	4	41	(24.0)
30	204	38	7	45	(22.1)
31	244	26	6	32	(13.1)
32	94	14	3	17	(18.1)
>32	231	16	3	19	(8.2)
Unknown	3	0	1	0	
Total	1338	340	29	369	(27.6)

HANDICAPS (tables I, III-V)

774 (82.0%) of the 944 surviving children who were assessed had no handicap; a minor handicap was recorded in 111 (11.8%); 59 (6.3%) infants had a major handicap.

Congenital malformations causing a major handicap included chromosomal abnormalities such as trisomy-21, 4p- -syndrome and Cri du Chat syndrome,



Charge syndrome, Cornelia de Lange syndrome, tuberous sclerosis, skeletal dysplasia, and fetal alcohol syndrome. Congenital hip dysplasia and Seckel syndrome were recorded as minor handicaps. 97 (57.1%) of the handicapped children had a central motor deficit, mainly cerebral palsy. In the group with a major handicap this was often accompanied by mental retardation. Types of cerebral palsy were hemiplegia (20), quadriplegia (14), diplegia (12), paraplegia (7), and triplegia and monoplegia (6). Hydrocephalus occurred in 9 children, 7 of whom had a ventriculoperitoneal drain. 2 of these children (1 with and 1 without a drain) had a minor handicap; the others had a major handicap. Another 6 children were epileptic. Some children had more than one of these disorders.

The visual impairments included blindness in 2 children, from retino-pathy of prematurity. 2 other children had, in addition to cerebral palsy, a less serious retinopathy of prematurity not leading to blindness. Other ophthalmological disabilities occurred in the children with Cri du Chat syndrome (microphthalmia), Charge syndrome (coloboma) and fetal alcohol syndrome (myopia). The incidence of retinopathy of prematurity not causing a visual impairment is not known, because standardised ophthalmological examinations were performed only in part of the study population.

3 children had sensorineural deafness, requiring hearing aids and special schooling. 3 other children had hearing loss due to middle ear effusion.

Speech retardation was diagnosed in 24 children, 7 of whom also had behavioural problems. Behavioural problems such as hyperkinetic behaviour, trichotillomania, and breath holding episodes were minor handicaps in another 5 children. Developmental disturbances due to understimulation, non-organic feeding problems, and child abuse were categorised as miscellaneous minor handicaps.

Table III - Number of children with a major or minor handicap

Category	Minor	Major	Total
Congenital malformation	6	9	15
Central motor deficit	41	12	53
Mental retardation (MR)	11	2	13
Central motor deficit and MR	13	31	44
Hearing impairment	3	3	6
Visual impairment	2	2	4
Behavioural problem	5	0	5
Speech retardation	24	0	24
Miscellaneous	6	0	6
Total	111	59	170

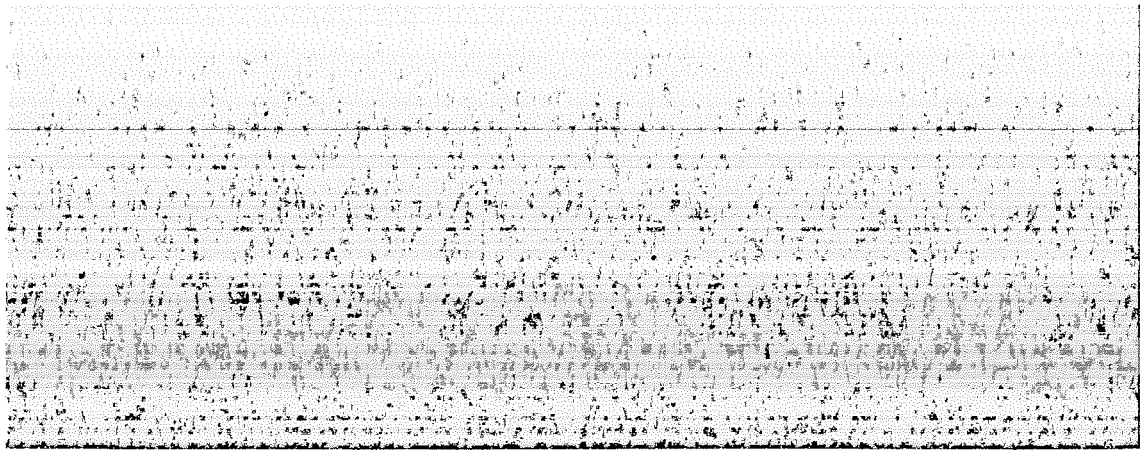


Table IV - Number of infants with minor and major handicaps in various gestational age categories

Gestational age (wk)	Surviving children	*Handicapped children*			*Handicap rates (%)*	
		Total	Minor	Major	Liveborn	Surviving
25	5	3	1	2		
26	28	4	3	1	5.2	14.3
27	56	10	6	4	9.7	17.8
28	88	21	14	7	15.4	23.9
29	130	29	20	9	16.9	22.3
30	159	24	13	11	11.8	15.1
31	212	32	24	8	13.1	15.1
32	77	11	6	5	11.7	14.3
>32	212	36	24	12	15.6	17.0
Unknown	2	0	0	0		
Total	969	170	111	59	12.7	17.5

Table V - Number of infants with minor and major handicaps in various birthweight categories

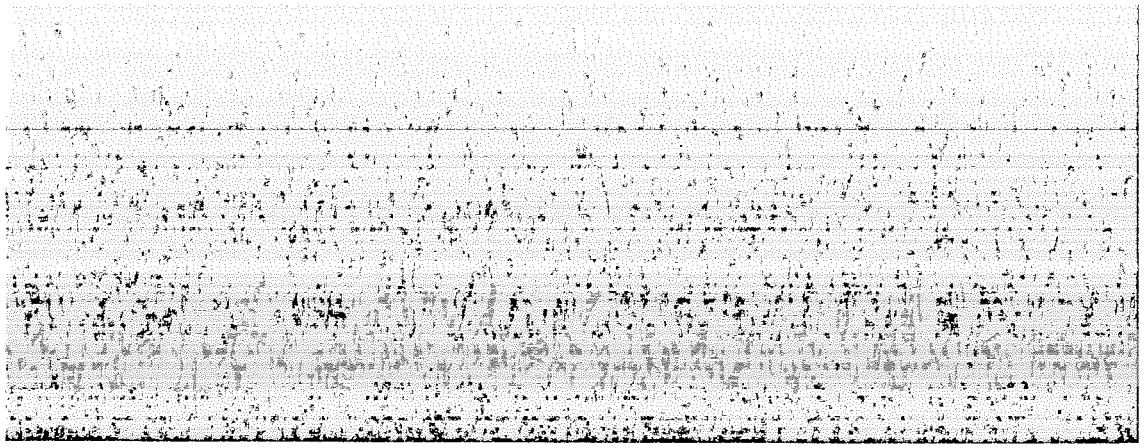
Birthweight (g)	No of infants	Surviving Children	*Handicapped children*			*Handicap rates(%)*	
			Total	Minor	Major	Liveborn	Surviving
< 500	5	0	0	0	0		
500-749	66	18	4	4	0	(6.1)	(22.2)
750-999	221	112	19	9	10	8.6	17.0
1000-1249	359	257	45	29	16	12.5	17.5
1250-1499	446	383	69	48	21	15.5	18.0
1500	241	199	33	21	12	3.7	16.6
Total	1338	969	170	111	59	12.7	17.5

DISCUSSION

The main finding of this work is that, in contrast to mortality,[1] handicap is not related to gestational age or birthweight.

The mortality rates in the present study were comparable with those in neonatal intensive-care units and general hospitals [10,11] but lower than those in regional studies similar to ours.[12,13] In the first year after discharge the postneonatal mortality rate and the total post-discharge mortality rate were similar to previous findings.[14,15] The incidence of cot death in the population of survivors (15 / 1000) was much higher than the incidence of 1.6-2 /1000 found in a general population.[16] Bronchopulmonary dysplasia accounted for a proportion of deaths during the postneonatal in-hospital period similar to that found in other studies.[11,17]

A major handicap-rate of 3.8% of liveborn infants and 10% of survivors in a neonatal intensive care unit (NICU) based study is a good result.[18] The 6.3% of surviving infants with a major handicap found in the present study compares



favourably with results of previous Dutch NICU-based studies.[15,19] The value of the results of this study at 2 years of age as far as ultimate number and gravity of handicaps are concerned remains to be established. For this purpose, a centralised assessment programme at the age of 5 years is in progress.

Bax has stated that in a study design based on a geographically defined population there should be a follow-up rate of at least 80%.[20] The advantages in such a design have been shown previously.[2,21,22] We were able to achieve a follow-up rate of 97.5% and therefore, a comparison with other such study populations was feasible. The follow-up study could have been designed either in a centralised or in a decentralised manner; because all infants were enrolled anonymously and financial resources were limited, the decentralised design was maintained. Because of the biases possibly introduced by non-participants and of the need to achieve an acceptable follow-up rate, frequent consultations between the study centre and the participating paediatricians took place. By such close cooperation the high follow-up rate was attained. Because of the decentralised organisation of the follow-up programme inter-observer variability was likely to occur, lowering the reliability of the collected data. However, the precoded questionnaires were designed to minimise the risk of ambiguous answers.

One year after the last child reached the corrected age of 2 years, data on 85 children were still missing at the study centre. Data on 13 of them remained incomplete and were lost to follow-up. Because the proportion of major and minor handicaps in the remaining 72 children was similar to that found in the other 859 survivors, these 72 children could have been excluded from the study, saving time and effort. However, previous investigators have claimed, that to avoid bias, such data must be included.[23-25] The fact that in our study there was no difference in handicap rates, could be attributed to the decentralised study design: when children were lost to follow-up the reason was likely to be organisational rather than related to their impairment. Therefore in a design such as ours, a follow-up rate of 90% may be acceptable.

Although handicaps in the surviving infants did not appear to be related to gestational age or birthweight, other risk factors, such as socioeconomic status, obstetrical history, fetal presentation, gender, mode of delivery, and the occurrence of idiopathic respiratory distress syndrome, and intracranial haemorrhage during the neonatal period have not been taken into account. Multivariate analysis will be required to establish the importance of each of these factors separately.

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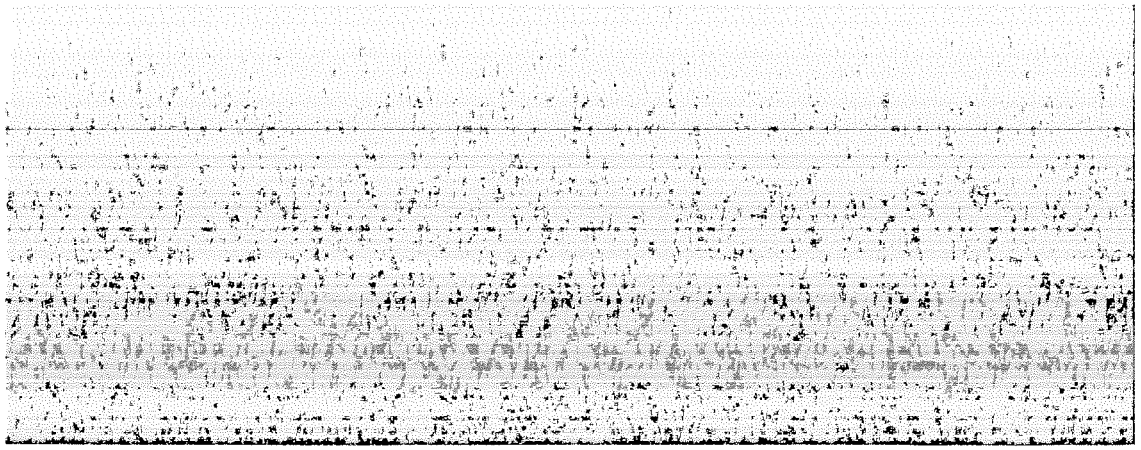

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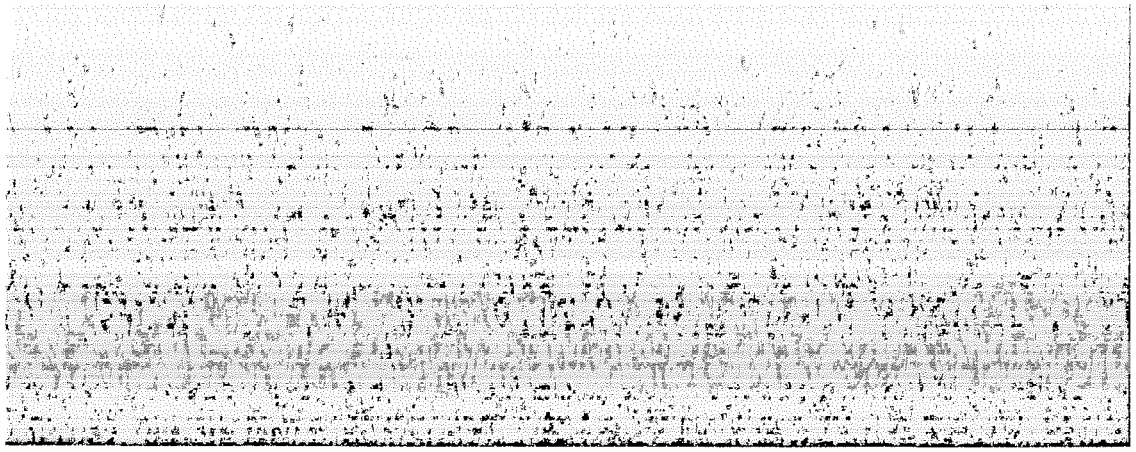

CHAPTER 3

MATERNAL HYPERTENSION AND VERY PRETERM INFANTS' MORTALITY AND HANDICAPS

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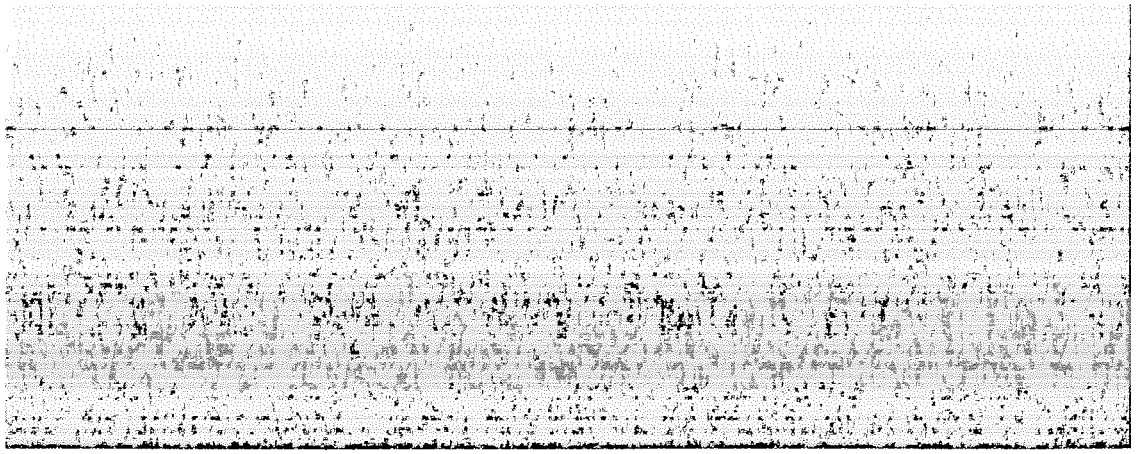
Submitted for publication



SUMMARY

In a nationwide survey on liveborn very preterm and/or very low birthweight infants in the Netherlands, mortality and handicaps at the corrected age of two years were studied in infants born to mothers with or without hypertensive disorders during pregnancy.

The neonatal and in-hospital mortality was significantly lower in infants born to hypertensive mothers. In surviving infants, a similar handicap rate was found at the corrected age of two years for both groups.

INTRODUCTION

Maternal hypertensive disorders during pregnancy are known to be an important clinical entity, often resulting in stillbirth or in elective preterm delivery [1]. Most reports on gestational hypertension deal with the etiology and the controversial clinical management, comparing different treatment protocols [2,3,4]. Much less has been published about the outcome of liveborn infants of mothers with hypertensive disorders [5], especially about preterm infants.

Paediatricians tend to regard the short term prognosis of such infants, once born alive, as more favourable than the prognosis of otherwise comparable infants born to normotensive mothers. Most obstetricians seem to concentrate on the prevention of perinatal mortality and the well-known serious maternal complications [6].

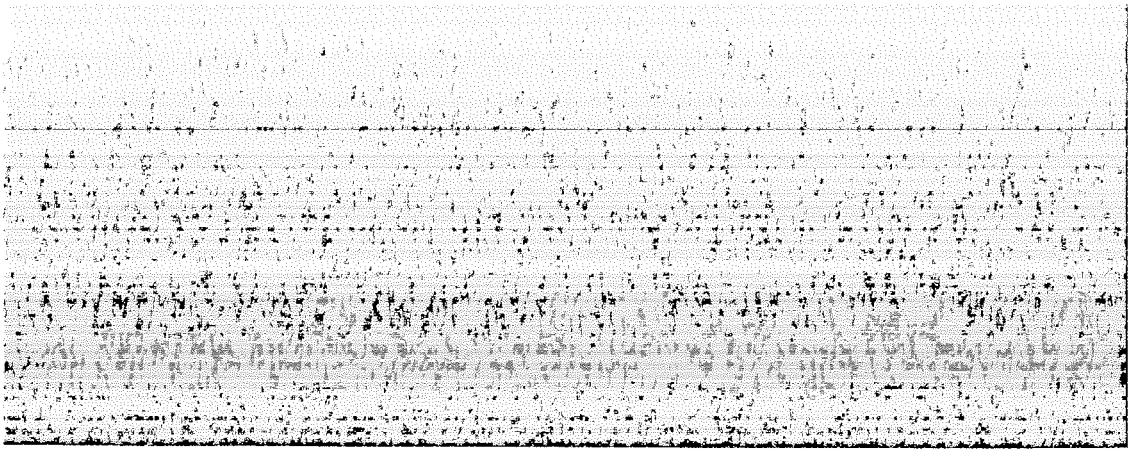
We used the opportunity offered by the nationwide survey "Project On Preterm and Small for gestational age infants" (POPS) [7], to study the effect of maternal hypertensive disorders during pregnancy on the outcome, i.e. mortality and handicaps, in otherwise comparable liveborn infants.

MATERIALS AND METHODS

In 1983, from January 1 to December 31, all liveborn infants with a gestational age of less than 32 completed weeks and/or a birthweight of less than 1500 g were enrolled in the study. Throughout the country, 101 paediatricians participated in the study and perinatal data were recorded on 1338 infants, representing 94% of all such infants in the Netherlands.

Maternal hypertensive disorders during pregnancy were considered present when the diastolic blood pressure equalled or exceeded 90 mm Hg on two or more occasions at least 24 hours apart [8]. The hypertensive disorders of pregnancy were not further classified and as a result no distinction was made between pre-existing or pregnancy induced hypertensive disorders.

Following the Amsterdam growth charts [9], all study infants were classified either as appropriate for gestational age (AGA /LGA, birthweight $\geqslant 10^{th}$ percentile for gestational age), as small for gestational age (SGA, birthweight $\geqslant 2.3^{rd}$



percentile for gestational age and <10th percentile) or as very small for gestational age (VSGA, birthweight <2.3rd percentile). Because these charts contain data from 25 gestational weeks onwards, and because in some cases sex of the infants or gestational age was missing, 33 infants (2.5%) could not be classified.

Neonatal mortality was defined as mortality during the first 28 days of life, in-hospital mortality as the total mortality during the initial hospital stay.

Elective delivery was defined as any delivery following intentional obstetric termination of pregnancy attempted at a time when no symptoms of spontaneous labour are present: e.g. an elective induction of labour or a primary caesarean section at a moment when fetal membranes are still intact and uterine contractions have not yet started.

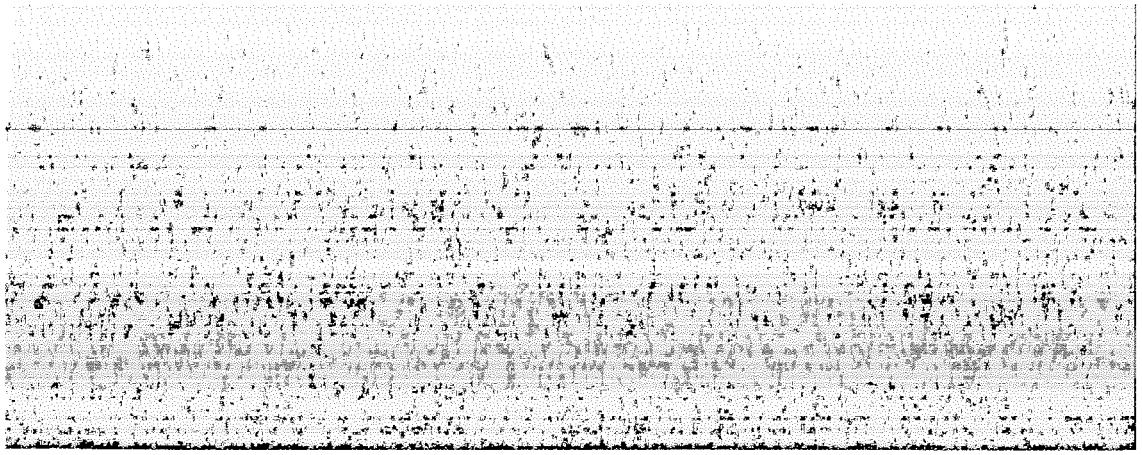
All infants discharged home after the initial hospital admission were eligible for follow-up. Examinations at the outpatient department by the local paediatrician or at the referral hospital were scheduled at the ages of 3, 6, 12 and 24 months corrected for preterm birth. Data on health, growth, development, rehospitalization and psychosocial problems were recorded by the attending paediatrician. Data processing and analysis were performed at the study centre using SPSS-X 2.1 and SAS [10].

At the corrected age of two years, each child had a neurodevelopmental assessment. All children were divided by outcome into three categories: major handicap, minor handicap or normal.

Major handicap was diagnosed when severe retardation was present (5 or more months retarded or developmental quotient (DQ) less than 80) and/or a severe neurological disorder existed such as a serious hemi-or quadriparesis and/or severe visual or hearing defects and/or serious psychosocial problems were present. Such disabilities are likely to prevent the child from going to a normal school, or (will) cause serious interference with normal function in society. A child was categorized as having a minor handicap when some retardation was present (3-4 months retarded or DQ between 80 and 90) and/or mild neurological disorder existed, such as a slight hemi-or quadriparesis and/or mild visual or hearing defects and/or moderate psychosocial problems appeared. Such disabilities are unlikely to prevent the child from going to a normal school, or to interfere seriously with normal life [11]. All other children were considered to be "normal".

The relationship between maternal hypertensive disorders during pregnancy, neonatal mortality, in-hospital mortality and handicaps at the corrected age of two years was studied using descriptive statistics as well as a multivariate statistical method (logistic regression analysis). Various perinatal factors were included in the statistical model as potential confounders to adjust for the possible effects of the uneven distribution of these factors that as such may be associated with mortality or handicap.

Two separate multivariate analyses were performed. In both analyses maternal hypertension (considered as exposure) and the selected perinatal factors (considered as potential confounders) were the independent variables. Mortality and



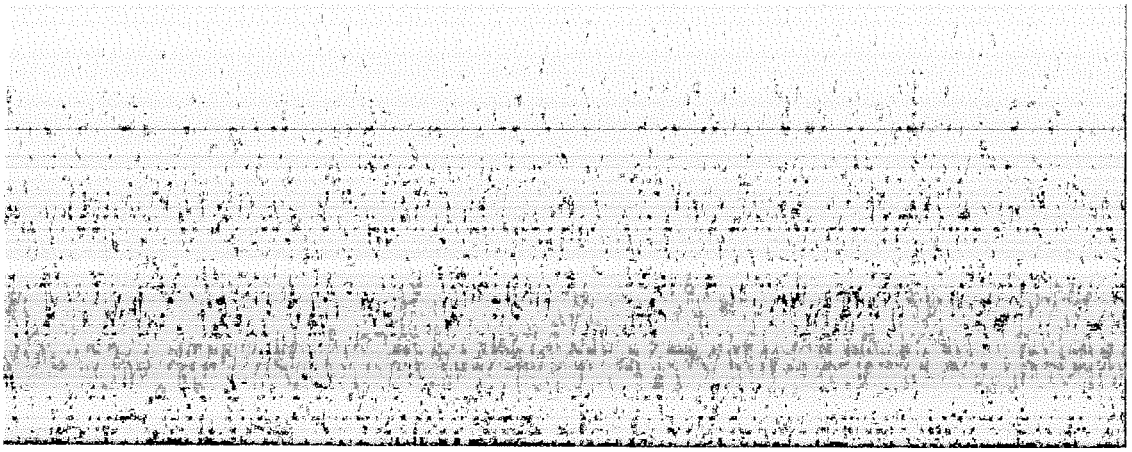
handicap, respectively, were dependent variables. In table 1 the confounding factors selected for the first analysis are shown.

Because the number of cases with the outcome variable handicap was much lower than the number of cases with the outcome variable death, the number of confounding factors in the second analysis had to be limited to 12 for methodological reasons. Based upon previous reports [7], the following factors were omitted: maternal age, parity, history of preterm birth or abortion, smoking during pregnancy, medication and intoxication, hospital admission during pregnancy, prolonged duration of ruptured membranes, chorioamnionitis and cardiotocography during pregnancy.

The results of these analyses are expressed using odds ratios: the odds for mortality (or handicap) in children *with* maternal hypertension versus the odds for mortality (or handicap) in children *without* maternal hypertension. An odds ratio of less than 1 indicates a lower risk for children with maternal hypertensive disorders, while an odds ratio of greater than 1 indicates a higher risk. An odds ratio is significantly different from 1 at the 5% level if, and only if, its 95% confidence interval does not include 1.

Table 1. Perinatal factors used in the first logistic regression analysis

1.	socio-economic class	1 (low) to 6 (high)[12]
2.	maternal age	in years
3.	pre-existing maternal disease	including heart disease, epilepsy, diabetes mellitus, renal disease
4.	parity	>0 versus 0
5.	history of preterm birth or abortion	≥ 1 preterm birth and (or) >1 abortion versus none or 1 abortion
6.	infants' sex	male versus female
7.	smoking during pregnancy	any versus none
8.	medication and intoxication	any (medication, alcohol, soft or hard drugs, smoking) versus none
9.	congenital malformation	any versus none
10.	hospital admission during pregnancy	1 or more days versus none or less than 24 hours
11.	multiple pregnancy	yes versus no
12.	antenatal transport	to a perinatal intensive care centre (level 3) versus no
13.	tocolysis	≥ 24 h. suppression of uterine contractions versus none or <24h.
14.	glucocorticoid administration	to the pregnant mother, yes versus no
15.	prolonged duration of ruptured membranes	≥ 24 h. versus none or <24 h.
16.	chorioamnionitis	yes versus no
17.	cardiotocography during pregnancy	abnormal versus normal tracing
18.	fetal presentation	breech and transverse presentation versus vertex
19.	gestational age	in days
20.	birthweight	in grams
21.	small for gestational age (SGA)	$<10^{th}$ percentile versus $\geq 10^{th}$ percentile [9]



RESULTS

A total of 1338 infants meeting the entry criteria were enrolled in the study; 300 infants were born to 290 mothers with hypertensive disorders. Pre-existing maternal hypertension was recorded in 50 mothers resulting in 51 liveborn infants. The other 249 infants were born to 240 mothers with pregnancy induced hypertension.

A high percentage of infants (65%, 195 /300) was born after elective delivery, mostly a caesarean section (n = 186). Of the 1038 infants born to normotensive mothers, 138 (13.3%) were born after elective delivery.

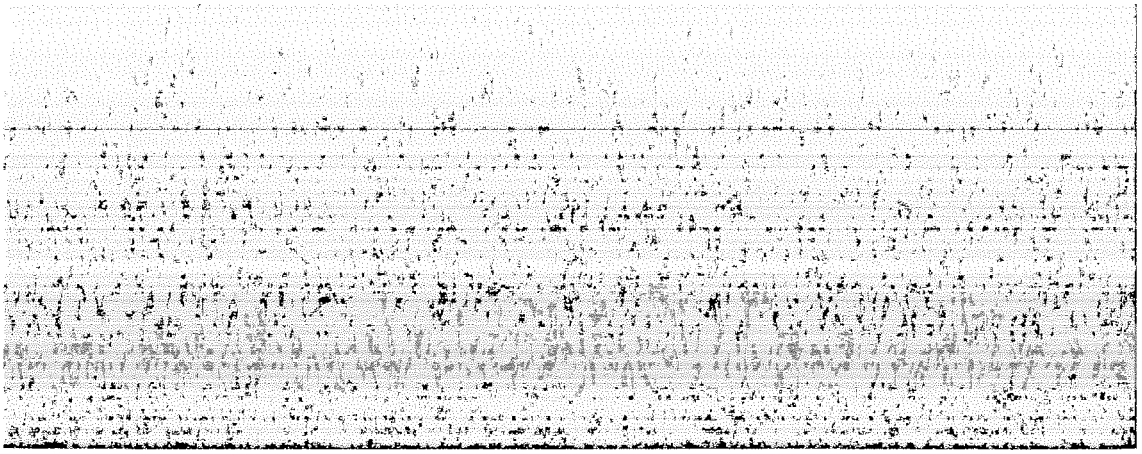
In the entire cohort, neonatal mortality was 23.3% (312 /1338) and the in-hospital mortality 25.4% (340 /1338) [13]. During the two years follow-up period another 29 infants (2.2%) died and 25 were irretrievably lost, because the family moved abroad or because the parents refused cooperation for financial or religious reasons. Of the remaining 944 children assessed at the age of 2 years corrected for preterm birth, 170 had a handicap: 59 a major and 111 a minor handicap [14]. Data necessary for the multivariate analyses were available in 897 cases.

Mortality

The crude mortality rates in the 300 infants born to mothers with hypertensive disorders during their pregnancy, were lower than in infants born to normotensive mothers (table 2).

Table 2. Crude mortality rates and handicap rates of infants born to mothers with and without hypertensive disorders

outcome	hypertensive disorders			
	present		absent	
	%	(n)	%	(n)
mortality				
neonatal	9.0	(27 /300)	27.5	(285 /1038)
in-hospital	11.0	(33 /300)	29.6	(307 /1038)
post-discharge	1.3	(4 /300)	2.4	(25 /1038)
total	12.3	(37 /300)	32.0	(332 /1038)
handicap				
major	5.8	(15 /260)	6.4	(44 / 684)
minor	10.4	(27 /260)	12.3	(84 / 684)
total	16.2	(42 /260)	18.7	(128 / 684)



However, the occurrence of cases with maternal hypertensive disorders increased considerably with advancing gestational age (table 3) [7] and since mortality is strongly related with gestational age [13], this observation may contribute to the difference in crude mortality rates.

Table 3. Hypertension in successive gestational age categories

gestational age (weeks)	number of infants n	hypertension n	(%)
⩽23	8	0	
24-25	67	1	(1.5)
26-27	180	11	(6.1)
28-29	307	39	(12.7)
30-31	448	88	(19.6)
⩾32	325	161	(49.5)
total	1335	300	(22.5)

The crude total mortality rates for infants born to mothers with or without hypertensive disorders during pregnancy were similar when classified by birthweight for gestational age (table 4).

In the logistic regression analysis (with correction for 21 potential confounding factors, table 1) the odds ratios for neonatal and in-hospital mortality were significantly lower than 1, for infants born to mothers with hypertensive disorders compared to mothers without (table 5).

Apparently, the difference in crude mortality is not only caused by the difference in gestational age or other perinatal factors, but there is clearly an independent effect of hypertension itself.

However, two perinatal factors related to intrauterine growth (i.e. birthweight and SGA) were used as potential confounders. Since intrauterine growth re-

Table 4. Crude mortality rates and handicap rates in AGA, SGA and VSGA infants born to mothers with and without hypertensive disorders during pregnancy.

	AGA				SGA				VSGA			
hypertension	present		absent		present		absent		present		absent	
	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)
outcome: *mortality*												
total	12.3	(10/81)	30.8	(237/770)	10.5	(11/105)	27.4	(31/113)	13.4	(15/112)	24.8	(34/125)
handicap												
major	10.0	(7/70)	13.4	(69/514)	9.7	(9/93)	7.5	(6/80)	11.5	(11/96)	10.0	(9/90)
minor	4.3	(3/70)	5.6	(29/514)	7.5	(7/93)	11.3	(9/80)	5.2	(5/96)	6.7	(6/90)
total	14.3	(10/70)	19.0	(98/514)	17.2	(16/93)	18.8	(15/80)	16.7	(16/96)	16.7	(15/90)

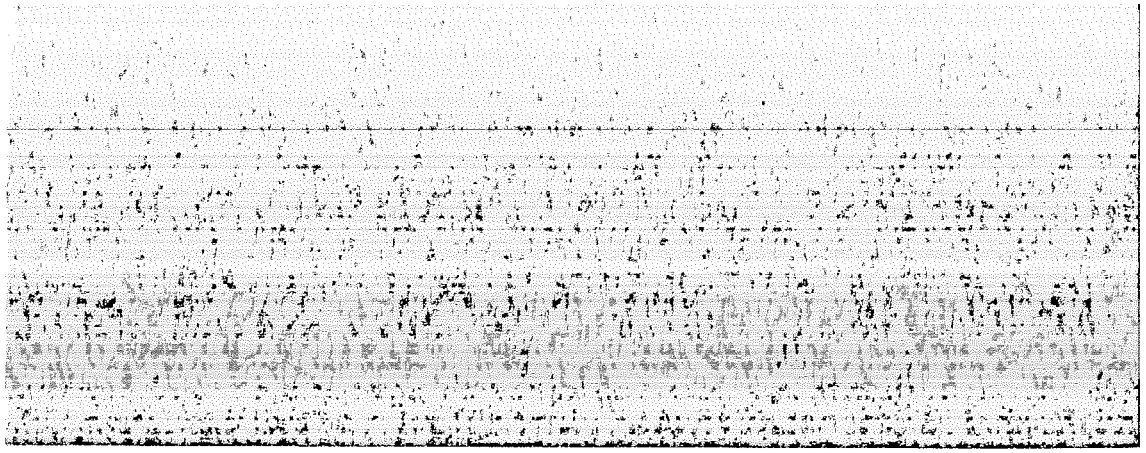


Table 5. Adjusted odds ratios (OR) for mortality and handicap of infants born to mothers with versus mothers without hypertensive disorders

outcome	OR	95% confidence interval	OR	95% confidence interval
mortality				
neonatal	0.36[1]	(0.19-0.67)*	0.45[3]	(0.25-0.82)*
in-hospital	0.43[1]	(0.24-0.78)*	0.56[3]	(0.33-0.96)*
handicap	0.74[2]	(0.46-1.21)	0.77[4]	(0.49-1.22)

*$p < 0.05$

[1] correction for 21 confounding factors

[2] correction for 12 confounding factors

[3] correction for 19 confounding factors (birthweight and SGA omitted)

[4] correction for 10 confounding factors (birthweight and SGA omitted)

tardation may be the result of maternal hypertension, correction for these factors may wrongly correct for the effect of hypertension itself.

Therefore, a second series of logistic regression analyses was performed without birthweight and SGA as potential confounders. As stated in table 5, these odds ratios were slightly closer to 1, in accordance with an increased number of growth retarded infants in the group with maternal hypertensive disorders.

The conclusion remains the same that there is an independent effect of maternal hypertension resulting in a decrease of neonatal and in-hospital mortality.

Handicap

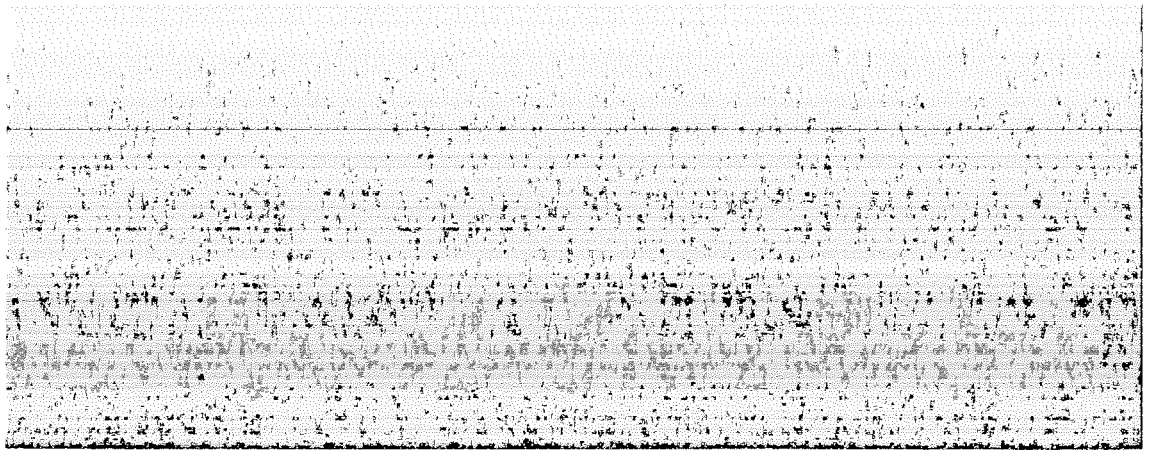
Of the children born to a hypertensive mother 5.8% (15/260) had a major and 10.4% (27/260) had a minor handicap. These percentages were similar in the non-hypertensive group (table 2).

Divided by birthweight for gestational age category, similar handicap rates were found in the AGA, SGA and VSGA infants born to mothers with as well as mothers without hypertensive disorders (table 4).

The logistic regression analysis performed with handicap at the corrected age of two years as the outcome (dependent variable) and adjusted for 12 or 10 (birthweight and SGA omitted) potential confounding factors, showed similar handicap odds for both groups as well (table 5).

DISCUSSION

Maternal hypertension in pregnancy is a well-known risk factor for the mother as well as the fetus. The results of the present study suggest that, once born alive, such infants have better survival chances without an increase in handicap risk, irrespective of their intrauterine growth. These findings are puzzling, especially because the etiology of gestational hypertension is largely unknown.



The syndrome is characterized by the haemodynamic changes such as increased resistance in the utero-placental circulation, decreased plasma volume and increased arterial pressure with subsequent vascular damage [15]. Various pathophysiologic processes are involved such as a marked increase in the sensitivity to angiotensin II [16]. In addition, an insufficient migration of throphoblasts along the spiral arteries may occur, preventing the arterial walls from converting to wide tubes of low pressure [17].

In order to study the outcome of infants born to hypertensive mothers more thoroughly, data on stillbirths in the investigated population would be necessary. Regrettably these data could not be included in the present survey. However, the mortality in the liveborn infants was significantly lower than in infants born to normotensive mothers.

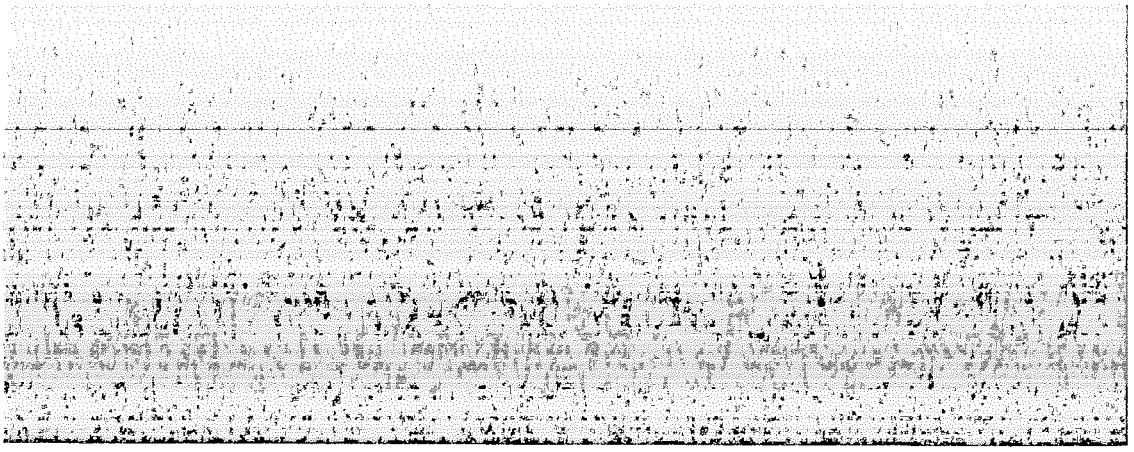
Recently, in a large prospective project on children born to mothers with hypertensive disorders, this same difference in mortality rate was found [18]. In the surviving infants similar handicap rates occurred in cases with and without maternal hypertensive disorders, a finding which does not support the idea of a continuum of reproductive casualty [19].

In the present study, no distinction was made between pre-existing and pregnancy-induced hypertension. Classification would encompass only a small portion of the variables that influence outcome; direct comparison of patients with the same classification would not necessarily eliminate or substantially reduce bias although it would standardize some of these variables between reports [20]. Furthermore the number of mothers with pre-existing hypertension (n=51) was too low to permit separate analyses.

In infants of mothers with pre-existing hypertension the crude in-hospital mortality (13.7%) and handicap rates (20.4%) were similar to those infants of mothers with gestational hypertension (10.8% and 15.7% respectively). The improved survival chance of all these infants may be due to circulatory changes in the fetus. It is speculated that the increased placental vascular resistance experienced by infants of hypertensive mothers, necessitates adaptations during intrauterine life that resemble those which usually takes place immediately after birth, due to the loss of the placenta with its low vascular resistance. These adaptations may provide the fetus with a better chance to survive the transition to extrauterine life when this occurs at an untimely moment.

Recent Doppler flow studies have demonstrated such a definite influence of maternal hypertension on the fetal and neonatal circulation [21]. Further Doppler flow studies may cast some light on the causative mechanisms involved.

At present, elective delivery is considered as the only possible therapeutic manoeuvre. Increasing understanding of the haemodynamic changes occurring before, during and after birth in such infants, may enable further development of rational treatment of very preterm infants both in case of maternal hypertension and otherwise endangered pregnancies.



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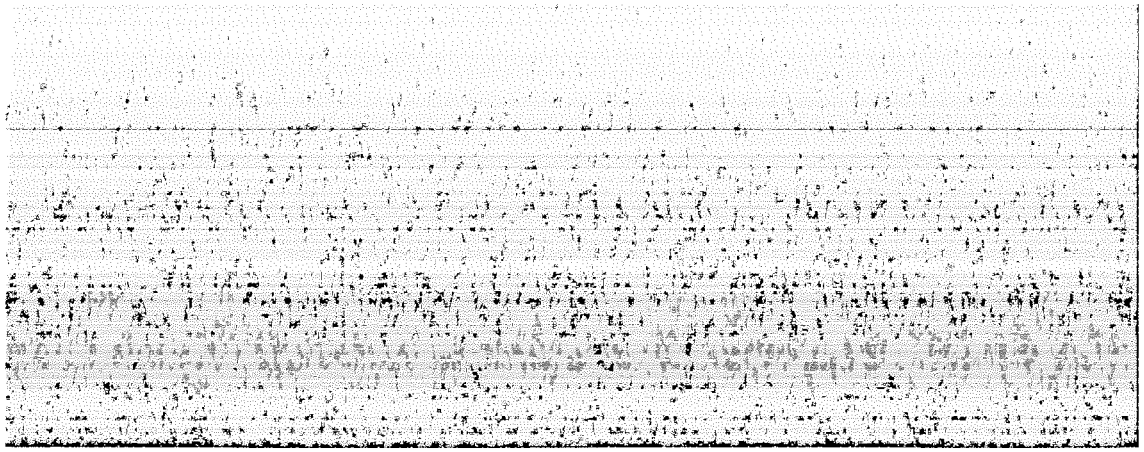

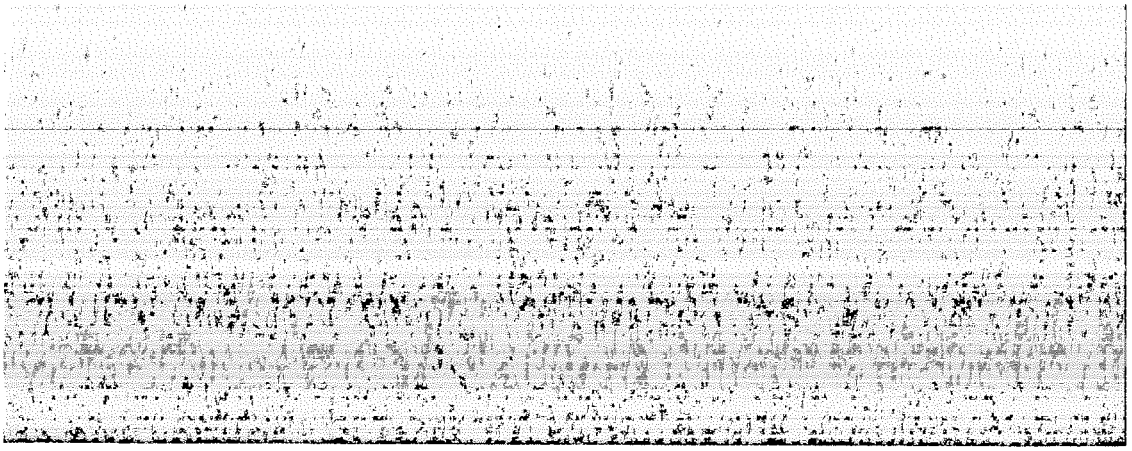

CHAPTER 4

THE MALE DISADVANTAGE IN VERY LOW BIRTHWEIGHT INFANTS: DOES IT REALLY EXIST?

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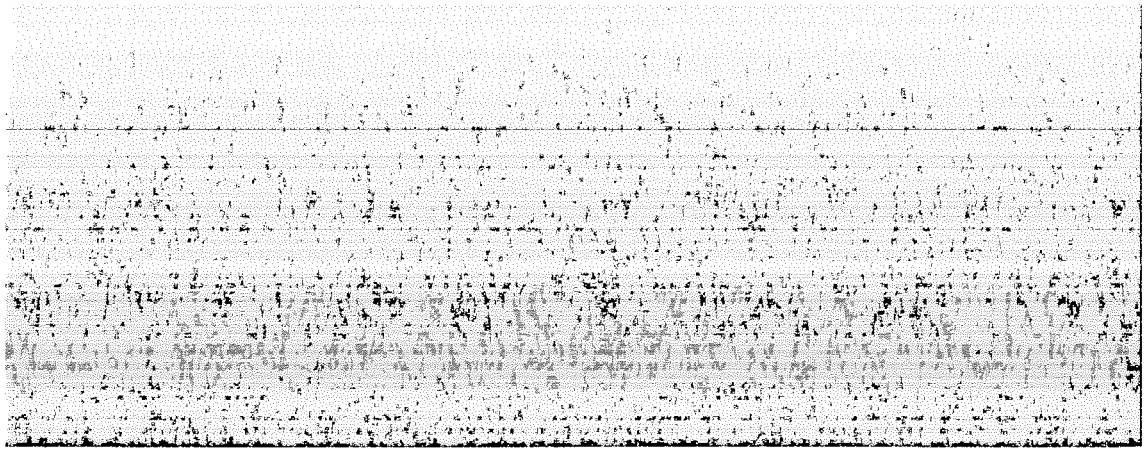


SUMMARY

In a nationwide collaborative study in the Netherlands perinatal and follow up data were collected on 1338 liveborn very preterm (<32 weeks) and/or very low birth weight (VLBW) (<1500 g) infants.

In this group, the mortality risk was similar for male and female infants. The handicap risk, however, was significantly greater for boys than for girls. This finding could not be explained as being due to the well-known delay in lung maturation in male infants as in idiopathic respiratory distress syndrome and need of assisted ventilation.

INTRODUCTION

Male very low birth weight infants are generally believed to have a smaller chance of survival than female infants. In addition, the surviving boys are said to be more often handicapped compared to girls.

However, most of the studies reporting such an excess risk of mortality and handicap in boys may have been biased, either by comprising only hospital-based populations [6] or by defining the study populations by birth weight alone [10-12, 21, 37].

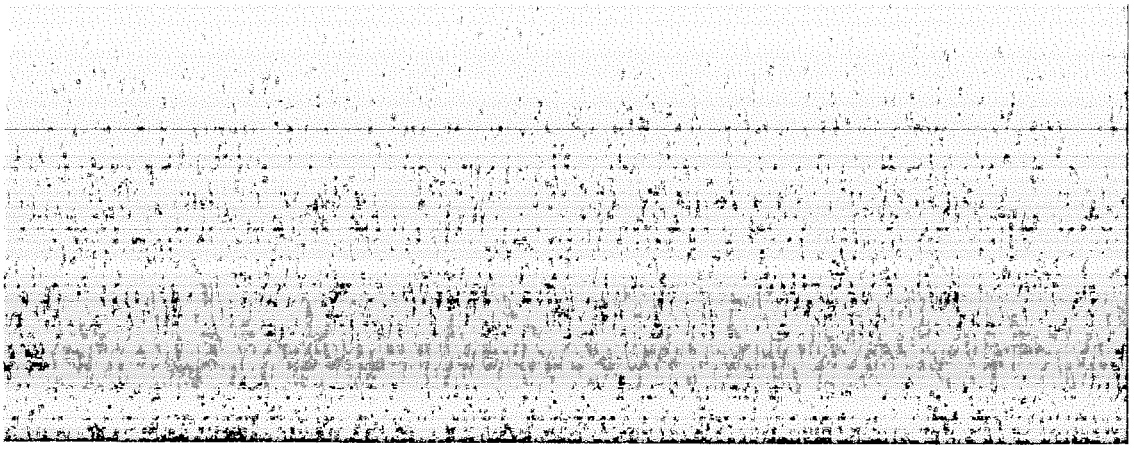
Therefore, we used the opportunity presented by the collaborative survey "Project On Preterm and Small for gestational age infants in the Netherlands" (POPS 1983) to study the relation between infants' sex, mortality and handicaps in a large, geographically defined group of very preterm and (or) VLBW infants.

PATIENTS AND METHODS

The "Project On Preterm and Small-for-gestational-age infants" is a nationwide collaborative survey, including 94% of all very preterm (less than 32 completed weeks gestational age) and (or) VLBW infants (<1500 g), liveborn in the Netherlands in 1983 [32, 33]. Following a protocol, data of 1338 infants were recorded by the attending paediatrician concerning pregnancy, birth, postnatal period until death or discharge and concerning a follow up period of the surviving infants up to the age of 2 years, corrected for preterm birth [39].

Gestational age

This was defined as the best obstetric estimate, based on menstrual dates, pregnancy testing and if necessary, on other evidence such as ultrasound examination. In all but 3 cases a "best obstetric estimate of gestational age" was available. The lowest gestational age recorded in the study population was 22 weeks + 2 days. The highest gestational age of an infant born in 1983 with a birth weight below 1500 g was 40 weeks + 6 days. The median gestational age of the study population was 30 weeks + 2 days.



Birth weight

This was defined as the first weight of the infant obtained after birth and was expressed in grams. In most cases this weight was measured directly after birth. However, in some cases the infant's condition warranted such expeditious treatment that weighing had to be postponed. Nevertheless, these delays were too short for appreciable postnatal weight loss to occur.

In all 1338 cases, birth weight was recorded the lowest recorded of a liveborn infant being 420 g.

Infants' sex

This was established by physical examination. Sex could be determined unequivocally in all but 5 infants. Four of these five infants were born after a very short gestation and died immediately after birth.

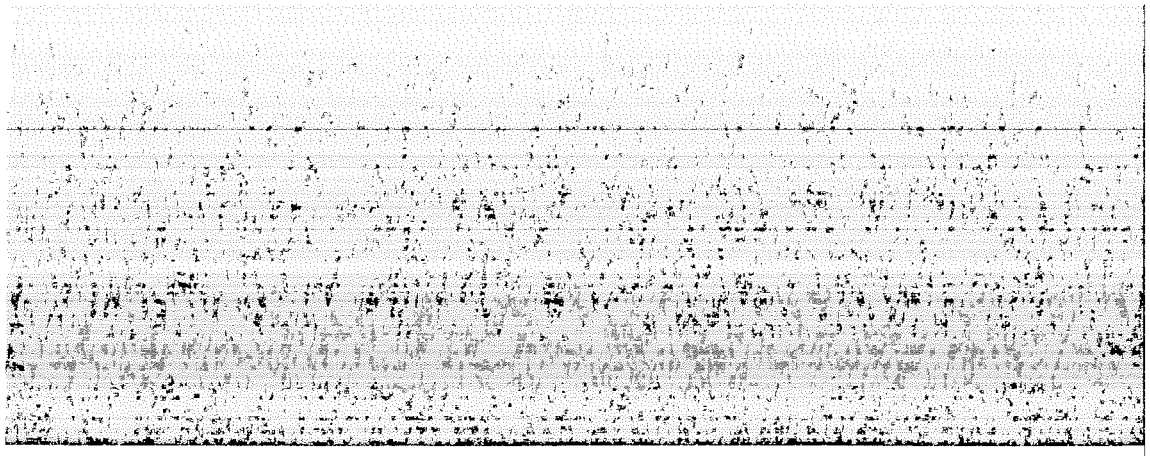
Of the 1333 cases with unequivocally determined sex, 698 infants (52.4%) were male and 635 infants (47.6%) were female.

In-hospital mortality

This was defined as all deaths during the initial hospital stay after birth. Total mortality was defined as all deaths up to 2 years of corrected age.

Of 969 surviving infants at the age of 2 years, corrected for preterm birth, 910 were assessed by their attending paediatrician and 34 by their general physician or at the health clinic. An overall developmental level was assessed using the Gesell test adapted for Dutch children [28], and neurological, visual and hearing examinations were carried out, when necessary by a multidisciplinary team. Methods will be described extensively elsewhere [38].

According to the outcome at 2 years of corrected age each child was categorized by the attending paediatrician into one of three groups: with major handicap, minor handicap or no handicap. A major handicap was diagnosed when severe retardation was present (5 or more months retarded or developmental quotient less than 80) and/or a severe neurological disorder existed such as hemi- or quadriparesis and/or severe visual or hearing defects and/or serious psychosocial problems were present. Such disabilities are likely to prevent the child from attending a normal school, or (will) cause serious interference with normal function in society. A child was categorized as having a minor handicap when some retardation was present (3-4 months retarded or developmental quotient between 80 and 90) and/or a mild neurological disorder existed such as a slight hemi- or quadriparesis and/or mild visual or hearing defects and/or moderate psychosocial problems appeared. Such disabilities are unlikely to prevent the child from attending a normal school, or to interfere seriously with normal life [30]. A child was considered to be without handicap, when there was no retardation and no motor, visual or hearing disabilities were present [39, 40]. The term



handicap was used deliberately, in agreement with the International Classification of Impairments, Disabilities and Handicaps [36]. The word handicap implies a disturbance of normal life [1] and as such it places the impairment or disability in a social context. The presence of a handicap was, in most cases, not deductable from the information provided on one of the previous forms. Therefore, the opinion of the paediatrician performing the follow up examinations was necessary to indicate whether a disability had caused a handicap. A description of some disabilities probably causing a major or minor handicap was given as an example.

STATISTICAL ANALYSIS

Firstly, we studied the relation between infants' sex, birth weight and gestational age in the total study population. Crude mortality and handicap rates were calculated for male and female infants.

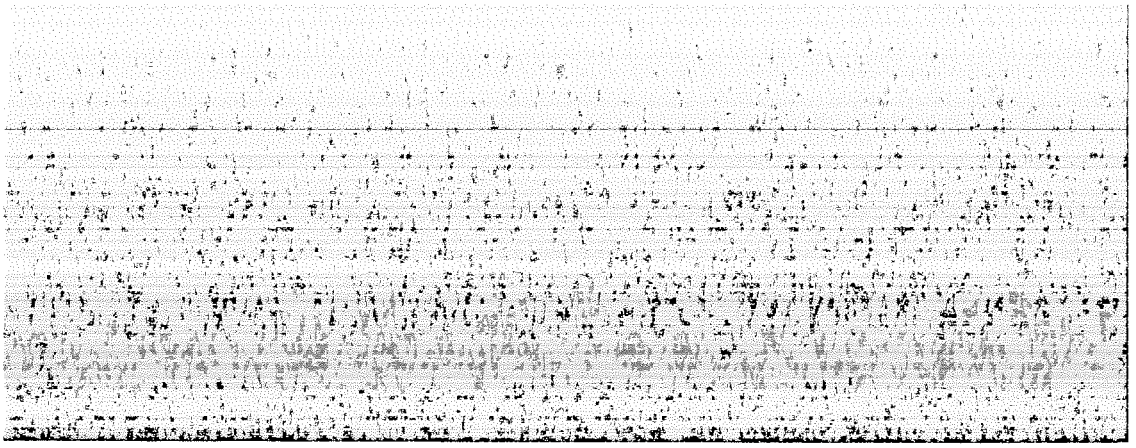
Secondly, we used a multivariate statistical technique, the logistic regression analysis [27], to adjust for possible uneven distributions of perinatal factors which may itself be associated with mortality or handicap. The definitions of the perinatal factors used in the proposed logistic regression models are stated in Table 1.

The results of the logistic regression analyses are expressed as an odds ratio (OR): the odds for mortality (or handicap) in male children versus the odds for mortality (or handicap) in female children.

An odds ratio of less than 1 indicates a lower risk, while an odds ratio of greater than 1 indicates a higher risk for boys. An odds ratio is significantly different from 1 at the 5% level if, and only if, its 95% confidence interval does not include 1.

Table 1. Perinatal factors used in the logistic regression analysis

Socio-economic class	1 (low) to 6 (high) [35]
Pre-existing maternal disease	Including heart disease, epilepsy, diabetes mellitus, renal disease
Maternal hypertensive disorders	Diastolic bloodpressure equal or exceeding 90 mm Hg, measured at least twice
Congenital malformation	Any
Multiple pregnancy	Twin, triplet, quadruplet
Antenatal transport	To a perinatal intensive care center (level 3)
Tocolysis	$\geqslant$24 h. suppression of uterine contractions
Glucocorticoids	Administration to the pregnant mother
Fetal presentation	Breech and transverse presentation
Gestational age	In days
Birth weight	In grams
Small for gestational age	$<$ 10th percentile [13]



RESULTS

The crude mortality and handicap rates for male and female infants are stated in Table 2, for the total population as well as for the subpopulation of very preterm infants (gestational age less than 32 weeks, n = 1010) and VLBW infants (birth weight less than 1500 g, n = 1092).

Table 2. Crude mortality and handicap rates

	Male infants		Female infants		Total	
	n	%	n	%	n	%
Total population (n=1338)						
In-hospital mortality	183/698	26.2	153/635	24.1	336/1333	25.2
Total mortality	205/698	29.4	160/635	25.2	365/1333	27.4
Major handicap	44/698	6.3	15/635	2.4	59/1333	4.4
Minor handicap	61/698	8.7	50/635	7.9	111/1333	8.3
Total adverse outcome	310/698	44.7	225/635	35.4	535/1333	40.1*
Birthweight <1500 g (n=1092)						
In-hospital mortality	162/547	29.6	140/545	25.7	302/1092	27.7
Total mortality	177/547	32.4	146/545	26.8	323/1092	29.6
Major handicap	33/547	6.0	14/545	2.6	47/1092	4.3
Minor handicap	48/547	8.8	42/545	7.7	90/1092	8.2
Total adverse outcome	258/547	47.2	202/545	37.1	460/1092	42.1*
Gestational age <32 weeks (n=1008)						
In-hospital mortality	171/549	31.1	137/459	29.8	308/1008	30.6
Total mortality	189/549	34.4	141/459	30.7	330/1008	32.7
Major handicap	34/549	6.2	8/459	1.7	42/1008	4.2
Minor handicap	41/549	7.5	40/459	8.7	81/1008	8.0
Total adverse outcome	264/549	48.1	189/459	41.2	453/1008	44.9**

* $p < 0.005$ (chi-square analysis, df = 2)
** $p = 0.08$ (chi-square analysis, df = 2)

In virtually all categories girls have a better outcome than boys. Especially neurodevelopmental disorders are far more frequent in boys (Table 3).

After correction for 12 potential confounding factors (Table 1) by using multivariate statistics, the odds for in-hospital mortality appeared to be similar in girls and boys. However, the odds for "major adverse outcome" (total deaths plus major handicaps) and for total handicaps in surviving children (major and minor handicaps) were significantly higher in boys compared to girls (Table 4).

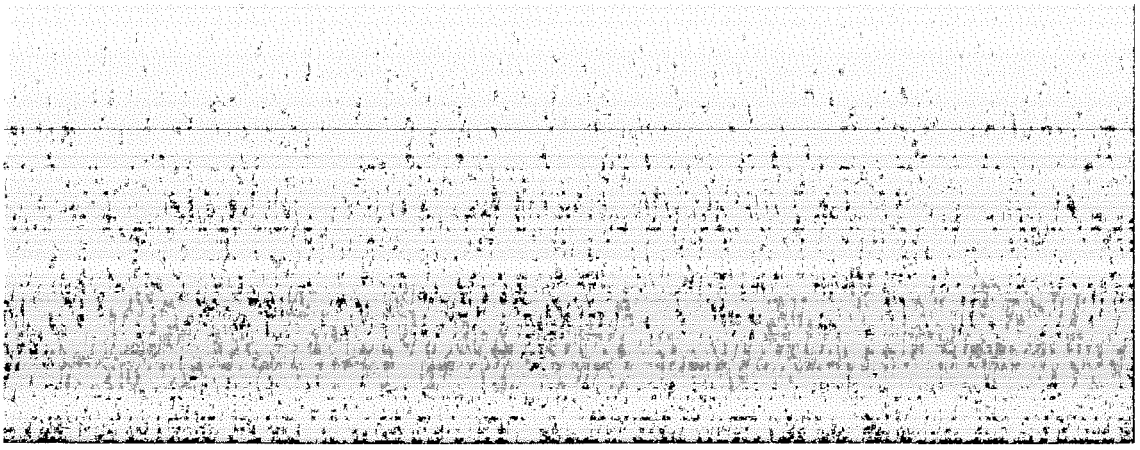


Table 3. Handicaps in surviving male and female children

	Number of children		
	Total	Male	Female
Categories of minor handicap			
Congenital malformation	6	3	3
Central motor deficit	41	19	22
Mental retardation (MR)	11	6	5
Central motor deficit and MR	13	11	2
Hearing impairment	3	3	
Visual impairment	2	1	1
Behavioural problem	5	1	4
Speech retardation	24	14	10
Miscellaneous	6	3	3
Total	111	61	50
Categories of major handicap			
Congenital malformation	9	4	5
Central motor deficit	12	9	3
Mental retardation (MR)	2	2	
Central motor deficit and MR	31	25	6
Hearing impairment	3	2	1
Visual impairment	2	2	
Total	59	44	15

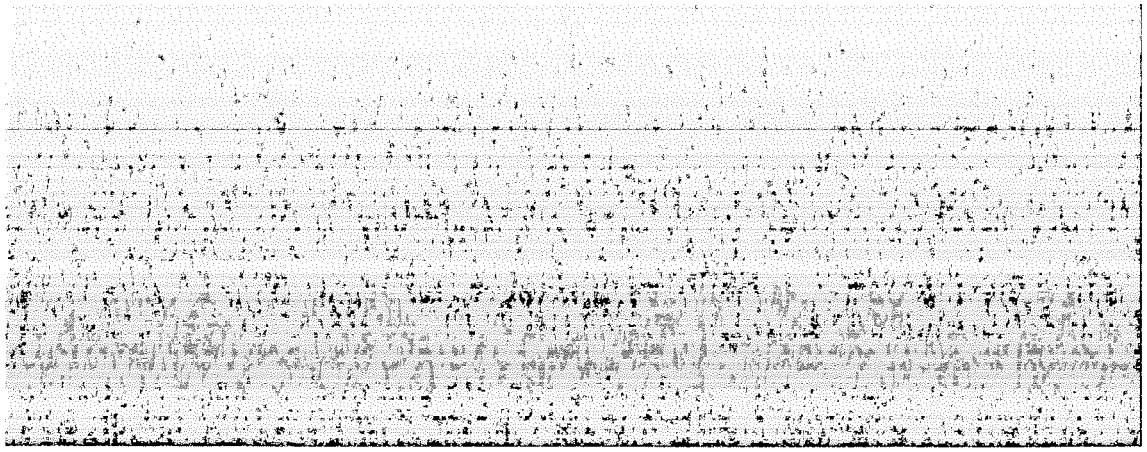
Table 4. Odds ratios (OR) and 95% confidence intervals (CI) for male infants compared to female infants

Outcome	Crude OR	Adjusted OR[a]	CI
In-hospital mortality	1.12	1.14	(0.81 - 1.61)
Major adverse outcome	1.46	1.59	(1.18 - 2.13)*
Total handicaps	1.72	1.68	(1.17 - 2.42)*

[a] logistic regression analysis; the models include all perinatal factors stated in Table 1
* $p < 0.05$

DISCUSSION

Equal mortality risks in boys and girls have been found before [23], but are contrary to the popular and well-publicised belief that preterm and VLBW boys have a higher mortality risk than girls. Most of the studies that report such a difference between the sexes originate from neonatal intensive care centers with highly selected study populations [6, 15]. Considerable selection bias in such study populations may have been introduced by referral of an excess of



more severily ill boys. Some studies are based on autopsies, without mentioning the autopsy rate in boys and girls, which may also introduce a selection bias [19].

Khoury et al. [12] studying a geographically defined population and adjusting for several perinatal and labour-related factors, also reported an excess neonatal mortality in males. However, adjustments were made for birth weight only (by comparing sex-specific neonatal mortality rates within each birth weight category) and not for gestational age, because gestational age was unknown in more than 40% of the deaths.

Paneth et al. [21] calculated an odds ratio of 1.62 ($p < 0.001$) for neonatal mortality of male infants compared to female infants. Although their study population was geographically defined as well, its cutoff point was by birth weight (501-2000 g). In the logistic regression model, adjustment was made for birth weight (by stratification) and "gestation-for birth weight" (quartiles), but not for gestational age and birth weight as separate variables.

Yu et al. [37] found a significantly lower percentage of females among deaths than among survivors (48% versus 65%; $p = 0.0309$, chi-square analysis with Yates' correction) in an inborn extremely low birth weight population (500-999 g), but the difference in mean gestational age between deaths and survivors (25 versus 27 weeks) was not taken into account. In VLBW infants, Brothwood et al. [6] reported an infant mortality of 41% in boys and 19% in girls. In addition to being a partly referred population, again the difference in mean gestational age of 1 week between boys and girls was not taken into account.

It is a generally accepted fact that male individuals are heavier than females of the same age. This is especially true in infancy and childhood, and is the reason for presenting separate growth charts all over the world for girls and boys[26]. The same holds true for "intrauterine" growth charts [3, 14, 17]. Therefore, differences in mortality between boys and girls cannot be analysed properly without taking into account differences in gestational age and birth weight, both factors being extremely important in relation to mortality [2, 8, 32].

The differences in crude mortality rates found in the present study (Table 2) may be explained in this way. The boys' mean gestational age is in most birth weight categories considerably shorter than that of the girls (Fig. 1) giving rise to higher mortality rates in nearly all birthweight categories (Table 5a), but similar mortality rates in gestational age categories (Table 5b).

After adjusting for the difference in gestational age and other perinatal factors by including these factors into the logistic regression model, the in-hospital mortality odds were similar for male and female infants.

The handicap risk, however, is significantly greater for boys than for girls, even when divided into gestational age categories (Table 6), and even after adjustment for the 12 perinatal factors stated. This is in agreement with previous findings of a higher neurological morbidity rate among boys [24], without a difference in obstetrical conditions [31], and with many reports of follow up

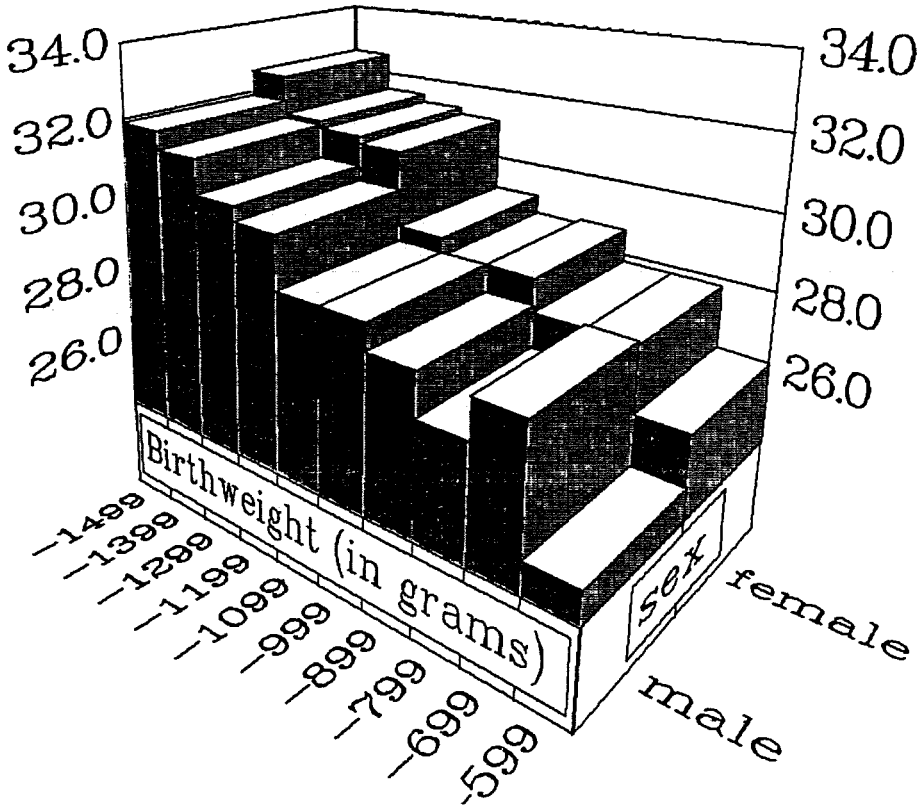


Fig. 1. Mean gestational age by birth weight and infants' sex

Table 5a. In-hospital mortality rates in male and female infants in various birth weight categories

Birth weight (g)	Male infants		Female infants	
	n	%	n	%
500- 599	5/ 5	100	8/ 9	89
600- 699	13/ 16	81	8/17	47
700- 799	19/ 25	76	13/25	52
800- 899	28/ 41	68	22/47	47
900- 999	18/ 54	33	16/46	35
1000-1099	18/ 52	35	25/72	35
1100-1199	15/ 71	21	17/68	25
1200-1299	24/ 84	29	15/76	20
1300-1399	10/ 88	11	6/91	7
1400-1499	11/110	10	7/91	8

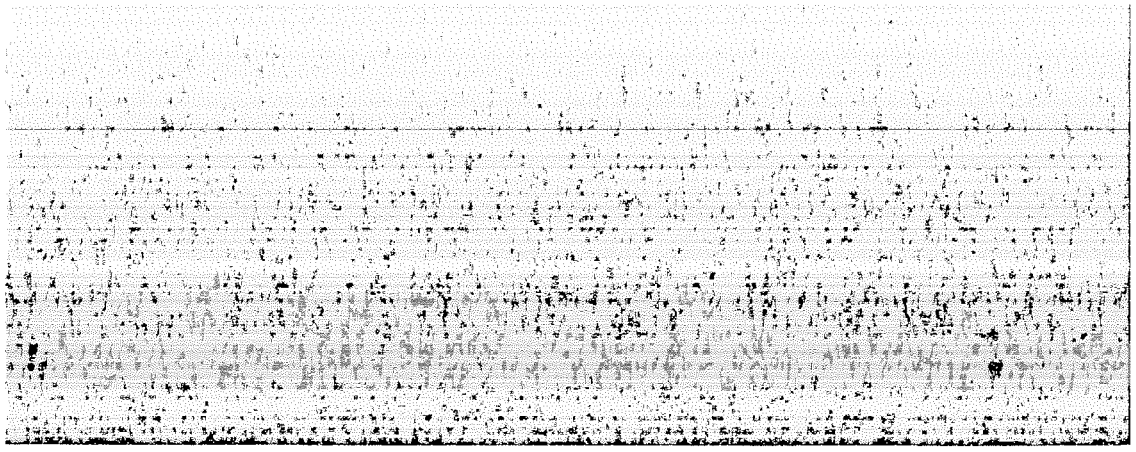


Table 5b. In-hospital mortality rates in male and female infants in various gestational age categories

Gestational Age (weeks)	Male infants		Female infants	
	n	%	n	%
24-25	32 / 36	89	27 / 30	90
26-27	54 / 98	55	40 / 81	49
28-29	47 /172	27	36 /135	27
30-31	34 /239	14	30 /209	14

Table 6. Total handicap rate (major plus minor handicaps) in surviving male and female children in various gestational age categories[a]

Gestational Age (weeks)	Male children		Female children	
	n	%	n	%
24-25	3 / 3	100	0 / 1	0
26-27	10 / 40	25	4 / 39	10
28-29	29 /117	25	21 / 95	22
30-31	33 /188	18	23 /173	13

[a] The denominators differ slightly from the numbers of children discharged home, due to deaths after discharge (n=29; 22 male,7 female) and loss to follow up (n=25; 14 male, 11 female)

studies in VLBW infants [7, 9, 16, 20, 25] all describing a male disadvantage in motor skills and school performance. None of the authors, however, offer an explanation for these differences in outcome.

To our knowledge, the only difference between male and female preterm infants of similar gestational age and birth weight that has been documented in recent years concerns a delay in lung maturation in boys [12, 18, 29]. Our findings in the present study population were consistent with these reports: the crude rates of idiopathic respiratory distress syndrome (IRDS) were higher in boys than in girls (51.0 and 41.6% respectively). Contrary to previous reports [22], such a higher risk of IRDS apparently does not necessarily lead to a higher death rate in boys. It may, though, lead to more severe and longer lasting illness in the neonatal period, thereby perhaps increasing the handicap risk. To study this hypothesis further, we re-analysed the sex difference for major adverse outcome and for total handicaps. Firstly, several perinatal factors associated with an increased risk of mortality but occurring later in time and, therefore, possibly related to the infants' sex, were included in the multivariate analysis as potential confounding factors (Table 7).

The occurrence of these neonatal factors in male and female infants is stated in Table 8; in addition to the excess of IRDS, the rate of seizures in the neonatal period was higher in male than in female infants.

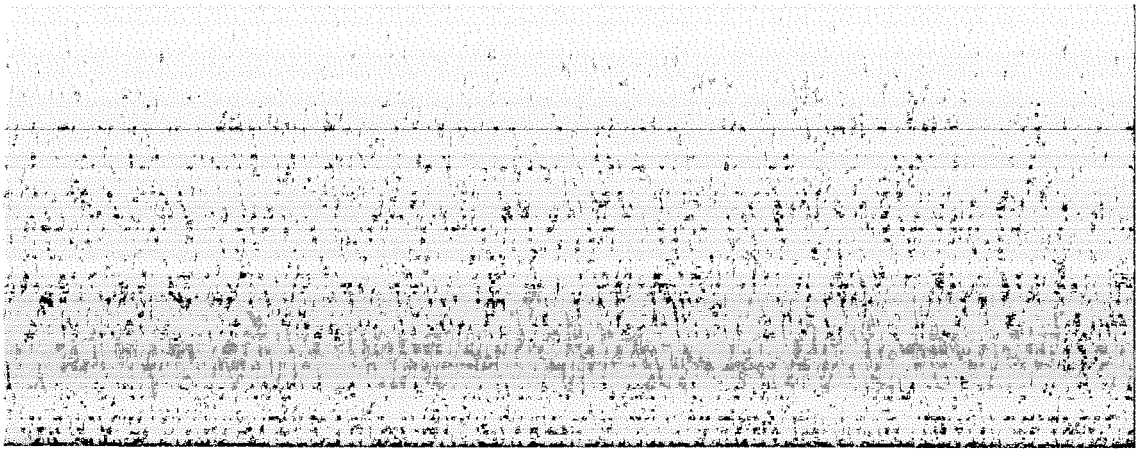


Table 7. Additional perinatal factors used in the 2nd series of logistic regression analyses

Hospital of birth, level of care	Level 1 (low), 2 (intermediate), 3 (high) [34]
Mode of delivery	Caesarean section versus vaginal
Apgar score 5 min.	< 7 versus $\geqslant 7$
Neonatal transport	To level 2, 3
IRDS	Clinical diagnosis (based on extra $O_2 > 24$ h, expiratory grunting, tachypnoea, sternal and intercostal retractions and nasal flaring) and /or typical x-ray
Intra cranial hemorrhage	Clinical diagnosis (based on rapid or saltatory deterioration, fall in hematocrit) and /or ultra-sound or computer tomography [4, 5]
Sepsis	Haematological findings (typical white blood cell count) and /or positive bloodculture
Seizures	Clinical versus none
Bilirubin	Maximal total serum bilirubin level
Assisted ventilation	Intermittent positive pressure ventilation and /or continuous positive airway pressure

However, stratification for IRDS and for seizures (Mantel-Haenszel estimate of the OR) did not change the results for major adverse outcome (unstratified OR 1.46 (95 % confidence intervals (CI) 1.16-1.83), OR stratified for IRDS 1.36 (1.08-1.72), OR stratified for seizures 1.40 (1.11-1.76)). The results for handicap (unstratified OR 1.55 (95 % CI 1.10-2.19), OR stratified for IRDS 1.57 (1.11-2.22), OR stratified for seizures 1.53 (1.09-2.17)) were similar as well. In the logistic regression analysis, including all factors from Table 7, the odds for handicap were still significantly greater for boys than for girls (OR 1.40, 95 % CI 1.08-1.82). Apparently neither IRDS nor seizures, although more frequent in boys, serves as an intermediate mechanism to explain the difference in handicap rate. Neither does any of the other factors, since in that case adjustment for those factors would have led to a reduced estimate of the effect of infants' sex. Secondly, we included the number of days of assisted ventilation (intermittent positive pressure ventilation (IPPV) and /or continuous positive airway pressure (CPAP)) as an additional factor, as a measure for the severity and duration of lung disorders. Although the crude rates were higher in male than in female infants (Table 8), infants' sex remained significantly associated with total handicap, after stratification as well as in the logistic regression analysis.

We therefore conclude that, although IRDS and seizures are more frequent disorders and may cause longer periods of more severe illness in boys than in girls of similar gestational age, this is not the origin of the difference in handicap risk between male and female children found at the age of 2 years.

Aware of the fact that the presence or absence of handicap at the age of 2 years may differ from findings at a later age, the total study population has been re-assessed again during 1988 at the age of 5 years. Preliminary results confirm the male disadvantage, presented in this paper.

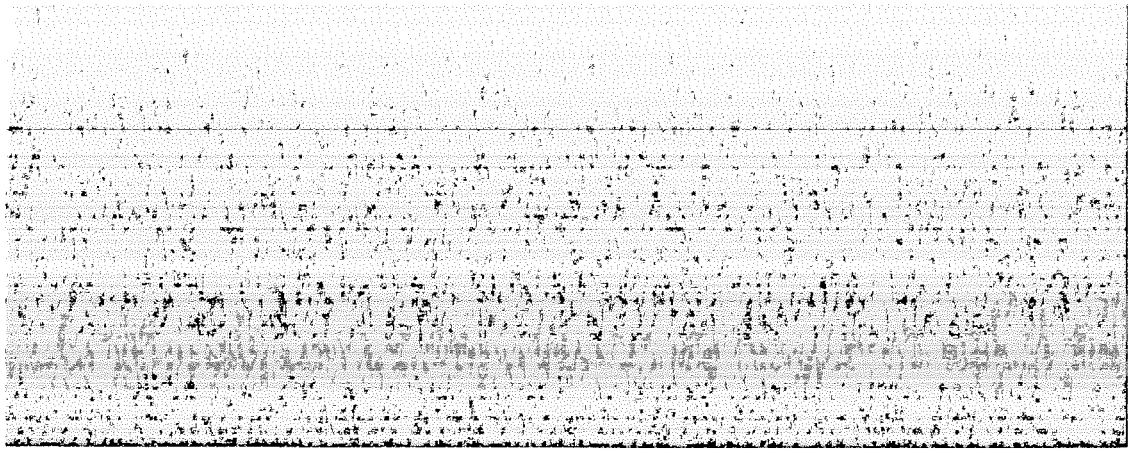


Table 8. Crude rates of various neonatal factors in male and female infants

Factor	Male infants		Female infants	
	n	%	n	%
Total number	698	100.0	635	100.0
IRDS	356	51.0	264	41.6
Intra cranial haemorrhage	177	25.3	156	24.5
Sepsis	233	33.6	210	33.3
Seizures	48	6.9	24	3.8
Total bilirubin				
>200 μmol/L	166/599	27.7	130/545	23.8
Assisted ventilation	419	60.0	317	49.9
of which 1- 7 days	257	36.9	218	34.4
8-28 days	132	18.9	83	13.1
>28 days	30	4.3	16	2.5

Modern intensive care techniques may have reduced the difference in mortality risk between the sexes. However, male very preterm and VLBW infants remain at a disadvantage concerning later handicaps. As in other populations, the pathophysiologic background of this difference remains unclear, and calls for further study.

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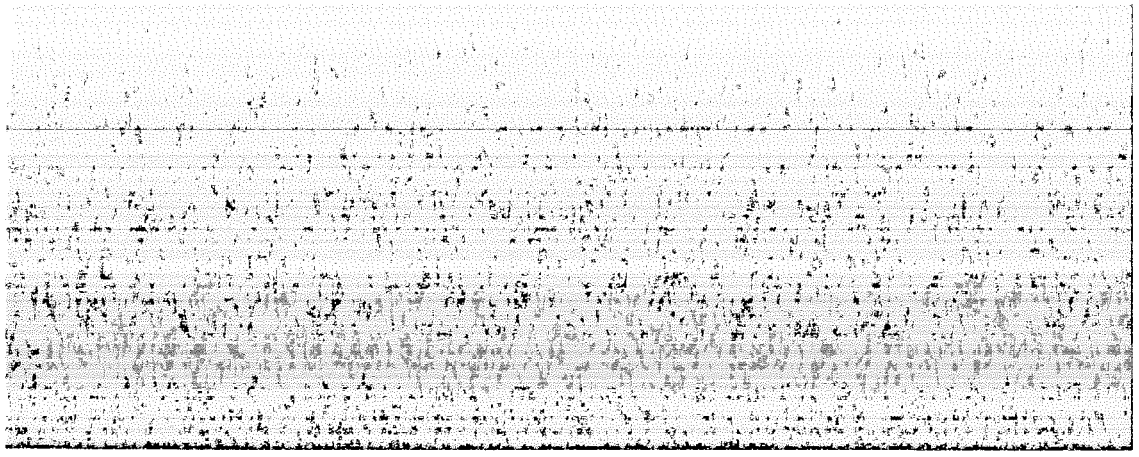

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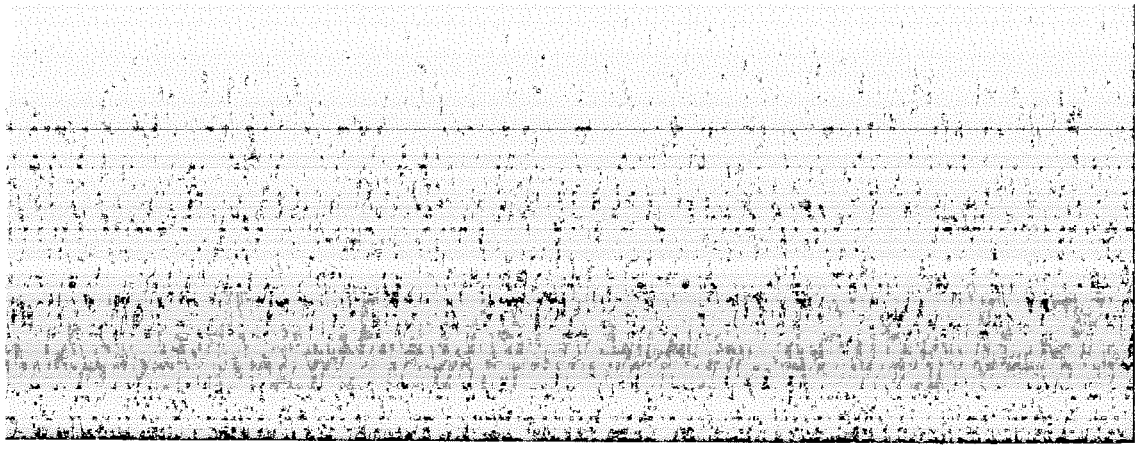

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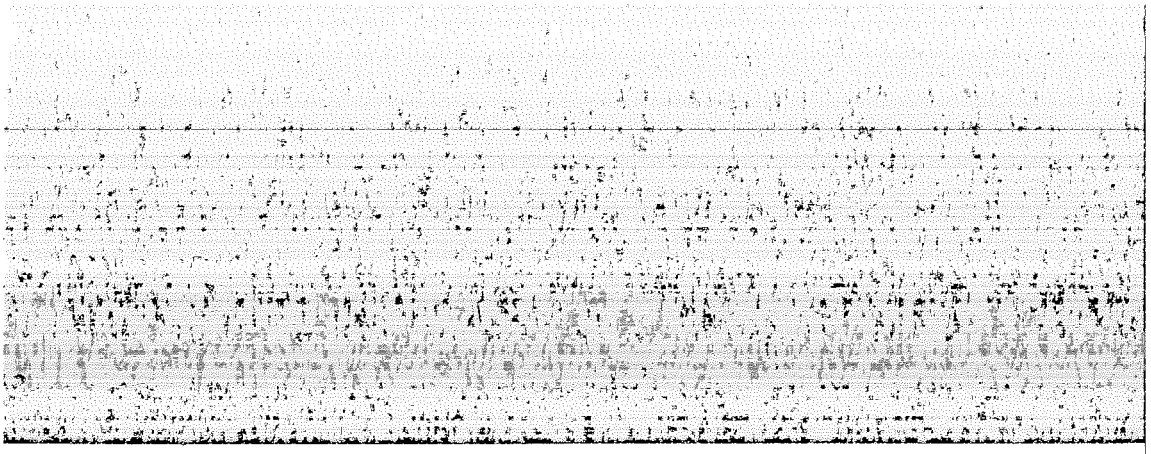
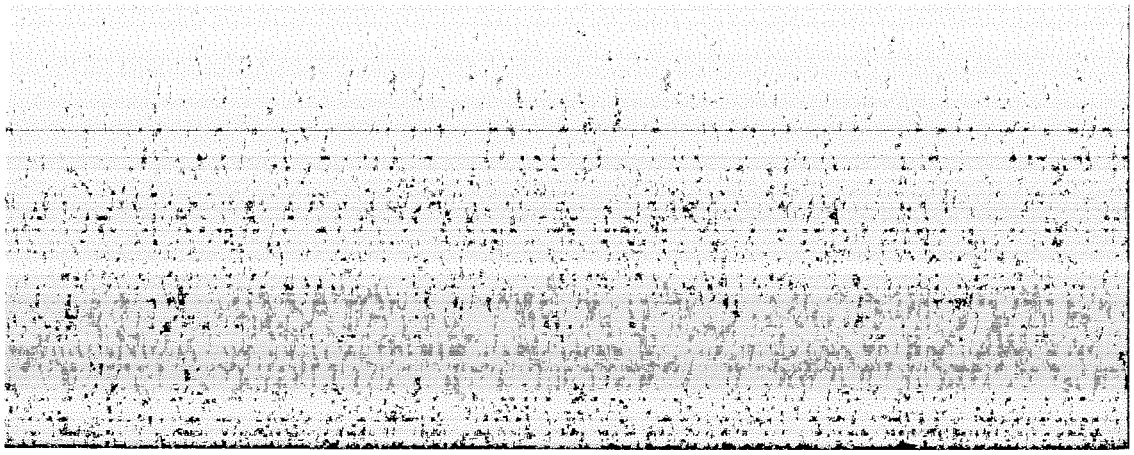




RESULTS

Incidence

Out of 1192 study infants 36 (3.0%) died before neonatal neurological examination could be performed. These 'unknown' infants were classified as neurological normal, and hence we are sure not to overestimate the effect of neurological dysfunction on mortality.

In 96 (8.1%) of the babies there was obvious neurological dysfunction and in 73 (6.1%) suspect dysfunction.

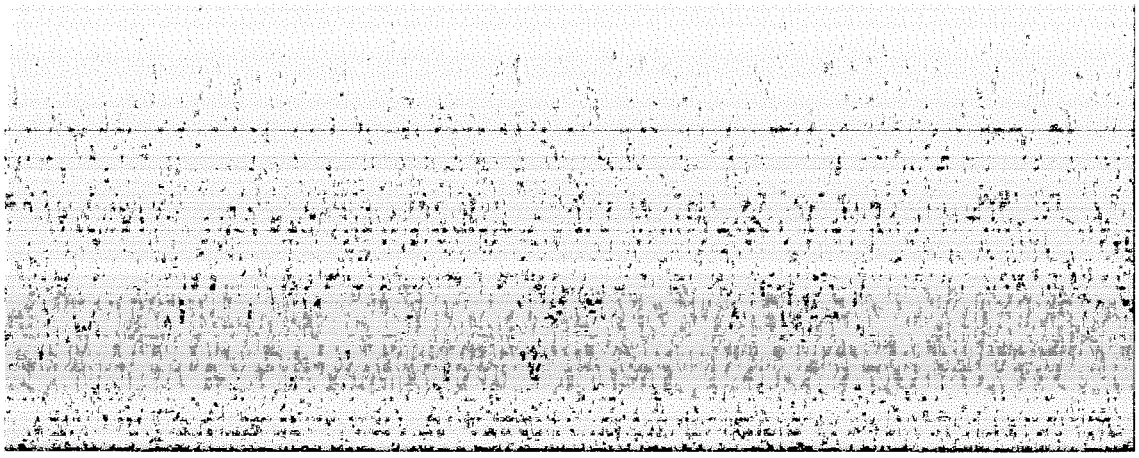
Relation to perinatal factors: univariate analysis

All perinatal factors divided in to the four time categories are shown in table 1. Of the prenatal factors, only non-vertex presentation was significantly more frequent in obvious and suspect ND infants. The difference in sex was not significant and the relation to multiple pregnancy could not be interpreted. Both

Table 1. Relation of neonatal neurological dysfunction to perinatal factors. Univariate analyses

	neurol normal n=1023		suspect ND n=73		obvious ND n=96		p
	n	%	n	%	n	%	
time category I							
sex (male)	530	51.9	39	53.4	54	56.3	ns
multiple pregnancy	243	23.8	12	16.4	35	36.5	<0.01
non-vertex presentation	256	25.0	22	30.1	35	36.5	<0.03
gestational age (mean ± sd)	30.4	(2.8)	29.6	(2.6)	28.9	(2.7)	<0.01*
birthweight (mean ± sd)	1270	(318)	1202	(312)	1113	(276)	<0.01*
time category II							
caesarean section	435	42.5	35	47.9	33	34.4	ns
level I	376	36.8	19	26.8	37	36.5	ns
level II	274	26.0	28	38.4	22	35.6	ns
level III	373	38.5	26	22.9	37	38.5	ns
time category III							
low Apgar score	160	15.6	21	28.8	34	35.4	<0.01
time category IV							
IRDS	440	43.0	49	67.1	72	75.0	<0.01
ICH	184	17.9	39	53.4	71	74.0	<0.01
seizures	25	2.4	10	13.7	30	31.3	<0.01
meningitis	5	0.5	5	6.8	4	4.3	<0.01

*non-parametric analysis of variance (Kruskal-Wallis); otherwise chi-square analysis



low gestational age and low birthweight were significantly associated with neurological dysfunction. The difference in caesarean section rate was not significant, no significant relation between obvious and suspect ND and the level of care was found.

Low Apgar score occurred more frequently in both obvious and suspect ND groups, even though we classified the 'unknown' infants as normal. Evidence of IRDS was found in 561 infants (47.1%) in the study population; 85% of them needed ventilatory support. ND infants appeared to have suffered significantly more frequent from IRDS (67.1% and 75% in suspect and obvious ND respectively) than neurologically normal infants (43%). As expected, other disorders of the central nervous system in the neonatal period (ICH, seizures and meningitis) were much more frequent in the infants with neurological dysfunction.

Relation to perinatal factors: multivariate analysis

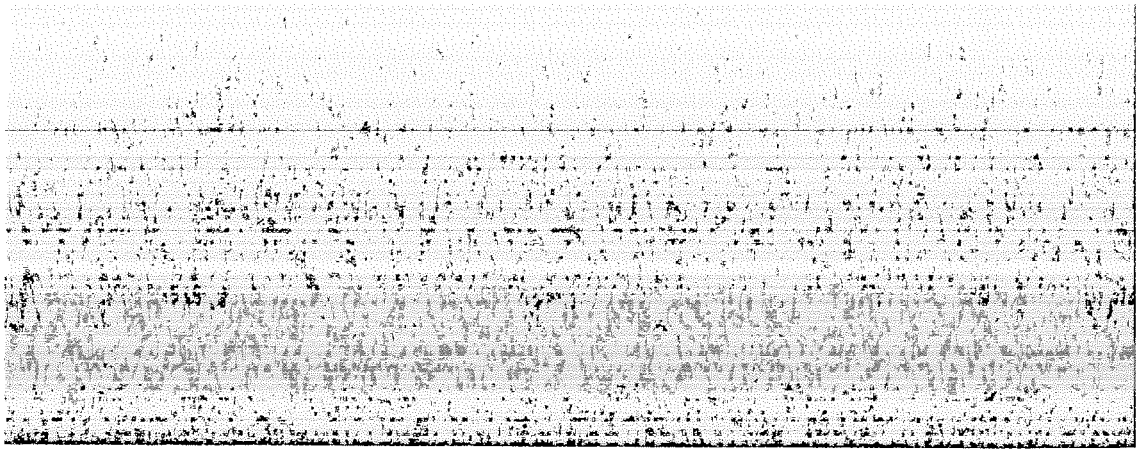
All perinatal factors listed in table 1 were included in the logistic regression model, except seizures and meningitis, because of the low frequency in which they occurred.

Stepwise logistic regression analysis showed that gestational age, birthweight, low Apgar score, IRDS and ICH were significantly associated with the odds for neurological dysfunction. ICH was by far the most predictive (table 2).

Of all other perinatal factors considered only non-vertex presentation was associated with neurological dysfunction, but not significantly at the 5% level.

Table 2. Adjusted odds ratios (OR), 95% confidence intervals (CI) and p values for neurological dysfunction

time category	risk factor	OR	CI	p
I	male vs female	1.16	0.8 - 1.6	ns
	multiple vs singleton	1.1	0.8 - 1.6	ns
	non-vertex vs vertex	1.4	0.98 - 2.0	ns
	gestational age per wk	0.89	0.83 - 0.96	<0.01
	birthweight per 100 gr	0.93	0.88 - 0.99	<0.03
II	caesarean section	1.3	0.9 - 1.9	ns
	level 1 vs 3	1.06	0.7 - 1.6	ns
	2 vs 3	1.3	0.9 - 2.0	
III	Apgar score			
	(low vs high)	2.0	1.3 - 3.0	<0.01
	(unknown vs known)	1.2	0.6 - 2.2	ns
IV	IRDS	1.9	1.5 - 3.4	<0.01
	ICH	6.9	4.7 - 10.3	<0.01



Mortality

Of the total population under study (n= 1192), 287 infants (24.1%) died during their initial hospital stay ("in-hospital" mortality). The in-hospital mortality in neurologically normal infants was 17,8% (n=183). In infants with neurological dysfunction this mortality was considerably higher: 35.6% (n=26) in the suspect ND infants, and 81.1% (n=78) in the obvious ND infants.

Follow-up at 2 years

The outcome at the age of 2 years, corrected for preterm birth, is shown in table 3.

Table 3. Neonatal neurological dysfunction and outcome at 2 years in infants discharged alive

	neurol norm n=840		suspect ND n=47		obvious ND n=18		total n=905	
	n	%	n	%	n	%	n	%
later death	16	2.0	4	8.7			20	2.3
major handicap	31	3.8	7	15.2	9	50.0	47	5.3
minor handicap	79	9.7	11	23.9	3	16.7	93	10.6
no handicap	689	84.5	24	52.2	6	33.3	719	81.8
unknown	25		1				26	

Of the 905 infants without congenital malformations and surviving the initial hospital stay follow-up data at 2 years of age were available for 879 (96.1%).

Outcome data were available of 815 infants without neurological problems in the neonatal period: 16 (2.0%) died in the first 2 years, 31 (3.1%) had a major handicap and 79 (9.7%) a minor handicap. The remaining 689 children (84.5%) were without handicap, although 5 of them were reported to have mild neurological abnormalities at that time.

The outcome data of the infants with suspect ND was less satisfactory; of the 46 survivors, available for follow up, 4 (8.7%) died during the first 2 years, 7 (15.2%) had a major handicap and 11 (23.9%) a minor handicap. Only 24 were without handicap or neurological abnormality.

In the infants with obvious ND the outcome was even worse. Of the 18 survivors 9 (50%) had a major handicap and 3 (16.6%) a minor handicap. The remaining 6 children were reported to be without handicap at the age of 2 years, although all of them had neurological abnormalities during the first year, that were still present in 2 of the "normal" children at the age of 2 years.

The handicaps in the suspect and obvious ND infants are described in table 4. Many children had more than one disability. A description of all children with handicaps at 2 years of age, including the children with congenital malformations, has been published (Chapter 2)(32).

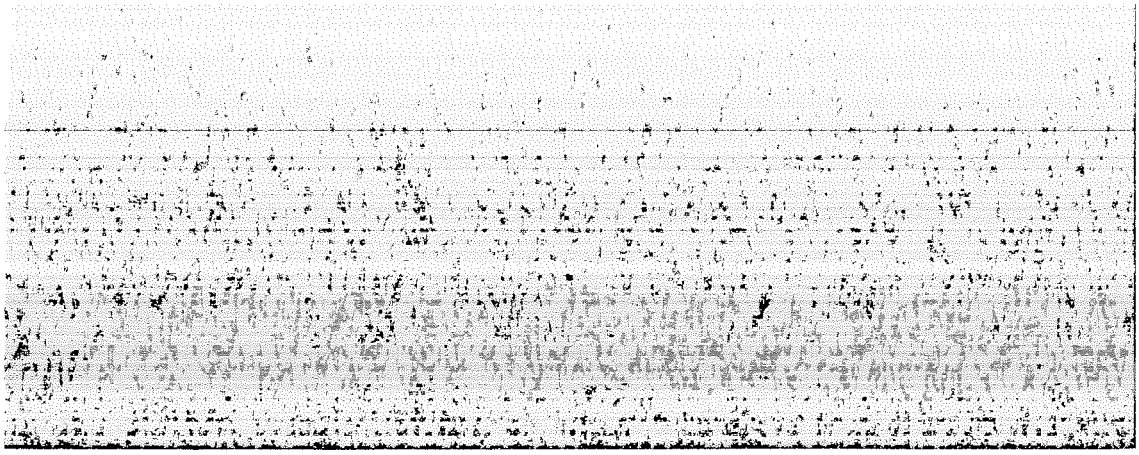


Table 4. Handicaps in infants with suspect and obvious neurological dysfunction

	suspect ND	obvious ND
major handicaps	n=7	n=9
mental retardation	3	6
cerebral palsy	6	8
epilepsy	1	2
visual impairment	2	3
squint	3	4
hearing impairment		3
ventriculo-peritoneal drain	2	3
minor handicaps	n=11	n=3
mental retardation	7	2
cerebral palsy	6	2
squint		2
hearing impairment	1	1
behavioural disturbances	2	1
other	3	1

Table 5. Incidence, mortality and major handicaps in preterm (<32 weeks) and VLBW infants (<1500 grams)

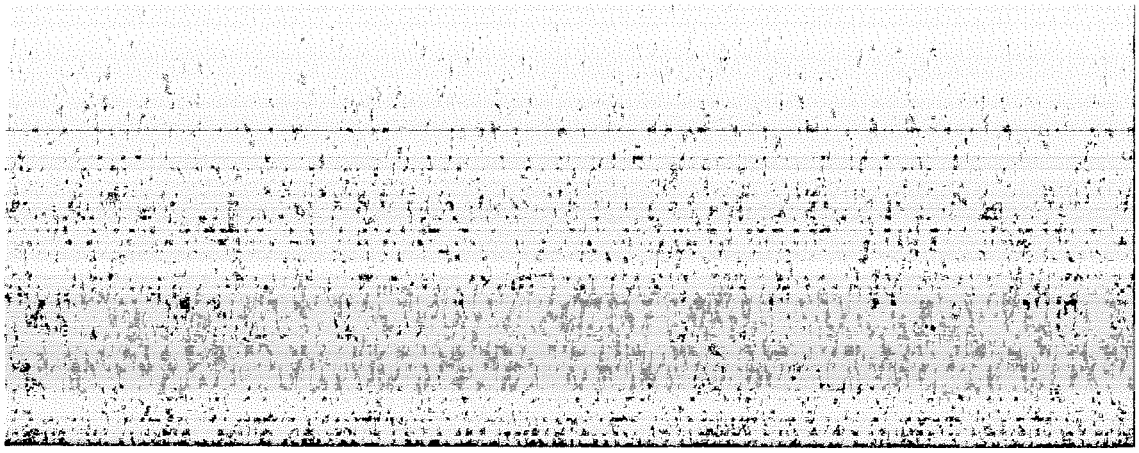
	<32 weeks n=914				<1500 grams n=971			
	suspect ND		obvious ND		suspect ND		obvious ND	
	n	%	n	%	n	%	n	%
incidence	60	6.5	86	9.4	61	6.2	89	9.1
in-hospital mortality	28		72		26		72	
major handicap	7		7		4		8	
no major handicap	25		7		31		9	

To enable comparison with other studies the incidence, mortality rate and handicap rate of neurological dysfunction is listed separately for very preterm (less than 32 weeks) and VLBW infants (less than 1500 gram) (table 5).

DISCUSSION

The incidence of neurological abnormalities in the neonatal period found in the present study population (14.1%) is much lower than the 46.5% found by Dubowitz et al (12).

This is mainly the result of a difference in definition of neurological abnormality. Whereas Dubowitz used a standardized and repeated neurological examination



- which needs an experienced observer - in our study only infants were included who had neurological disturbances severe enough to be diagnosed by routine paediatric examination in all levels of care, mostly without a standardized, detailed neurological examination. The lower incidence is further explained by a difference in study populations: infants in a neonatal intensive care centre, versus a national birthcohort of which 55% was treated in a general hospital.

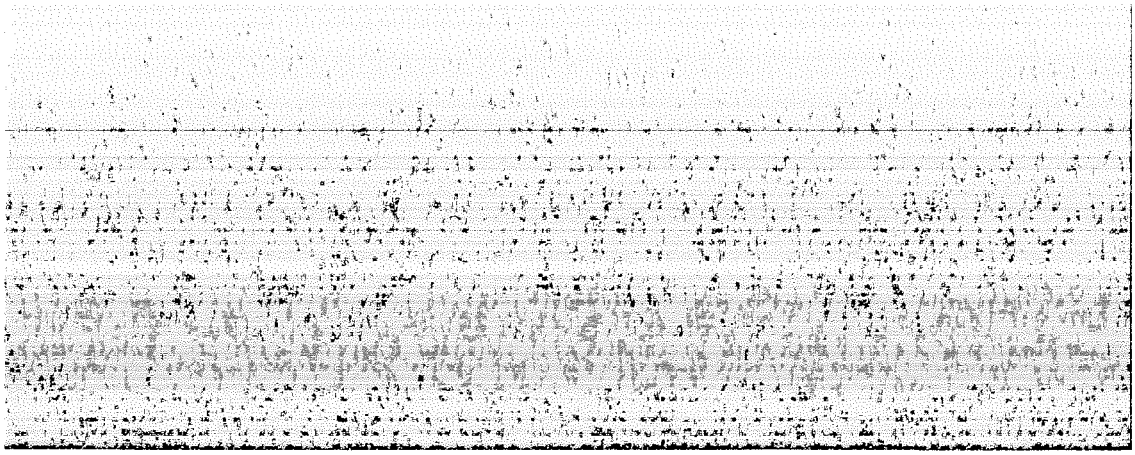
Of all perinatal factors examined gestational age, birthweight, low Apgar score, IRDS and ICH were significantly associated with neonatal neurological dysfunction both in univariate and multivariate analysis. Apgar scores are known to be related to the maturity of the newborn; low Apgar scores can be expected in the more immature infants (10). But also when the lower gestational age of the neurological dysfunctioning infants is taken into account (multivariate analysis) low Apgar score in this group is significantly more frequent. The relation between gestational age, birthweight and low Apgar scores on the one hand and neonatal neurological abnormality on the other is in agreement with the results of the Groningen Perinatal Project (14, 15, 25). The occurrence of IRDS was taken as a measure of illness in the neonatal period. Therefore the association with neonatal neurological dysfunction is not surprising. The association between ICH and neonatal neurological dysfunction is obvious.

The in-hospital mortality rate was strikingly high in the neurologically affected infants even while early deaths without neurological examination were classified as 'normal'. This high mortality rate in the neurologically dysfunctioning infants may be partly explained by their being younger, smaller and more acutely ill than the neurologically normal infants, and by increased withdrawal of treatment, because further treatment was thought either impossible or unethical.

At most 18% of the infants with neurological abnormalities (obvious and suspect) survived without handicap. Only 6% of the children with obvious neurological abnormalities during the neonatal period appeared to be without handicap at 2 years, although neurological abnormalities persisted during the first year. Close follow-up in later years will be necessary, because the risk of later developmental problems (e.g. learning disturbances) is still considerable in children with transient neurological problems in the first year of life (17).

The specificity of normal neonatal neurological function as a predictor of absence of later death and handicaps is excellent (689 /719: 95.8%). The sensitivity however is low (34 /160: 21.2%). Only 16 of the 47 children with a major handicap could be pointed out by neonatal neurological examination.

Other methods of investigation of neurological functioning (e.g. ultrasound examination of the brain, cerebral bloodflow measurements, magnetic resonance imaging) may prove better predictors of later neurological disturbances in the very preterm and /or VLBW population (4, 5, 7, 8, 30, 31) than routine paediatric examination. These methods, however, are not routinely available for all infants at risk for developmental problems and probably never will be. Moreover, it is likely that a standardized and repeated neurological examination is an even better predictor of later neurological disturbances (2, 12).



The present study suggests that, using routine physical examination, a quarter of the very preterm or VLBW infants with later neurological disturbances may be identified. The regular use of a more standardized neurological examination could be incorporated in the routine examination of newborns in all levels of care. This may improve the sensitivity of the neonatal neurological examination and thereby improve early identification of infants at risk for handicaps.

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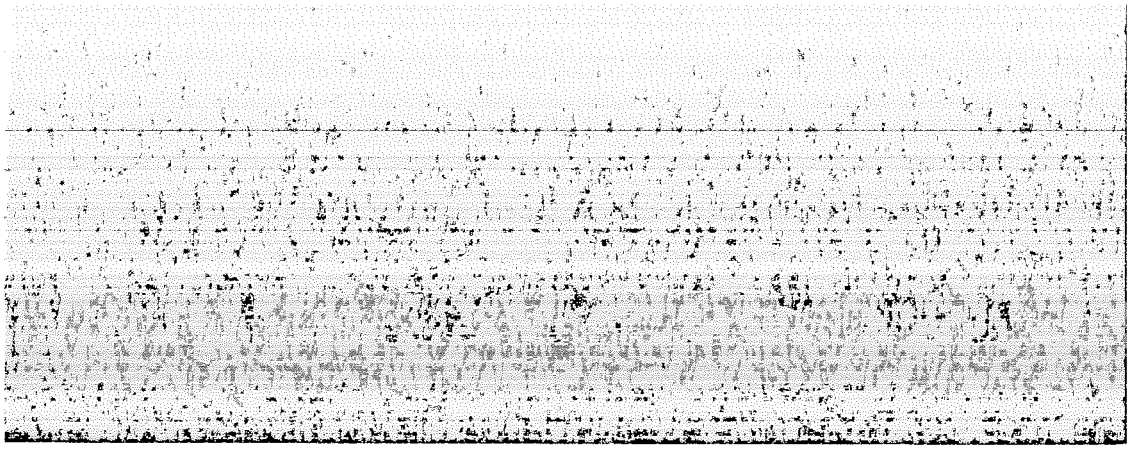

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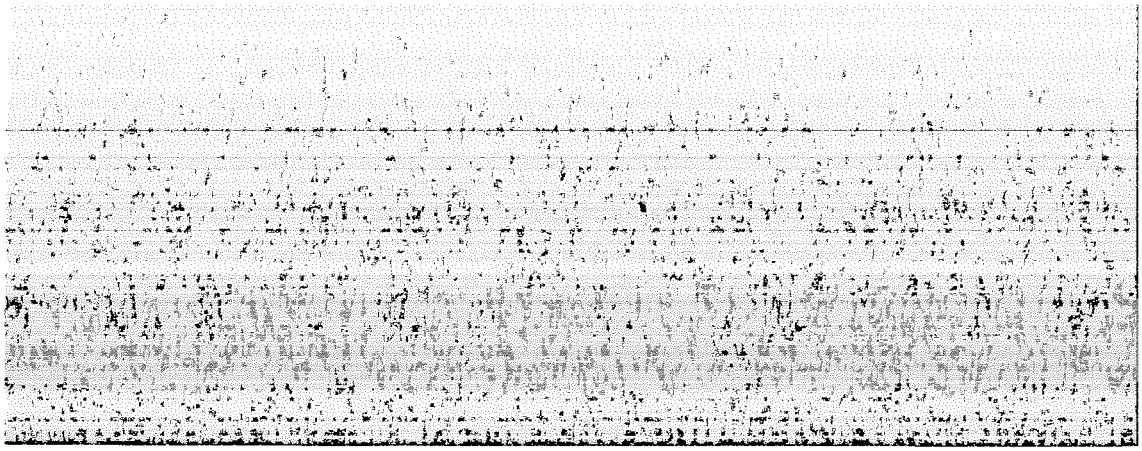

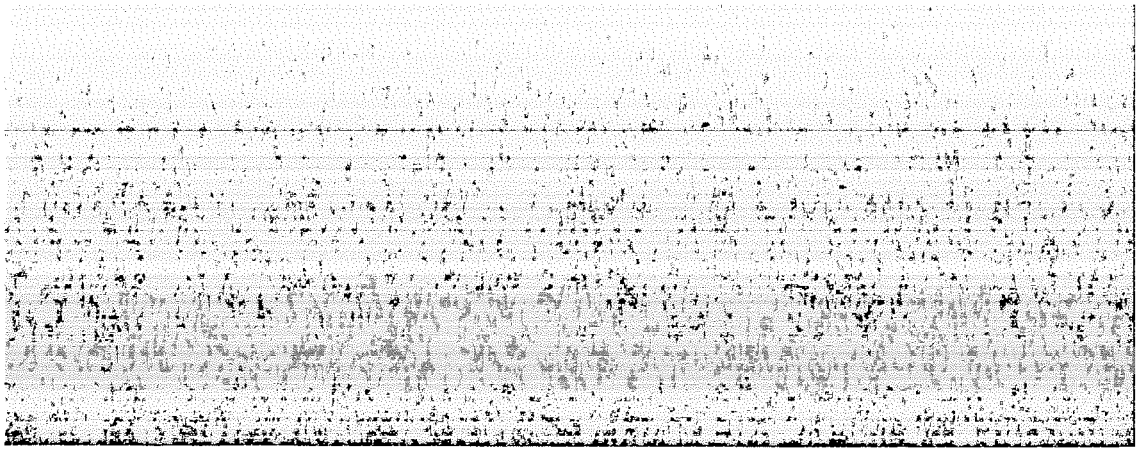

CHAPTER 6

NEONATAL SEIZURES IN VERY PRETERM AND /OR VERY LOW BIRTHWEIGHT INFANTS: MORTALITY AND HANDICAPS AT TWO YEARS OF AGE IN A NATIONWIDE COHORT

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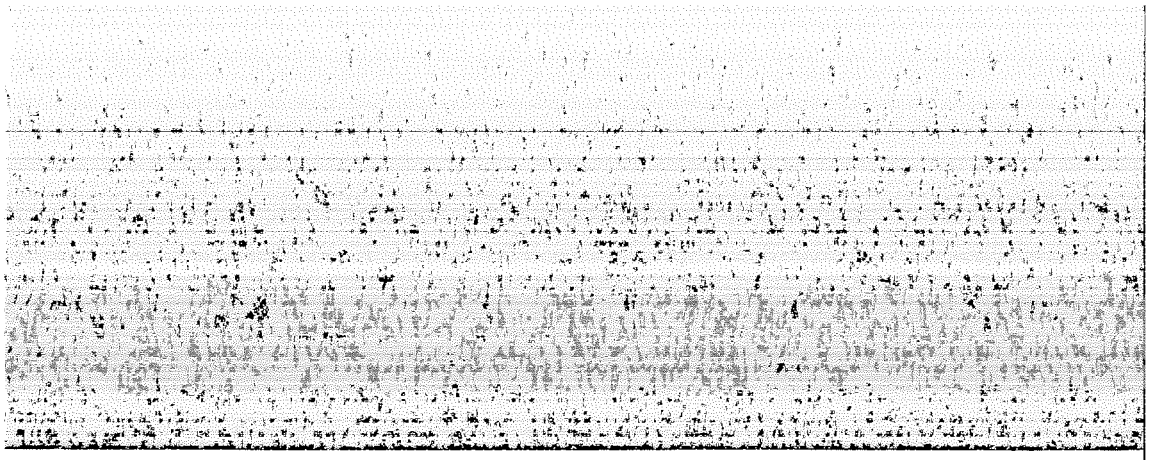


SUMMARY

In a nationwide, prospective survey on very preterm and /or very low birthweight infants (<32 weeks of gestational age and /or <1500 g birthweight) we studied the outcome at the corrected age of two years of children with neonatal seizures.

Of the 1338 infants, originally enrolled in the study, 72 had neonatal seizures; of these 44 died and 11 developed a major handicap.

Using a multivariate statistical method, a significantly increased risk of death as well as handicap was found in infants with seizures compared to infants without seizures.

Nevertheless, 16 of the 28 survivors with neonatal seizures were considered normal at the corrected age of two years.

INTRODUCTION

In general, seizures in the neonatal period are considered to be powerful predictors of the risk of subsequent death or handicap in term infants (9, 10, 14). The prognosis depends on various factors such as etiology, time of onset and duration, EEG-findings and other neonatal neurological signs. The prognostic value in preterm infants, however, is less clear (13).

As part of a national collaborative survey in the Netherlands on morbidity and mortality in very preterm and /or very low birthweight infants, the relationship between neonatal seizures and mortality and neurodevelopmental outcome at the corrected age of two years was studied.

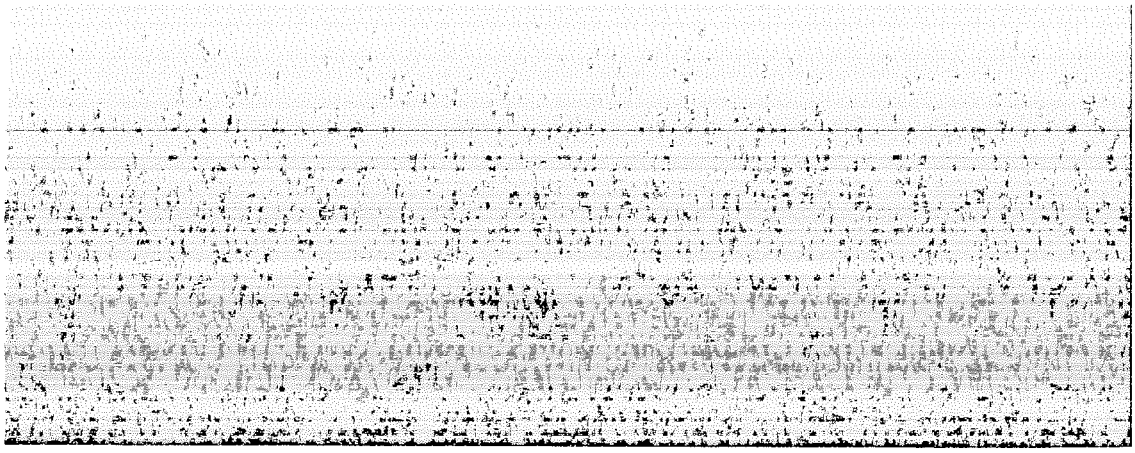
MATERIALS AND METHODS

In 1983, from January 1 to December 31, all infants liveborn with a gestational age of less than 32 completed weeks and /or a birthweight less than 1500 g were enrolled in a prospective national survey. Throughout the Netherlands, paediatricians in 101 paediatric departments participated in the study. Perinatal data on 1338 infants were recorded, representing 94% of all liveborn infants meeting the entry criteria.

Results regarding the pre-, peri- and neonatal period and part of the follow-up study have been published previously (1, 4, 5, 6, 7, 17, 18, 19, 24).

On the precoded forms concerning the perinatal period, all seizures (clinical definition: including subtle seizures, generalized tonic, multifocal clonic, focal clonic and myoclonic seizures (8,20)) were recorded together as either "absent", or as present "on the first day of life", "on the 2nd till 4th day of life" or "on the 5th day or later". In-hospital mortality was defined as all deaths during the initial hospital stay after birth.

After discharge home, all infants were enrolled in a follow-up programme with health examinations at the age of 3, 6, 12 and 24 months corrected for preterm birth. Data were collected on health, growth, development, rehospi-



talization, and psychosocial problems at the outpatient department by the local paediatrician or at the referral hospital according to the parents' preference.

Data processing and analyses were performed at the study centre using SPSS-X 2.1 and SAS (15).

At the age of two years, corrected for preterm birth, a neurodevelopmental assessment was made. According to the outcome, each child was categorized into one of three groups: with major handicap, with minor handicap or normal. A major handicap was diagnosed when severe retardation was present (5 or more months retarded or a developmental quotient (DQ) less than 80), and / or a severe neurological disorder existed such as a hemi-or quadriparesis, and / or severe visual or hearing defects, and /or serious psychosocial problems were present. Such disabilities are likely to prevent the child from going to a normal school, or (will) cause serious interference with normal function in society. A child was categorized as having a minor handicap when some retardation was present (3-4 months retarded or DQ between 80 and 90), and /or a mild neurological disorder existed such as a slight hemi-or quadriparesis, and /or a mild visual or hearing defect, and /or moderate psychosocial problems appeared. Such disabilities are unlikely to prevent the child from going to a normal school, or to interfere seriously with normal life (16). All other children were considered to be "normal".

The relationship between neonatal seizures, in-hospital mortality and handicap (major and minor) at the corrected age of two years, was studied using descriptive statistics followed by a multivariate statistical method (logistic regression analysis). In this analysis no distinction was made between the time of onset of the seizures.

In the multivariate statistical model various perinatal factors were included as potential confounders to adjust for the possible effects of the uneven distribution of these factors, which as such may be associated with mortality or handicap.

Two separate multivariate analyses were performed. In both analyses "seizures" (considered as exposure) and the selected perinatal factors (considered as potential confounders) were the independent variables. Mortality and handicap, respectively, were dependent variables. The definitions of the selected perinatal factors used as confounders are stated in table 1.

Because the number of cases with the outcome handicap was much lower than the number of cases with the outcome death, the number of confounding factors in the handicap-analysis had to be limited for methodological reasons. Based upon previous reports (18) the following factors were omitted: maternal age, parity, history of preterm birth or abortion, smoking during pregnancy, medication and intoxication, hospital admission during pregnancy, prolonged duration of ruptured membranes, chorioamnionitis, cardiotocography during pregnancy, and elective delivery. In the handicap-analysis bilirubin (expressed as maximal total serum bilirubin level) was included as an extra confounder in view of the association we found previously in this cohort between handicap and the maximal total serum bilirubin level (chapter 7) (7).

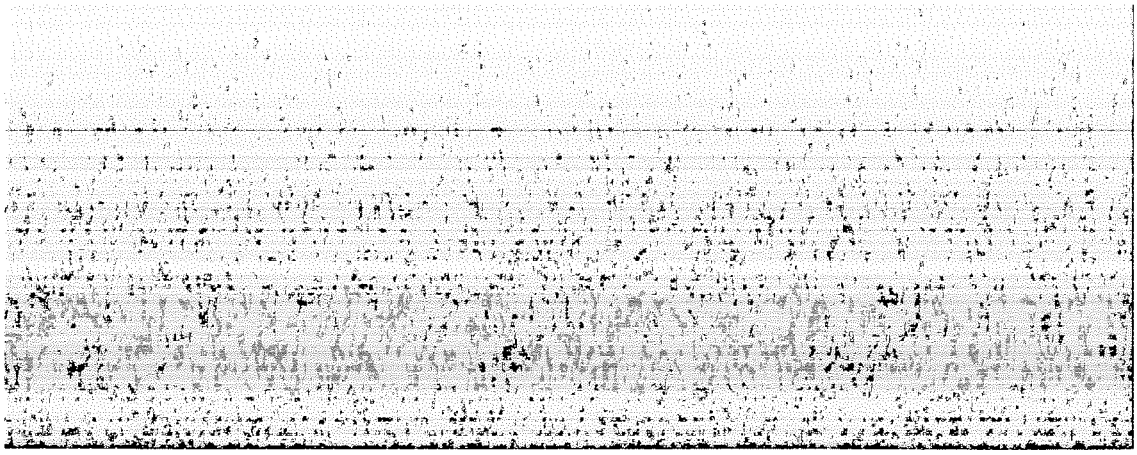
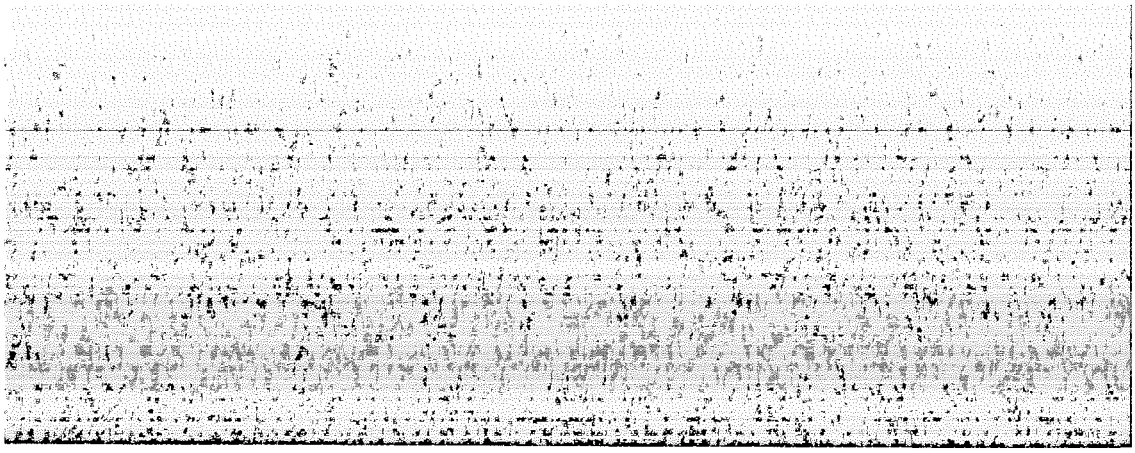


Table 1. Perinatal factors used in the logistic regression analysis

1.	socio-economic class	1 (low) to 6 (high)(22)
2.	maternal age	in years
3.	pre-existing maternal disease	including heart disease, epilepsy, diabetes mellitus, renal disease, hypertension (diastolic blood pressure ≥90 mmHg) versus none
4.	parity	>0 versus 0
5.	history of preterm birth or abortion	≥1 preterm birth and (or) >1 abortion versus none or 1 abortion
6.	infants' sex	male versus female
7.	smoking during pregnancy	any versus none
8.	medication and intoxication	any (medication, alcohol, soft or hard drugs, smoking) versus none
9.	maternal hypertensive disorders during pregnancy	diastolic blood pressure ≥90 mmHg, measured at least twice versus none
10.	congenital malformation	any versus none
11.	hospital admission during pregnancy	1 or more days versus none or less than 24 hours
12.	multiple pregnancy	yes versus no
13.	antenatal transport	to a perinatal intensive care centre (level 3)(19)
14.	tocolysis	≥24 h. suppression of uterine contractions versus none or <24 h.
15.	glucocorticoid administration	to the pregnant mother, yes versus no
16.	prolonged duration of ruptured membranes	≥24 h. versus none or <24 h.
17.	chorioamnionitis	yes versus no
18.	cardiotocography during pregnancy	abnormal versus normal tracing
19.	fetal presentation	breech and transverse presentation versus vertex
20.	gestational age	in days
21.	birthweight	in grams
22.	small for gestational age	$<10^{th}$ percentile versus $\geq 10^{th}$ percentile (12)
23.	hospital of birth	level 1 (low) versus level 3 (high) level 2 (intermediate) versus level 3 (high) (19)
24.	elective delivery	yes versus no
25.	mode of delivery	caesarean section versus vaginal
26.	Apgar score 5 min.	<7 versus ≥7
27.	neonatal transport	to level 2, 3
28.	idiopathic respiratory distress syndrome (IRDS)	clinical diagnosis (based on extra O_2 >24 h., expiratory grunting, tachypnoea, sternal and intercostal retractions and nasal flaring) and /or typical x-ray versus none
29.	intracranial haemorrhage (ICH)	clinical diagnosis (based on rapid or saltatory deterioration, fall in haematocrit) and /or confirmation by ultrasound or computerized tomography versus none
30.	septicaemia	haemotological findings (typical white blood cell count) and /or positive bloodculture



The results were expressed as an odds ratio (OR): the odds for mortality or handicap in children with neonatal seizures versus the odds for mortality or handicap in children without neonatal seizures. An odds ratio greater than 1 indicates a higher risk; an odds ratio smaller than 1 indicates a lower risk for the children with seizures (exposed), compared to the children without seizures (non-exposed). An odds ratio is significantly different from 1 at the 5% level if, and only if, its 95% confidence interval does not include 1.

RESULTS

Originally, 1338 very preterm and/or VLBW infants were enrolled in the survey. The in-hospital mortality was 25.4% (340/1338). During the two years follow-up period another 29 infants (2.2%) died and 25 were lost to follow-up, mainly because the parents moved abroad or refused further cooperation on financial or religious grounds. Of the remaining 944 children assessed, the data, necessary for the described multivariate analyses, were available in 897 cases.

Neonatal seizures were recorded in 5.4% of the infants (n=72), occurring on the 1st day of life (n=15), 2nd till 4th day (n=25), and on the 5th day or later (n=32).

Mortality

During the initial hospital stay 40 (56.5%) infants with neonatal seizures died, a much higher percentage compared to the infants without seizures (23.7%, 300/1226). Half of them died during the first week of life, another 15 during the first month. After discharge home up to the corrected age of two years another 4 infants died (table 2).

In the logistic regression analysis, after correction for all perinatal factors described in table 1, the odds ratio for in-hospital mortality for infants with seizures versus infants without seizures was 2.7 (table 3).

Table 2. Crude mortality rates of infants with and without neonatal seizures

outcome	neonatal seizures			
	present		absent	
	%	(n)	%	(n)
mortality				
neonatal	49	(35/72)	22	(277/1266)
in-hospital	56	(40/72)	24	(300/1266)
post-discharge	6	(4/72)	2	(25/1266)
total	61	(44/72)	26	(325/1266)

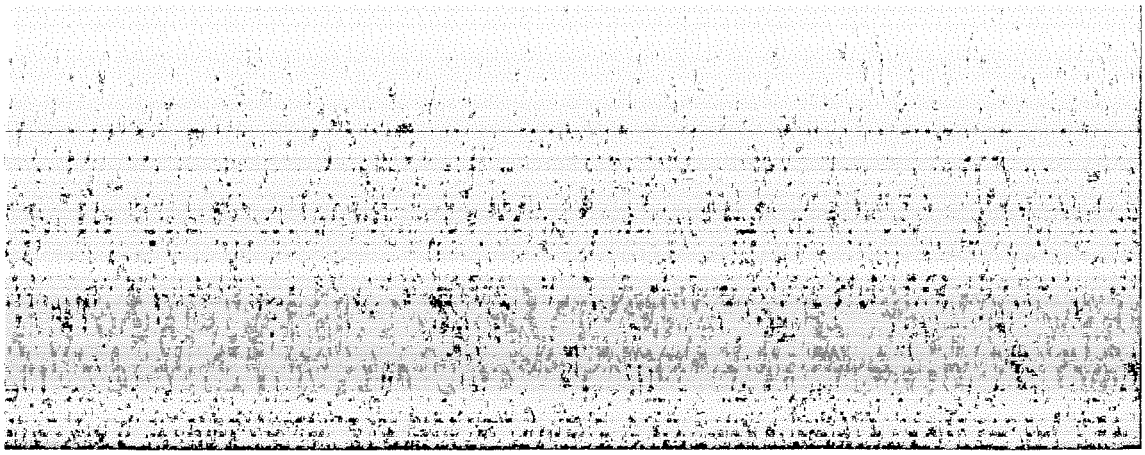


Table 3. Results of the logistic regression analyses comparing infants with neonatal seizures to infants without neonatal seizures

outcome	odds ratio (OR)	95% confidence interval
in-hospital mortality	2.7	(1.4 - 5.3)*
handicaps in survivors		
1st (with factor ICH)	2.9	(1.2 - 6.8)*
2nd (without factor ICH)	3.6	(1.6 - 8.2)*

*p <0.05

Handicap

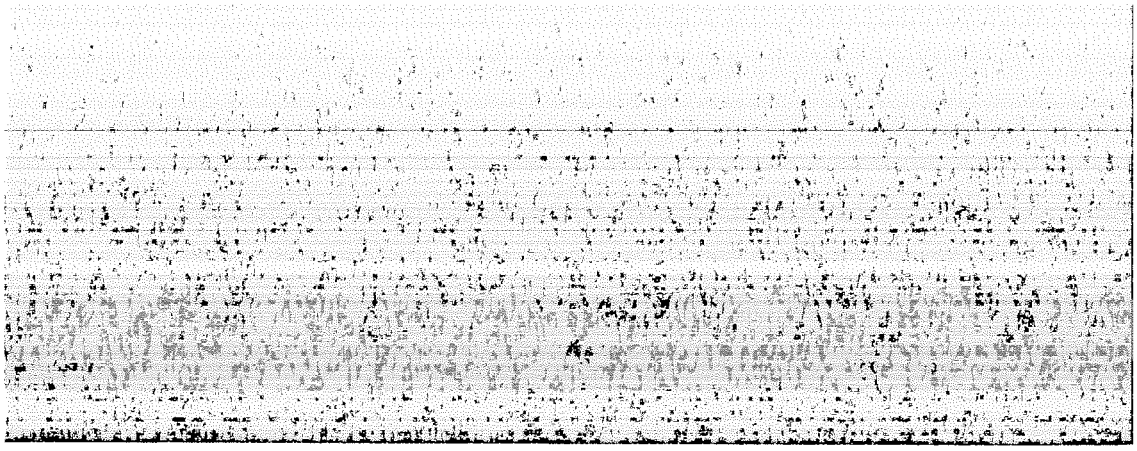
Amongst 944 children assessed at the corrected age of two years 774 were considered normal and 170 were handicapped: 59 children had a major and 111 a minor handicap (24). The total numbers and percentages of normal and handicapped children in the groups with or without neonatal seizures, are shown in table 4, further divided by time the seizures occurred.

Table 4. Numbers and percentages of handicapped children in survivors with or without neonatal seizures

neonatal seizures	liveborn	infants assessed at 2 years	normal	handicapped					
				total		minor		major	
	n	n	n	n	(%)	n	(%)	n	(%)
yes	72	28	16	12	(43)	1	(4)	11	(39)
1st day	15	5	3	2				2	
2nd-4th day	25	7	7						
≥5th day	32	16	6	10		1		9	
no	1266	916	758	158	(17)	110	(12)	48	(5)
total	1338	944	774	170	(18)	111	(12)	59	(6)

From the infants with seizures occurring between their 2nd till 4th day of life, 68% died in hospital, none of the survivors, however, was handicapped at the age of two years. Most handicaps emerged in the children with seizures on their 5th day of life or later.

Surprisingly, 16 out of the 28 children surviving with neonatal seizures were considered normal at two years of age. One may wonder why these infants did not develop a handicap. Looking at the clinical neonatal data of these children, it appears that there is a difference in the severity of their neonatal complications. In almost all surviving infants an intracranial haemorrhage (ICH) was diagnosed



in the neonatal period as well as an idiopathic respiratory distress syndrome (IRDS). In the infants with a handicap these problems were more severe, necessitating assisted ventilation for longer period. Moreover in 6/11 children with a major handicap a hydrocephalus was diagnosed in the neonatal period.

Almost all children with neonatal seizures and handicapped at the age of two years, had developed a major handicap (11/12, 92%); this is contrary to the division of major and minor handicaps in the entire study population (59/170, 35%) or in the group of infants without neonatal seizures (48/158, 30%).

In the logistic regression analysis, neonatal seizures appeared to be a strong predictor for later handicap (OR: 2.9) (table 3).

DISCUSSION

The odds for mortality as well as for handicap was significantly increased in infants with seizures during the initial hospital stay, compared to infants without seizures.

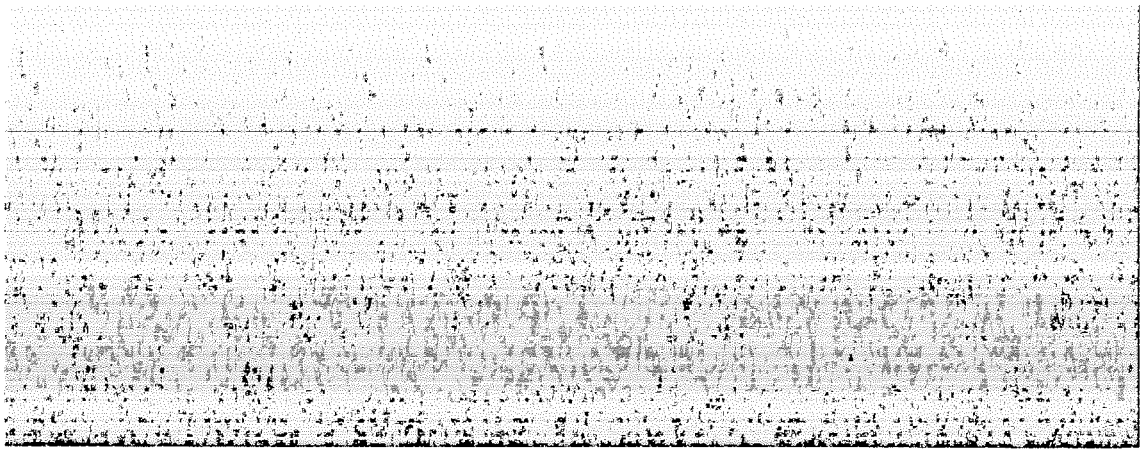
The relationship between seizures and mortality may be the result of the clinician's tendency to refrain from further treatment of infants who are considered severely neurologically damaged following seizures (23). To investigate this possibility we calculated the percentages of infants with and without seizures, in which further treatment was recorded as withheld or withdrawn. This had happened in 73% (29/40) of the deceased infants with seizures, contrary to the much lower percentage of 50 (149/300) of the deceased infants without seizures (chi-square 5.98; $p < 0.05$) (table 5).

This confirms the idea that intensive treatment was often withdrawn in infants with neonatal seizures whose outcome was considered to be probably death or severe handicap (3).

Table 5. In-hospital mortality of infants with and without neonatal seizures divided by way of death

neonatal seizures	liveborn	in-hospital mortality			
		spontaneous	treatment withdrawn/withheld	accidental*	total
	n	n	n (%) of total mortality	n	n
yes	72	11	29 (73)		40
1st day	15	2	6 (75)		8
2nd-4th day	25	7	10 (59)		17
≥5th day	32	2	13 (87)		15
no	1266	146	149 (50)	5	300
total	1338	157	178 (52)	5	340

*death due to medical fault or inaccuracy



In infants with seizures on their 5th day of life or later about half died either spontaneously or after withdrawal of treatment and the majority of the survivors appeared severely handicapped (table 4). Although we did not study the etiology of these seizures, our results confirm the idea that late onset seizures have an unfavourable outcome (2,8,21).

When seizures concurred with obvious neurological dysfunction in the neonatal period an extremely high number (7 /9) of handicaps were found.

However, even when no neurological dysfunction apart from seizures was signalized during the neonatal period, still 5 out of 19 infants were handicapped (Ouden L. den, personal communication).

Generally, the origin of the seizures predetermines the prognosis of the infant and may vary from good in case of late-onset hypocalcemia or drug-withdrawal to (very) bad in case of intracranial infection or intracranial haemorrhage (ICH). In the present study, ICH was included as a confounding factor in the logistic regression analysis. The clinical diagnosis of ICH was used, to minimize a possible bias caused by underestimation of probable, but unconfirmed ICH. Cases of ICH that may have gone clinically unnoticed were assumed to have been of such a mild nature that neonatal seizures were unlikely to occur; by missing these, the confounder (ICH) might have been present more frequently in the group of infants without seizures. Therefore, the results of the analyses may only underestimate the effect of neonatal seizures alone.After omitting ICH from the logistic regression analysis the odds ratio for handicap was higher (table 3), suggesting that part of the association between seizures and handicaps is indeed due to ICH.

We conclude that neonatal seizures in very preterm and very low birthweight infants are clearly associated with mortality during the initial hospital stay as well as with later handicap; this also holds true after adjustment for intracranial haemorrhage. Still, 16 out of 28 survivors were described as normal at the corrected age of two years. Although the risk of handicap is obviously increased in these children, neonatal seizures do not seem to exclude a normal development.

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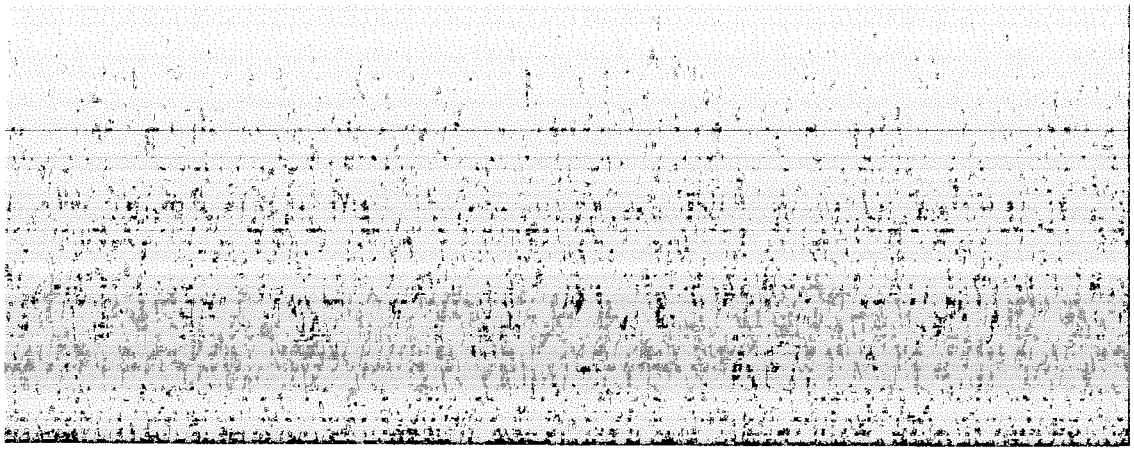

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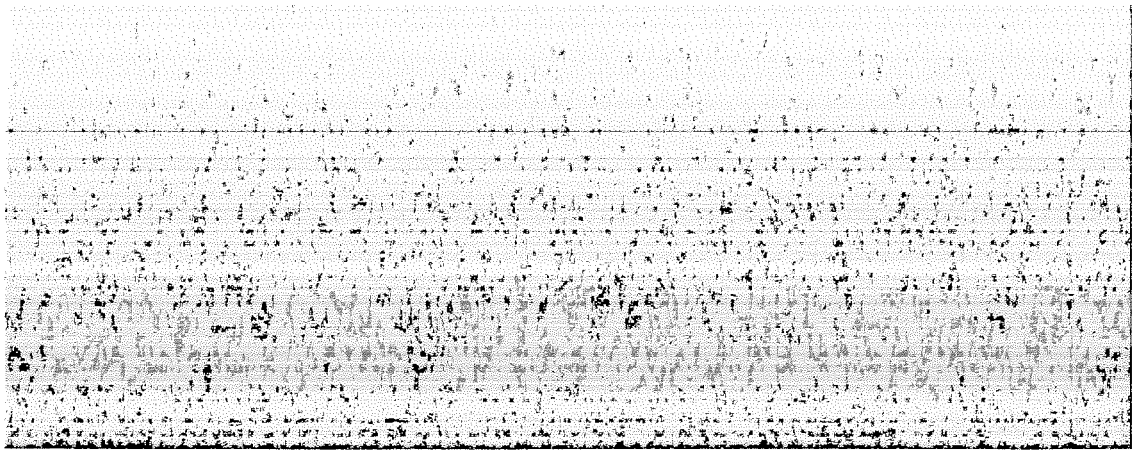

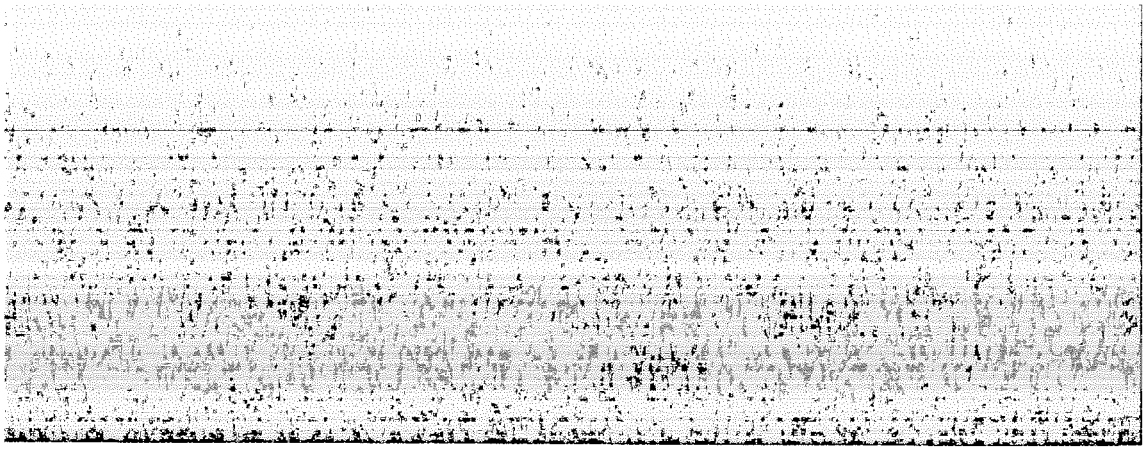

CHAPTER 7

HYPERBILIRUBINEMIA IN PRETERM INFANTS AND NEURODEVELOPMENTAL OUTCOME AT 2 YEARS OF AGE: RESULTS OF A NATIONAL COLLABORATIVE SURVEY

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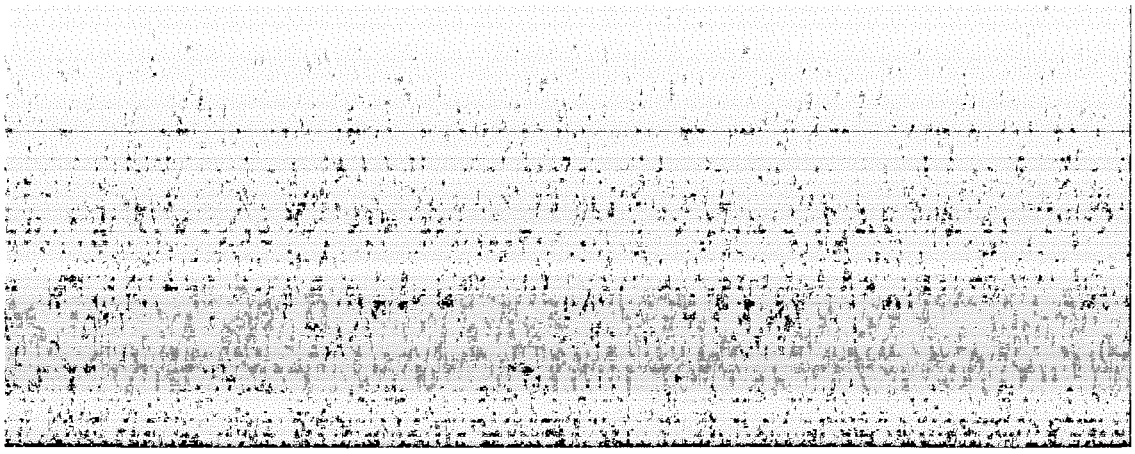


SUMMARY

As part of a prospective national survey of preterm and small for gestational age infants in the Netherlands, the relationship between maximal serum total bilirubin concentration in the neonatal period and neurodevelopmental outcome at the corrected age os 2 years was studied.

Initially, 1,338 infants with a gestational age of less than 1,500 g were enrolled in the study; 146 were subsequently excluded because of congenital malformations and 361 died during the study period.

At the corrected age of 2 years, 831 children were available for follow-up. Children with minor and major handicaps had significantly greater maximal serum total biblirubin concentrations than the children with a normal neurodevelopmental outcome (P=.02). A consistent increase in prevalence of handicaps was found for each 50-μmol/L (2.9 mg/dL) increase of maximal serum total bilirubin concentration. The handicaps consisted mainly of cerebral palsy.

Logistic regression analysis involving seven suspected confounding factors (gestational age, birth weight, seizures, intracranial hemorrhage, respiratory distress syndrome, ventriculomegaly, and bronchopulmonary dysplasia) revealed that the odds ratio was 1.3. This indicates that, on a multiplicative scale, the risk of a handicap increased by 30% for each 50-μmol/L (2.9 mg/dL) increase of maximal serum total bilirubin concentration (P=.02). Further analysis treated bilirubin as a categorized exposure. A striking systematic increase was found, suggesting a causal relationship between maximal serum total bilirubin concentration and neurodevelopmental outcome.

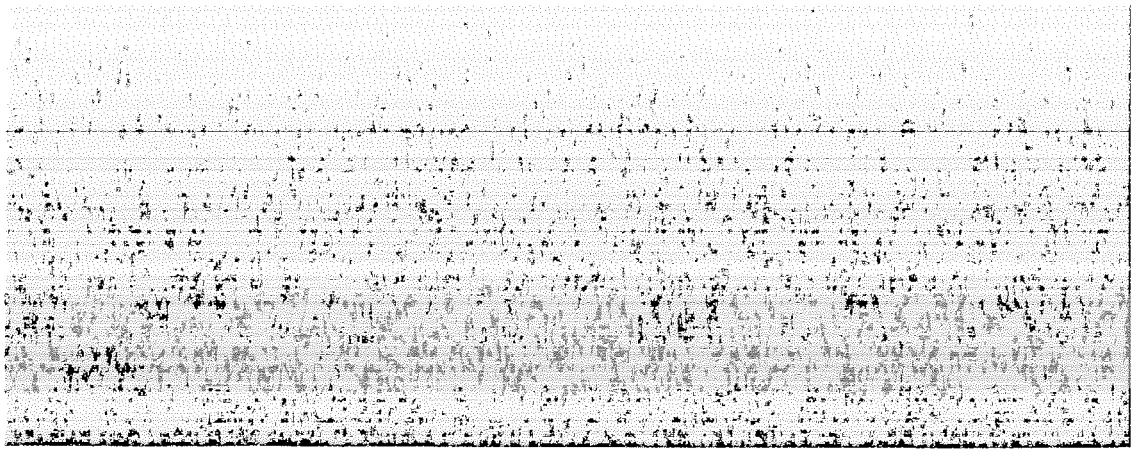
INTRODUCTION

Neurotoxic effects of moderately elevated serum bilirubin concentrations in preterm infants during the neonatal period have been the source of ample discussion.[1,2] One of the areas of uncertainty results from the fact that no prospective studies to assess the neurotoxic effects of maximal serum bilirubin concentrations in preterm infants have been carried out since the introduction of routine ultrasound scanning of the brain.

As part of a national collaborative survey of morbidity and mortality in preterm an small for gestational age infants in the Netherlands, we prospectively studied the neurodevelopmental outcome at the corrected age of 2 years in children born after less than 32 weeks' gestation and/or with a birth weight of less than 1,500 g. The aim of the present study was to establish the risk of impaired neurodevelopmental outcome for various maximal serum total bilirubin concentrations in the neonatal period.

PATIENTS AND METHODS

In 1983, 1,338 infants born in the Netherlands with a gestational age of less



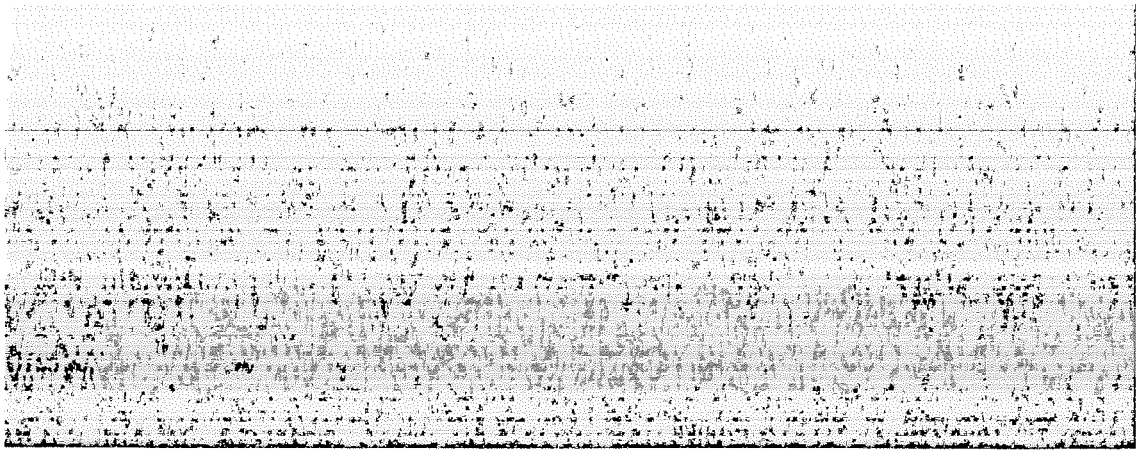
than 32 completed weeks and/or a birth weight of less than 1,500 g participated in a prospective national survey of morbidity and mortality, which had a compliance rate of 94%.[3] That means that 94% of all live-born infants meeting the entry criteria were enrolled in this survey. The reliability of the gestational age classification has been described elsewhere.[3]

This survey provided the opportunity to prospectively study the effects of various concentrations of maximal serum total bilirubin on neurodevelopmental outcome in the 831 surviving children. Children with congenital malformations (all reported organ and/or chromosomal abnormalities) were excluded from the study (n = 146), and 361 children died during the study period.

Serum total bilirubin determinations were done for all infants. They were initiated based on clinical criteria and repeated based on clinical or chemical criteria. The American Optical bilirubin test was generally used in the participating hospitals. Calibration of all equipment was performed on a routine basis. The highest observed neonatal serum total bilirubin concentration was used for analyses. Most participating hospitals followed the guidelines for phototherapy and exchange transfusion as described by Maisels.[4]

Neurodevelopmental outcome was assessed by the attending pediatrician in all surviving children at the corrected age of 2 years. It was inevitable that the pediatricians were aware of the patients' neonatal histories. Because of the decentralized organization of the follow-up program, inter-observer variability was likely to occur. However, the precoded questionnaires were designed to minimize the risk of ambiguous answers as much as possible. An overall developmental level was assessed using the adapted Gesell test for Dutch children[5] and supplemented by neurologic, visual, and hearing examinations. A child was considered to have a normal outcome, when the developmental quotient was more than 90 and no neurologic or hearing abnormalities or retinopathy of prematurity were present. A child was categorized as having a minor handicap when some retardation was present (3 to 4 months retarded or developmental quotient between 80 and 90) and/or mild cerebral palsy and/or slight hearing defects and/or mild retinopathy of prematurity were present. Such disabilities do not, or are unlikely to, prevent the child from going to a normal school or to interfere seriously with normal life. A major handicap was diagnosed when severe retardation was present (5 or more months retarded or developmental quotient less than 80) and/or severe cerebral palsy and/or severe hearing defects and/or severe retinopathy of prematurity were present. Such disabilities are likely to prevent the child from going to a normal school or to cause serious interference with normal function in society.[6]

Statistical assessment of the association of maximal serum total bilirubin concentration and the odds of "handicap" (minor and major) was carried out by cross-tabulation and logistic regression analysis. χ^2 tests were used to analyze the neurodevelopmental outcome for the various maximal serum total bilirubin concentration categories. To assess the association between maximal serum total bilirubin concentration and the various outcome variables, Mann-Whitney tests



were performed. Kruskal-Wallis tests were used to study differences in neonatal factors between the three handicap groups. Furthermore, we applied logistic regression analysis with unconditional maximum likelihood estimation by means of the program PROC LOGIST from SAS in assessing the relationship between maximal serum total bilirubin concentration and neurodevelopmental outcome.[7] All confounders used in the prospectively designed analysis were agreed upon in advance of the enrollment of the patients on the basis of clinical experience and a literature review.[8] A P value of $<.05$ was considered to be significant.

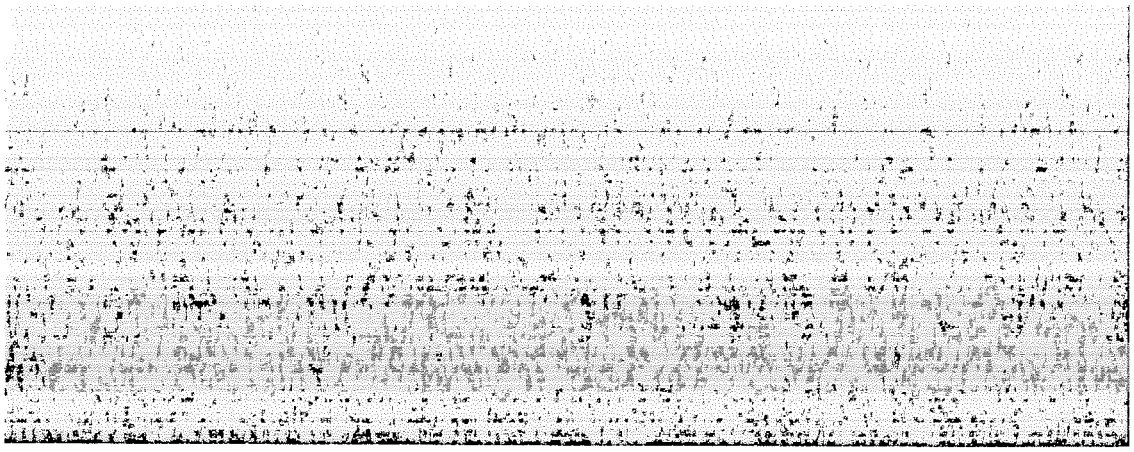
Gestational age was defined as the best obstetric estimate, based upon menstrual dates and, if necessary, upon other evidence such as ultrasound. Birth weight was the first weight of the infant after birth (in grams). Seizures were any subtle, generalized tonic, multifocal clonic, focal clonic and myoclonic activity. Intracranial hemorrhage was based on clinical diagnosis (rapid or saltatory deterioration, decrease in hematocrit value), which was confirmed in 82% by ultrasound and/or computed tomography. Respiratory distress syndrome was defined by the need for extra oxygen for more than 24 hours, expiratory grunting, tachypnea, sternal and intracostal retractions, and nasal flaring, which was in 72% confirmed by typical roentgenographic findings (reticulogranular aspect of lungs; air bronchogram for more than 24 hours). Ventriculomegaly was defined as an obvious increase in lateral ventricular size on repeated ultrasounds. Bronchopulmonary dysplasia was defined by the need for extra oxygen for more than 28 days.

RESULTS

At the corrected age of 2 years, all 831 children were available for follow-up. Mean (SD) gestational age of this group was 31.0 (2.5) weeks (range 25 to 40 weeks) and mean (SD) birth weight was 1,322 (285) g (range 560 to 2,580 g). There were 178 children with gestational ages of more than 32 completed weeks but birth weights of less than 1,500 g; 165 had gestational ages of less than 32 weeks but birth weights of more than 1,500 g.

Mean (SD) maximal serum total bilirubin concentration for the children in our study population was 178.5 (44.1) μmol/L (range 39 to 346 μmol/L) or 10.4 (2.6) mg/dL (range 2.3 to 20.2 mg/dL), whereas mean (SD) maximal serum total bilirubin concentration of the infants who died during the study period was 147.1 (66.7) μmol/L or 8.6 (3.9) mg/dL. The mean (SD) day on which this was reached was 5.1 (4.0) (days range 0 to 54 days) after birth. Phototherapy was the method of treatment for 83% of the infants with a mean (SD) duration of 3.5 (2.9) days (range 1 to 22 days), whereas 37 infants also required at least one exchange transfusion.

Neurodevelopmental outcome of the 831 studied children showed that 89 (10.7%) had a minor handicap and 45 (5.4%) a major handicap. The mean maximal serum total bilirubin concentration in children with handicaps was significantly greater than in children with a normal development. Normal infants



had a mean (SD) maximal serum total bilirubin concentration of 176.8 (43.6) μmol/L or 10.3 (2.5) mg/dL; the values for those with a minor handicap were 183.7 (43.8) μmol/L or 10.7 (2.6) mg/dL and for those with a major handicap 195.0 (48.7) μmol/L or 11.4 (2.8) mg/dL; (P =.02).

The follow-up population was divided into six categories according to maximal serum total bilirubin concentrations; a consistently increasing prevalence of especially minor handicaps existed (Table 1).

Table 1. Neurodevelopmental Outcome According to Maximal Serum Total Bilirubin Concentration During Neonatal Period for 831 Children*

Maximal Serum Total Bilirubin (μmol/L [mg/dL])	No Handicap	Handicap	
		Minor	Major
≤100 (≤5.8)	19 (90.4)	1 (4.8)	1 (4.8)
101-150 (5.9-8.7)	166 (86.5)	19 (9.9)	7 (3.6)
151-200 (8.8-11.6)	337 (85.1)	41 (10.4)	18 (4.5)
201-250 (11.7-14.6)	136 (79.1)	22 (12.8)	14 (8.1)
251-300 (14.7-17.5)	35 (79.6)	6 (13.6)	3 (6.8)
>300 (>17.5)	4 (66.7)		2 (33.3)
≤100->300	697 (83.9)	89 (10.7)	45 (5.4)

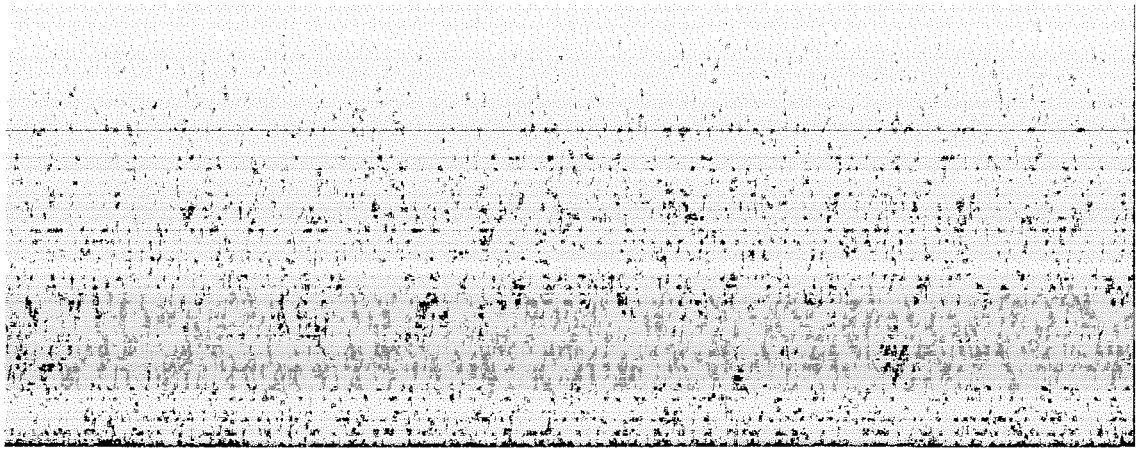
*Results are numbers (%) of children.

There was no significant difference in number of reached milestones between the six categories. However, cerebral palsy occurred more with increasing maximal serum total bilirubin concentration, except for maximal serum total bilirubin concentration between 251 to 300 μmol/L (14.7 to 17.5 mg/dL) (Table 2). There was no difference between the various maximal serum total bilirubin

Table 2. Infants With Abnormal Neurologic Outcomes for the Various Maximal Total Bilirubin Concentrations During Neonatal Period

Maximal Serum Total Bilirubin (μmol/L [mg/dL])	Cerebral Palsy	Seizures	Hearing Defects	Retinopathy of Prematurity
≤100 (≤5.8)	9.5	0	0	0
101-150 (5.9-8.7)	6.6	4.5	3.5	1.2
151-200 (8.8-11.6)	12.3	3.6	4.2	0.6
201-250 (11.7-14.6)	18.6	2.5	4.1	1.4
251-300 (14.7-17.5)	7.2	2.4	0	0
>300 (>17.5)	40.0	20.0	0	0

*Results are percentages of infants. For cerebral palsy, P=.02 by χ^2 test. Number of missing observations were as follows: 60 cerebral palsy, 62 seizures, 63 hearing defects, 67 retinopathy of prematurity.



concentration groups with regard to seizures, hearing defects, and retinopathy of prematurity. The Mann-Whitney test was used to assess the association between maximal serum total bilirubin concentration and the various outcome variables. Children with cerebral palsy had a significantly higher mean maximal serum total bilirubin concentration than children without cerebral palsy (193.1 v 176.5 μmol/L or 11.3 v 10.3 mg/dL; P=.02), whereas there were no differences in mean maximal serum total bilirubin concentration found for the other outcome variables.

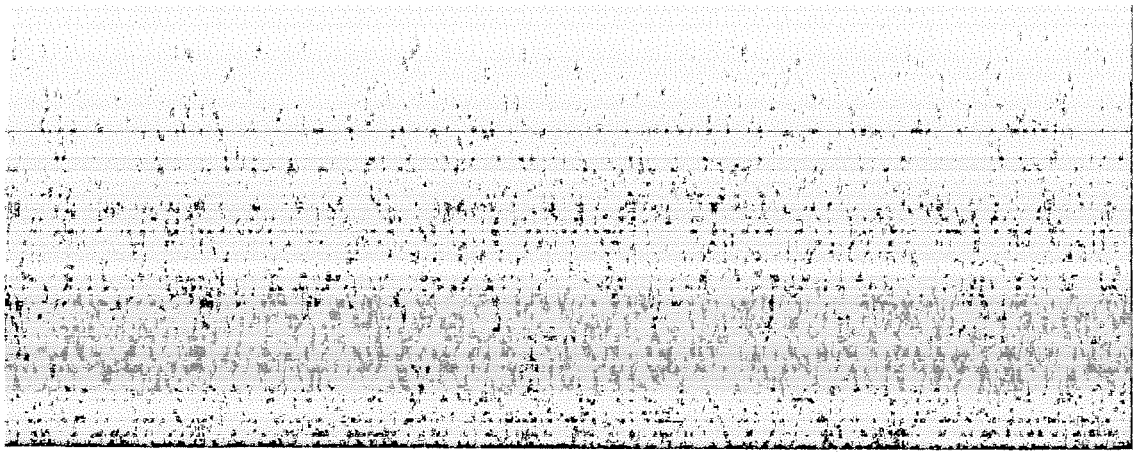
However, these data were not adjusted for suspected confounding factors. The occurrence of these risk factors for the various handicap groups is indicated in Table 3. Logistic regression analysis with maximal serum total bilirubin

Table 3. Suspected Confounding Neonatal Factors In Relation to Neurodevelopmental Outcome

	No Handicap (n=697)	Handicap		P Value*
		Minor (n=89)	Major (n=45)	
Gestational age (mean wk ± SD)	31.0 ± 2.4	30.9 ± 2.5	30.6 ± 2.9	NS[a]
Birth wt (mean g ± SD)	1,324 ± 284	1,315 ± 265	1,295 ± 292	NS[a]
Seizures (No.)	2.2	1.1	22.2	<.0001[b]
Intracranial hemorrhage (No.)	14.5	19.1	37.8	<.001[b]
Respiratory distress (No.)	38.0	47.2	42.2	NS[b]
Ventriculomegaly (No.)	1.7	2.2	22.2	<.001[b]
Bronchopulmonary dysplasia	1.3	6.7	8.9	<.001[b]

*Handicap (minor and major) v no handicap: [a]Kruskal-Wallis nonparametric analysis of variance; [b]χ^2 test.

concentration as a continuous variable (minor and major handicaps versus normal) rendered an estimate of the odds ratio on a handicap (minor and major) for maximal serum total bilirubin concentration, when the data were adjusted for the potentially confounding factors gestational age, birth weight, seizures, intracranial hemorrhage, respiratory distress syndrome, ventriculomegaly, and bronchopulmonary dysplasia. The odds ratio was then to be interpreted as the overall increase on a multiplicative scale of the odds on a handicap for each 50-μmol/L (2.9-mg/dL) increase of maximal serum total bilirubin concentration. The odds ratio turned out to be 1.3 with a 95% confidence interval between 1.03 and 1.62 (P=.02). The risk of a handicap was not too high and, therefore, one may interpret the odds ratio as the risk ratio. Hence, for each 50-μmol/L (2.9-mg/dL) increase in maximal serum total bilirubin concentration, the odds (risk) of a (minor or major) handicap was, on the average, increased by a factor 1.3 (30%), which means that for a 100-μmol/L (5.8-mg/dL) increase, the risk of a handicap increases with $(1.3)^2 = 69\%$. Although strong correlations between some of the confounders were present (eg, gestational age and birth weight), they did not defeat the mathematics of the logistic regression.



In the second analysis, the exposure maximal serum total bilirubin was divided into six categories. Its purpose was to strengthen a possible causal interpretation (by looking for a dose-response relationship) and to estimate whether the overall increase of the odds on a handicap as expressed by the odds ratio of 1.3 was reflected in each maximal serum total bilirubin concentration category (Table 4). The systematic increase in the separately estimated coefficients was striking and supports the possibility of a causal effect.

Table 4. Odds Ratio for Various Maximal Serum Total Bilirubin Concentrations in 831 Infants (134 With Handicaps)

Maximal Serum Total Bilirubin (μmol/L [mg/dL])	Odds Ratio*
101-150 (5.9-8.7)	1.4
151-200 (8.8-11.6)	1.6
201-250 (11.7-14.6)	2.3
251-300 (14.7-17.5)	2.2
>300 (>17.5)	3.0

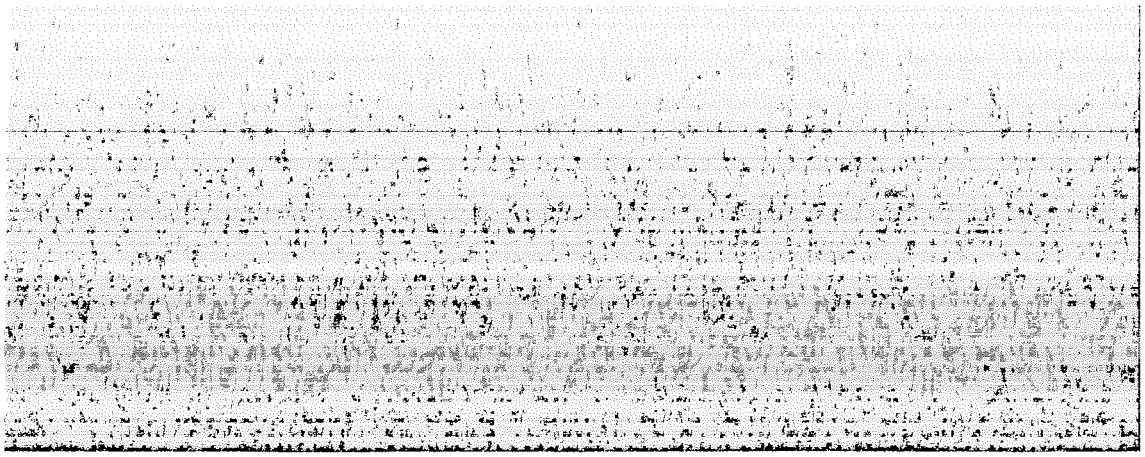
*Versus maximal serum total bilirubin ≤100 μmol/L (≤ 5.8 mg/dL).

DISCUSSION

Hyperbilirubinemia can lead to kernicterus, but whether it causes other, milder forms of neurologic and developmental damage remains unknown.[1] Most of the human research concerning brain toxic effects of bilirubin was performed during a period when routine ultrasound scanning of the brain was not available, and it has been suggested that much of the so-called effects of hyperbilirubinemia could have been merely the effects of hemorrhagic-ischemic brain lesions not detected at the time of the studies.[2]

A mortality rate of 27.0% (361/1,338) may seem high given the apparent gestational age and weight distribution. However, this may be explained by the widely accepted policy in the Netherlands to withdraw life support from preterm infants with a poor neurodevelopmental prognosis. This policy certainly increases the mortality rate of very low birthweight infants.

In our prospective study, ultrasound scanning of the brain was performed routinely in 484 infants of whom 294 surviving children were assessed at the corrected age of 2 years. Incidence and prediction of intracranial hemorrhage and outcome of these infants have been described elsewhere.[9,10] In the remaining infants, ultrasound examination was performed in most cases to confirm a clinical suspicion of intracranial hemorrhage. In the present study, the clinical diagnosis of intracranial hemorrhage was used as a confounding factor, to minimize a

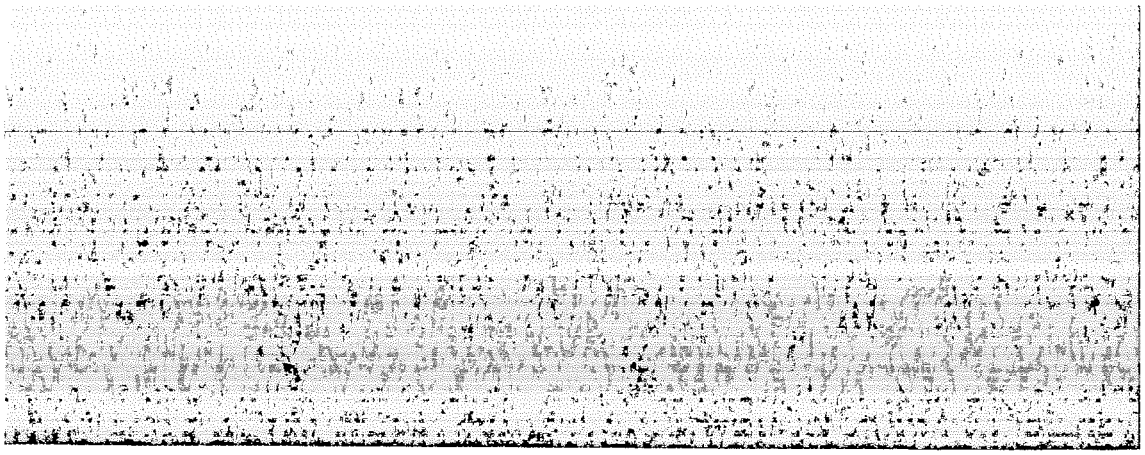


possible bias caused by underrepresentation of probable, but unconfirmed, intracranial hemorrhage. Cases of intracranial hemorrhage that may have gone unnoticed were assumed to have been of such a mild nature that a consequent substantial increase in serum total bilirubin concentration was unlikely in these infants.[11] By omitting these infants, we may underestimate the effect of bilirubin. After we adjusted the data for the suspected confounding factors, an association was found between maximal serum total bilirubin concentration and the risk of impaired neurodevelopmental outcome. The risk of a handicap increased on the average by 30% for each 50-μmol /L (2.9-mg /dL) increase in maximal serum total bilirubin concentration. This systematic increase in the separately estimated odds ratio indicates a dose-response relationship between maximal serum total bilirubin concentration and neurodevelopmental outcome. Therefore, long-term brain toxic effects seem to occur already at mildly to moderately elevated maximal serum total bilirubin concentrations. The logistic regression analysis allowed us to include only a limited number of confounding factors. Therefore, several clinical data (eg, mean Apgar scores, amnionitis, sepsis) were not included in the analysis. We selected our confounding factors initially on the basis of a literature review,[8] but they were later confirmed by descriptive statistics of our data.

Bilirubin toxicity may occur when non-albuminbound bilirubin passes the blood barrier and is bound to the neurons, where it exerts its toxic effects. The blood-brain barrier in preterm infants does not seem to be more permeable for larger molecules than in adults, although there is a higher passive permeability for nonlipid-soluble molecules in the immature brain.[12]

Our results are based on total bilirubin concentrations. Lower serum albumin concentrations and a reduced binding capacity of albumin for bilirubin, due to displacing agents, eg, sulfonamides[13] and free fatty acids,[14] in sick preterm infants, will increase the serum concentrations of unbound bilirubin, which is presumed to pass the blood-brain barrier easily.[15] The binding of bilirubin to albumin does, however, not seem to be affected by pH.[16] Hypercarbia[17] and hyperosmolality[18] conditions that occur frequently in sick preterm infants, increase the permeability of the blood-brain barrier. This will also allow bilirubin bound to albumin to enter the brain. Collection of several of the clinical data (eg, hypoxemia, hypercarbia, and acidosis), which also may influence the neurodevelopmental outcome, was not feasible in this collaborative study, although causes and consequences of these conditions, like respiratory distress syndrome and intracranial hemorrhage, were included in the analysis.

The handicaps were mainly caused by cerebral palsy. We did not find a relation between maximal serum total bilirubin concentration and hearing defects. However, in our study, audiologic examinations were only done when clinically indicated. We might, therefore, have missed minor hearing defects. These findings were contrary to those of De Vries et al[19] but similar to those of Johnson and Boggs.[20] The latter also found that duration of hyperbilirubinemia was a better predictor of neurodevelopmental outcome than maximal serum total bilirubin



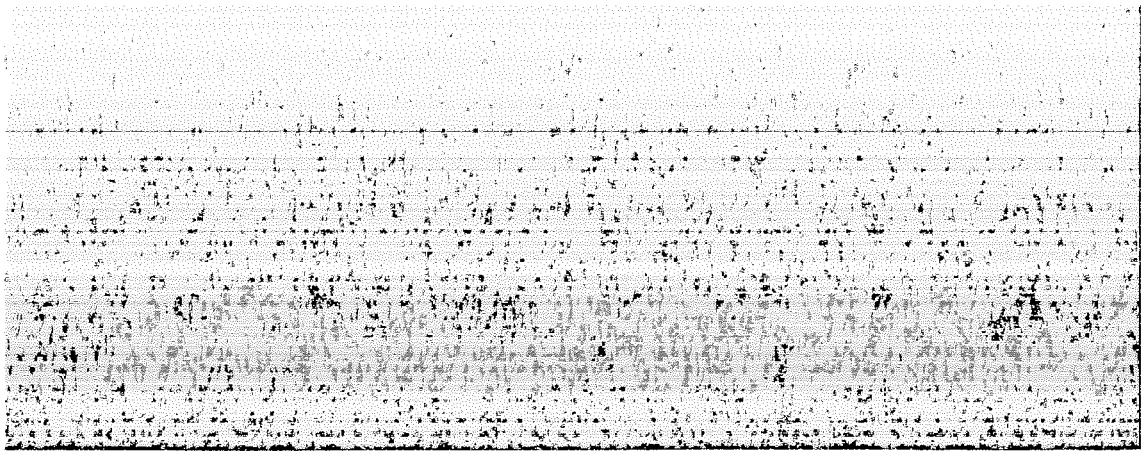
concentration. Duration of hyperbilirubinemia was not recorded in our study and, therefore, we cannot report its importance for neurodevelopmental outcome.

Whether our results are caused by hyperbilirubinemia itself or by unknown side effects of phototherapy or other unknown confounders remains a source of speculation. Neonatal mortality, on the other hand, did not differ between infants treated with phototherapy and their controls.[21] The National Institute of Child Health and Human Development trial of phototherapy for neonatal hyperbilirubinemia showed no adverse outcome of phototherapy treatment at 6 years of age.[22] In our survey, we did not find a relationship between duration of phototherapy and neurodevelopmental outcome (P=.80). However, our survey was not designed to study the effect of hyperbilirubinemia treatment. Although the infants treated with exchange transfusions had more handicaps (16% minor and 16% major), we may not draw any conclusion from this survey regarding effectiveness of treatment. Furthermore, we have to consider that exchange transfusions were only performed when phototherapy failed to control serum bilirubin concentration.

We are not aware of previous epidemiologic studies in which the influence of hyperbilirubinemia on neurodevelopmental outcome was studied in so large a population of children with a gestational age of 32 week and/or a birthweight of less then 1,500 g, as reported here. Scheidt et al[23] reported that in a large cohort of term and preterm infants the risk of impaired motor performance at 12 months of age was associated with hyperbilirubinemia in the neonatal period, especially when the maximal serum total bilirubin concentration exceeded 170 μmol/L (10.0 mg/dL). However, in that study the number of surviving children with a birthweight of less than 1,500 g was small and no suspected confounding factors were included in the analyses. The infants in our survey were tested at a relatively young age (corrected age of 2 years). Differences in neurodevelopmental status at an early age may not be found at 4 to 7 years of age.[24] We are, therefore, now in the process of testing all infants again at the corrected age of 5 years.

This survey generates the hypothesis that mild to moderate hyperbilirubinemia is causally related to impaired neurodevelopmental outcome. Although logistic regression analysis of observational evidence is useful in clarifying questions about possible associations, it is not a substitute for experimental test of those associations. Only a clinical trial can test whether intervention based on serum bilirubin concentrations will improve outcome. Therefore, altering current clinical practice is not justified until a trial to test our hypothesis is carried out.

In conclusion, our data demonstrate that, after adjustment for many (but not all) confounding factors, mild to moderate hyperbilirubinemia in preterm infants is associated with impaired neurodevelopmental outcome, especially cerebral palsy; a linear increase in risk of a handicap existed for each 50 μmol/L (2.9 mg/dL) increase of maximal serum total bilirubin concentration.



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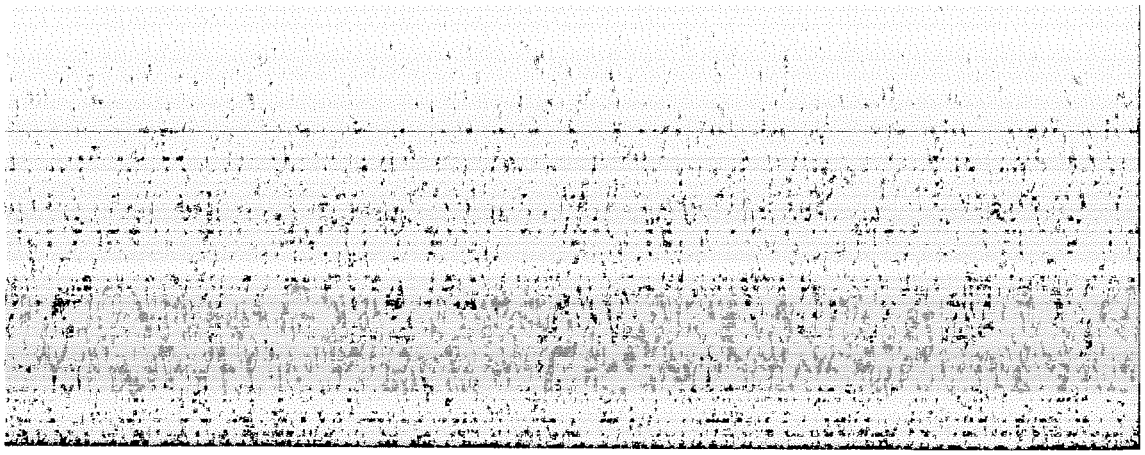

CHAPTER 8

USE OF HEALTH SERVICES IN THE FIRST TWO YEARS OF LIFE IN A NATIONWIDE COHORT OF VERY PRETERM AND /OR VERY LOW BIRTHWEIGHT INFANTS IN THE NETHERLANDS

I: REHOSPITALIZATION

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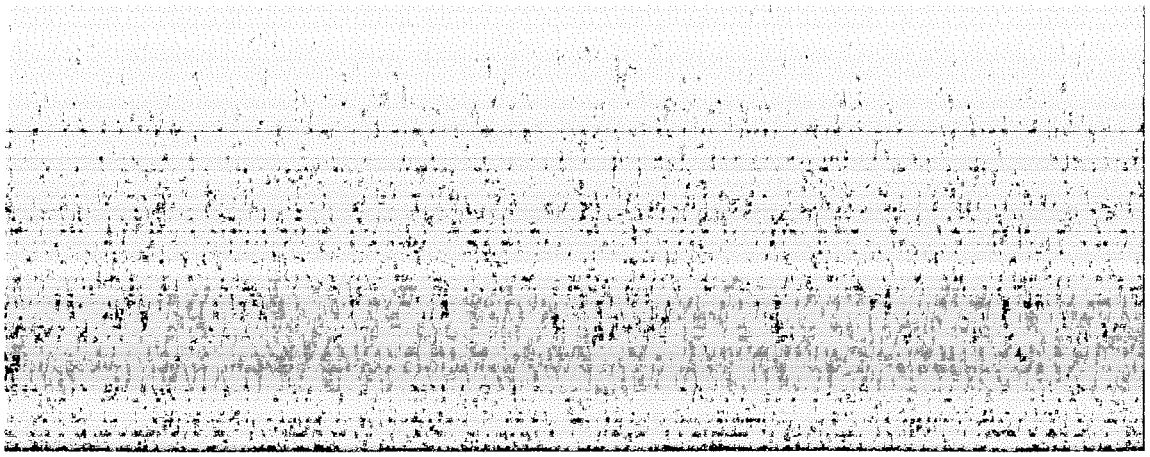
Submitted for publication



SUMMARY

In a prospective collaborative study on very preterm (<32 weeks) and/or very low birthweight infants (<1500 g) in the Netherlands, the incidence of and reasons for rehospitalization were studied. Out of 1338 liveborn infants, 998 survived the initial hospital stay.

During the period between discharge and the age of 24 months corrected for preterm birth 320 infants (34%) were readmitted 481 times.

The main reasons for rehospitalization were surgical procedures, of which inguinal herniorrhaphy was the most prominent, and respiratory tract disorders: 149 admissions (31%) and 147 (31%) admissions respectively. The remaining reasons for rehospitalization occurred less frequent and consisted of reasons such as congenital malformations, sequelae of preterm birth, digestive tract and central nervous system disorders, infections and a small group of miscellaneous.

In a multivariate analysis both sex and the length of the initial hospital stay was shown to be significantly associated with an increased risk of rehospitalization.

Handicapped children were readmitted more often than non-handicapped children.

A comparison with data from the the general Dutch population in the second year of life revealed a similar rehospitalization rate in non-handicapped children as in children from the general population.

INTRODUCTION

The decrease in mortality in very low birthweight (VLBW) infants has induced general interest in the long-term outcome of preterm birth. Disorders, like cerebral palsy, chronic lung disease or retinopathy of prematurity (ROP), that may lead to disability or handicap are the focus of attention. However, the prevalence of more moderate or temporary morbidity, necessitating frequent use of clinical health services, has not been studied systematically till recently.[1]

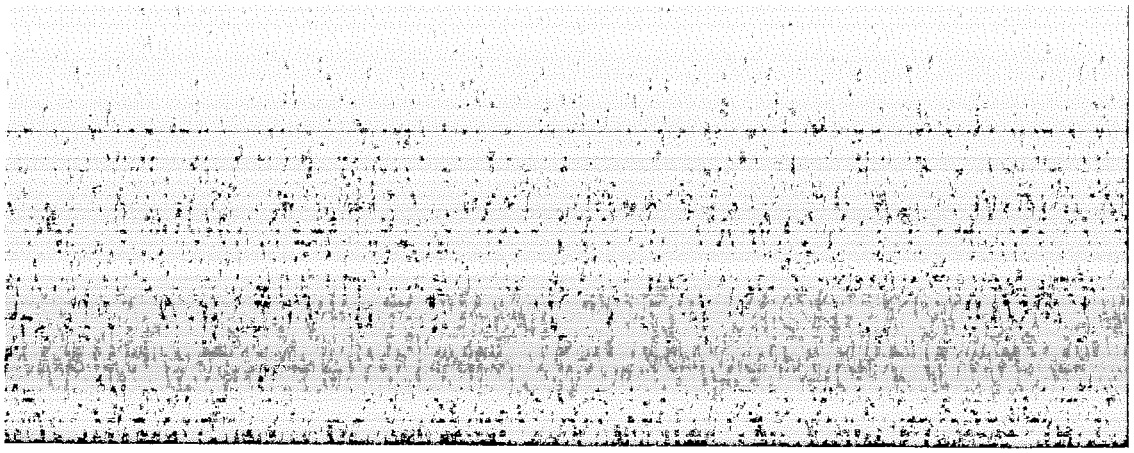
Therefore, rehospitalization rates have been used as a measure of total morbidity and use of clinical health services.[2-7]

With this objective, we evaluated the rates of and reasons for rehospitalization in the nationwide collaborative survey on very preterm and/or VLBW infants, that was started in the Netherlands in 1983.[8]

PATIENTS AND METHODS

The Project On Preterm and Small for gestational age infants (POPS) collected data on 1338 infants born alive in the Netherlands between January 1 and December 31, 1983 with a gestational age of less than 32 completed weeks and/or a birthweight of less than 1500 g. This study population comprised 94% of all infants meeting these criteria.

From the 1338 infants originally enrolled in the survey, 340 died during the



initial hospital stay.[9] All 998 surviving infants were asked to participate in a follow-up programme of examinations planned at the age of 3, 6, 12 and 24 months, corrected for preterm birth.

The clinical and socio-economic data of the population are shown in table 1.

Table 1. Clinical and socio-economic data of the study population (n = 998: infants discharged home after the initial hospital stay)

variable	mean (± standard deviation) or percentage
gestational age (wk)	31.0 ± 2.5 (range 25 - 40)
birthweight (g)	1313 ± 284 (range 560-2580)
sex (male)	51.6
multiple pregnancy	20.9
congenital malformation	9.3
IRDS	25.8
ICH	13.5
CNS-disorder	8.5
BPD	9.1
clinical condition at discharge (satisfactory)	90.3
socio-economic status low (class 1 or 2 out of 6)	32.2
length of the initial hospital stay (days)	68 ± 32 (range 6-380)

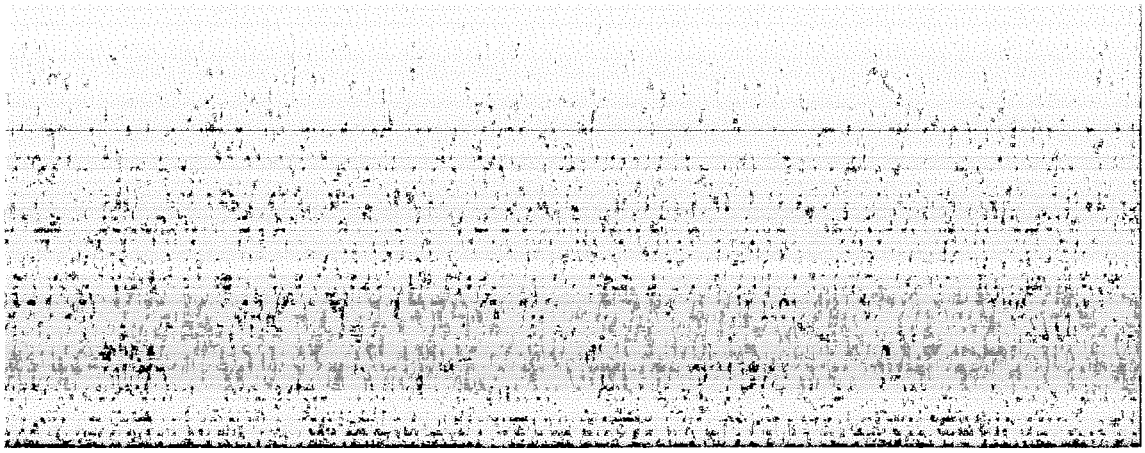
Rehospitalization was defined as a hospital admission during the period between the initial discharge and the corrected age of 24 months.

At the corrected age of 3 months, 16 infants were still hospitalized from birth onwards, at 6 months this number had decreased to 7. The reasons for these extremely long initial hospital admissions were bronchopulmonary dysplasia (BPD) (5), congenital malformations (9), and other problems arising from the neonatal period like necrotizing enterocolitis and tracheal cyst (2). These cases are not included as readmissions.

During the follow-up period 29 infants died, 12 of them during a hospital stay. Data from these infants were included for the time they participated in the survey.

In the course of the follow-up period a further 25 children were lost to follow-up because the families moved abroad (n = 12), were untraceable (n = 7) or refused further cooperation (n = 6). On another 25 children, information was not complete. These 50 cases were excluded from the analysis. In 34 children follow-up by the attending paediatrician was discontinued before the age of 2 years; remaining data were provided by their family doctor or the community child health centre personnel instead. As a result complete data on rehospitalization were recorded for 948 children.

Separate data were collected on rehospitalization for each follow-up interval. Multiple readmissions in the same interval were not recorded as such. No information was available about the length of the various hospital admissions,



precluding any comparisons in that respect. The reasons for rehospitalization were stated by the attending paediatricians in their own words, and categorized afterwards in 7 groupings.

In the surviving children neurodevelopmental outcome was assessed at the age of two years corrected for preterm birth by the attending paediatrician or in some cases at the community child health centre. An overall developmental level was assessed using the Gesell test adapted for Dutch children[10] and supplemented by neurological, visual and hearing examinations, when necessary performed by a multidisciplinary team. The children were divided by outcome into three groups: "major handicap", "minor handicap" and "normal".[11]

The relationship between outcome and rehospitalization was studied for the whole follow-up period as well as for the first and second year separately.

The Netherlands Health Interview Survey, performed by the Central Bureau of Statistics[12], enabled us to compare our results with data from the general Dutch population (Central Bureau of Statistics, Heerlen, The Netherlands, personal communication).

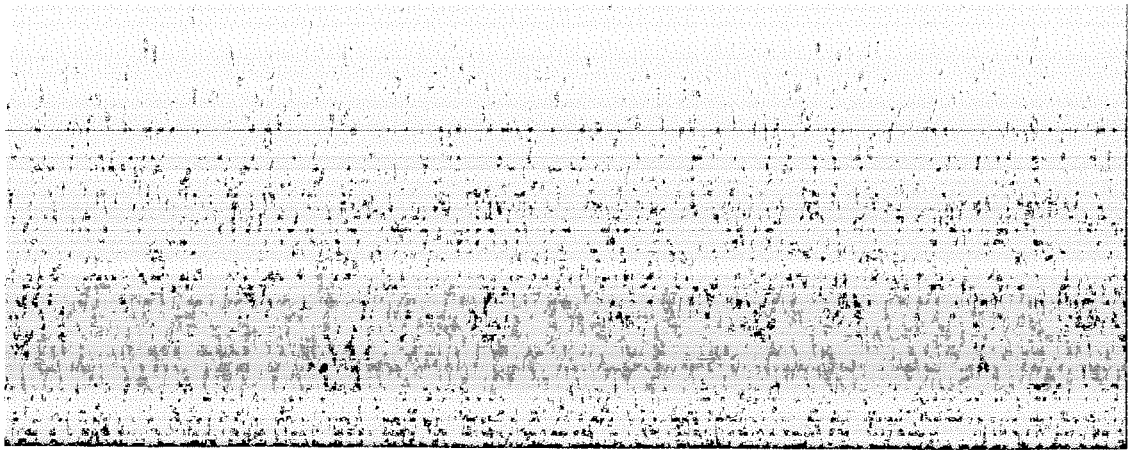
To evaluate whether there was any relationship between the risk of rehospitalization and perinatal characteristics, a multivariate statistical technique (stepwise logistic regression analysis)[13] was used. Such a technique allows estimation of the effect of a single factor while adjusting the possible confounding effect of the other factors involved. Rehospitalization was the dependent variable, while several perinatal factors were entered as independent variables. The measure of association between rehospitalization and any of the risk factors was expressed in odds ratios (OR).[14]

Based on data from the literature and clinical experience, some perinatal risk factors were a priori decided to be included in the analysis. These factors were: gestational age (weeks): the best obstetric estimate based on last menstrual period, pregnancy testing and ultrasound[9]; birthweight (grams); gender; socio-economic status, based on education and occupation of both parents[15]; multiple pregnancy; congenital malformation; idiopathic respiratory distress syndrome (IRDS): based on a clinical diagnosis[8]; intra cranial haemorrhage (ICH): all grades as diagnosed by ultrasound or CT-scan; any distinct central nervous system (CNS)-disorder during the initial hospital stay; bronchopulmonary dysplasia (BPD); clinical condition at discharge: as recorded by the attending paediatrician; length of the initial hospital stay (days).

RESULTS

Frequency of readmission

Of the 948 infants with complete data on rehospitalization, 320 (34%) were rehospitalized 481 times during one or more of the follow-up intervals between discharge and the corrected age of 3, 6, 12 and 24 months. In the first year 264 infants (28%) and in the second year 123 children (13%) were readmit-



ted. The number of readmission in the four follow-up intervals, and the number of infants divided by number of readmissions are presented in table 2. Most infants (n = 198, 62%) were hospitalized only once, particularly during the first interval. The large majority of readmissions (n=358, 74%) occurred during the first year, and concerned 82% of all infants ever readmitted.

As shown in table 3, the rehospitalization rate varied only slightly in different gestational age categories.

Table 2. Rehospitalization during the first two years of life

number of readmissions per infant	number of infants	total number of readmissions	number of readmissions *corrected age in months*			
			-3	3-6	6-12	12-24
1	198	198	72	28	42	56
2	89	178	44	46	45	43
3	27	81	21	21	21	18
4	6	24	6	6	6	6
total	320	481	143	101	114	123

Table 3. Rehospitalization in gestational age categories

gestational age (weeks)	study infants n	rehospitalized infants n	(%)
<24	0		
24-25	5	4	
26-27	80	29	(36)
28-29	212	82	(39)
30-31	362	114	(31)
⩾32	286	91	(32)
unknown	3		
total	948	320	(34)

Related to the neurodevelopmental outcome assessed at the age of two years, a much higher percentage of major but also of minor handicapped children were rehospitalized compared to normal children; both during the whole follow-up period and during the two years separately. The numbers and percentages are shown in table 4.

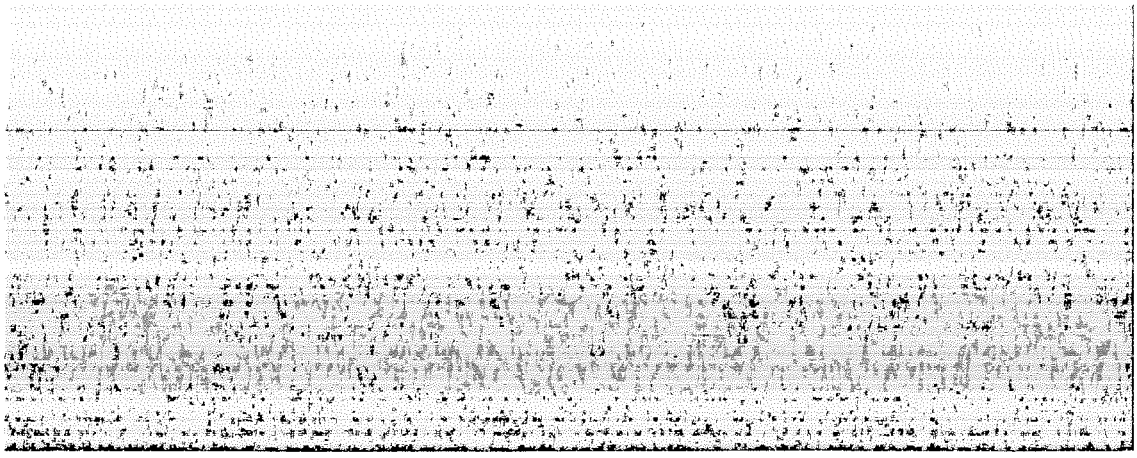


Table 4. Numbers and percentages of children rehospitalized in their 1st and/or 2nd year of life according to neurodevelopmental outcome at the corrected age of two years

follow-up period	normal		handicapped			
			minor		major	
	n=774		n=111		n=59	
	n	(%)	n	(%)	n	(%)
1st year	181	(23)	43	(39)	34	(58)
2nd year	78	(10)	19	(17)	23	(39)
1st + 2nd year	223	(29)	49	(44)	41	(69)

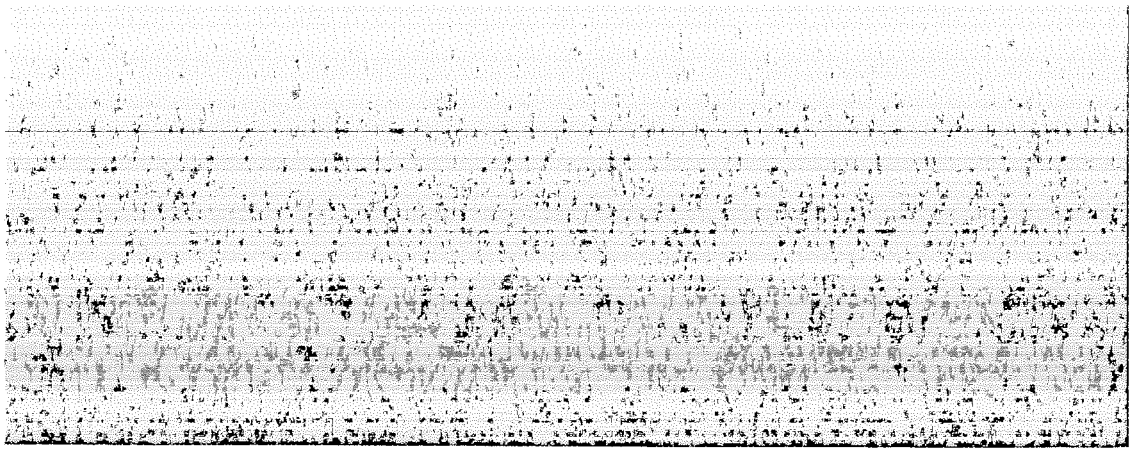
Reasons for readmission

The reasons for admission were arbitrarily divided into 7 broad groupings; the number of admissions in each category is shown in table 5 for the total follow-up period, as well as for the 1st and 2nd year separately.

Table 5. Number of rehospitalized children in the first and second year of life according to reason of readmission

category	1styear	2ndyear	total	(%)
surgical procedures	104	45	149	(31)
respiratory tract disorders	117	30	147	(31)
digestive tract disorders	48	12	60	(13)
central nervous system disorders	29	21	50	(10)
congenital malformations and sequelae of preterm birth	24	1	25	(5)
other infections	16	1	17	(3)
miscellaneous	20	13	33	(7)
total	358	123	481	(100)

Surgical procedures and respiratory tract disorders were the main reasons for readmission (62%) throughout the complete follow-up period. In the first year the greater part of surgical procedures were inguinal herniorrhaphies (n=72). An inguinal hernia was diagnosed in 111 infants (12% of the study population) of whom 96 underwent operation. Inguinal herniorrhaphy took place in 85% (66/78) of the unilateral and 91% (30/33) of the bilateral hernias. In the second year of life, procedures in the field of ear, nose and throat (ENT) surgery were the main surgical procedures, such as tonsillectomy and/or adenoidectomy (n=19) and the insertion of middle ear ventilation tubes (n=5). In the group of respiratory tract disorders, infections (n=73, mostly pneumonia), were the main reason for readmission. Only in 9 of the 147 cases BPD was recorded as the main reason for readmission.



Digestive tract disorders included infections and feeding problems. In the second year the number of readmissions due to central nervous system disorders was similar to that in the first year, due to a relatively high number of convulsive disorders (n=13), mainly febrile convulsions. Other reasons for readmission varied from sequelae of preterm birth such as bloodtransfusions for anaemia (n=7) or cryocoagulation for ROP (n=2), to various infections such as meningitis (n=5) and urinary tract infections (n=2). Several readmissions were caused by accidents like intoxications and bone fractures. Each of these reasons for readmission concerned relatively few children, but the total amounted to almost 30% of all readmissions.

Relationship with perinatal factors

In the stepwise logistic regression analysis gender was significantly associated with an increased risk of rehospitalization: the OR for boys versus girls was 1.4 (95% confidence interval 1.1-1.9).

Furthermore, the risk of rehospitalization was significantly associated with the length of the initial hospital stay. For an increment of 28 days in the duration of the initial hospital stay the OR was 1.4 (95% confidence interval 1.2-1.7). No other variable met the 0.05 significance level for entry in the model.

DISCUSSION

Frequency of rehospitalization

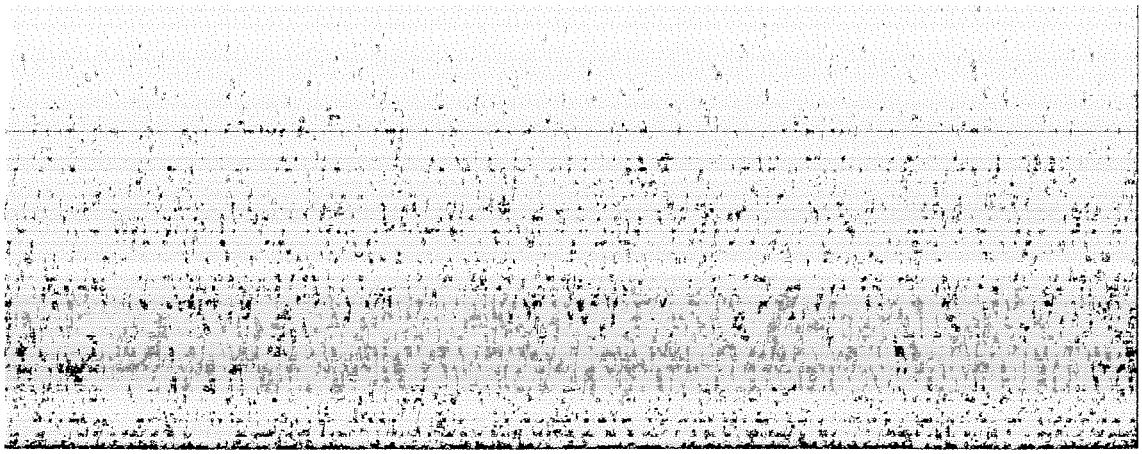
It has been known for many years that preterm infants have a greater risk of rehospitalization than term infants.[16-18] While the chance of survival has increased dramatically for VLBW children after the introduction of neonatal intensive care, the rate of rehospitalization has increased as well.[19,20,21]

Changes over time documented in a geographically defined population in the United Kingdom have confirmed this rise. In the periods 1968-1972 and 1974-1978 the survival rates improved from 35% to 48%, while the rehospitalization rates increased from 22% to 27%.[5] In a third period between 1979-1983 this trend appeared to continue, with a survival and rehospitalization rate of 58 and 44% respectively.[22]

In the U.S.A. in 1976 it was found that 8.4% of the infants born with a normal birthweight were rehospitalized during their first year of life, a percentage that rose to 38.2% for infants with a birthweight < 1500 g.[2]

The results of the present survey on very preterm and/or VLBW infants in the Netherlands show a rehospitalization rate of 34%, similar to the above mentioned rates. No previous data on Dutch VLBW infants are available, precluding a statement on secular changes in rehospitalization rates in the Netherlands.

Data from the general Dutch population revealed that in 1983-1987, 15%



of all infants were hospitalized in their first, and almost 10% in their second year of life.[12] Very preterm and very low birthweight infants, therefore, were rehospitalized twice as many times in their first year of life compared to Dutch children in the general population. This difference became much smaller in the second year of life, mainly due to the great fall in number and percentage of hospital readmissions of children in our population considered "non-handicapped".

Although the "non-handicapped" children had a rehospitalization rate of 23% in their first year of life, this dropped to 10% in the second year of life, a percentage similar to that found in the general population. A decrease in the rehospitalization rate of handicapped children also occurred in the second year of life: however, they did not reach the percentages found in the general population.

Reasons for rehospitalization

Like in other surveys respiratory tract disorders and inguinal herniorrhaphies were the main reasons for rehospitalization.[1,2,17]

Although BPD is very often described as a reason for rehospitalization,[23] this was not the case in the present population. In the group of respiratory disorders, BPD was only in 9 cases recorded as the main reason for rehospitalization. However, out of 86 surviving infants with BPD 19 were rehospitalized because of an upper respiratory tract infection.

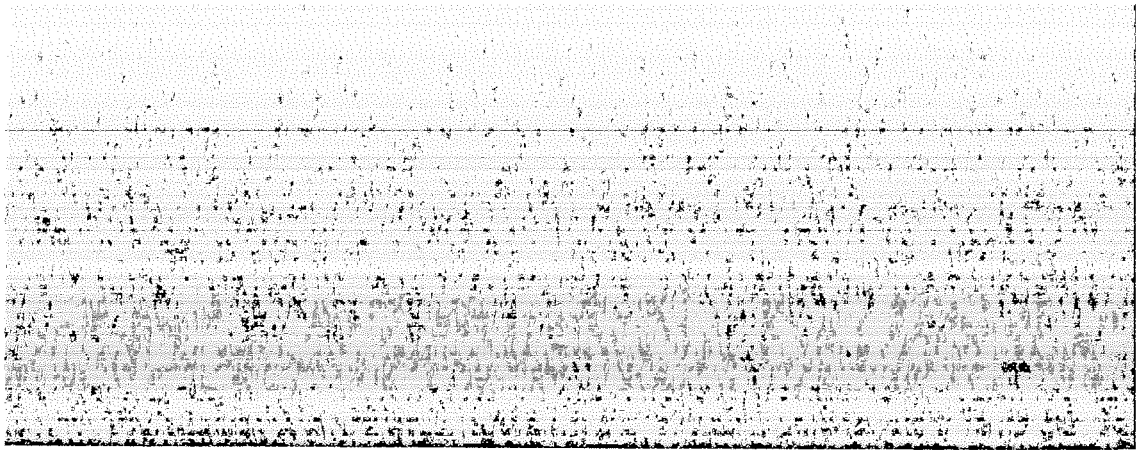
As expected, a great number of infants (n=72) were rehospitalized for repair of an inguinal herniation. Since not all of these were recorded as readmissions, some of the operations were apparently performed during the initial hospital stay or during daytime nursing. In 40 children (12% of all readmitted children), the admission for herniorrhaphy was the only rehospitalization recorded.

In a population of otherwise healthy term infants a much lower incidence of inguinal hernia was described (0.2-2%).[24] The high incidence in our study population (12%) is in accordance with previous reports on VLBW infants (11%)[25,26] and on ELBW infants (30%).[27] The large number of children merely rehospitalized for inguinal herniorrhaphy had considerable impact on the total number of rehospitalized infants.

Perinatal characteristics

Being generally accepted that preterm infants have a higher risk of rehospitalization than term infants, it is of interest to determine predicting factors. In a previous prospective study on term and preterm infants in a geographically defined area,[28] increasing birth order was the most important predicting factor, followed by male sex and low maternal education.

Our analysis assigned the greatest predicting value to gender. The excess of readmissions in boys (n=187) compared to girls (n=132) is explained by the great number of boys hospitalized for herniorrhaphy (55 boys, 17 girls).



The other variable meeting significance in our analysis was the length of the initial hospital stay. This factor reflects the influence of many variables not included in the analysis such as pneumothorax or NEC as well as the severity of the perinatal disorders. After excluding the length of the initial hospital stay from the analysis, the condition of the infant at discharge and BPD attained significance for the risk of rehospitalization as well.

While the chances of survival of VLBW infants are still improving[7] a high percentage of infants suffer from ongoing medical problems which in many cases lead to rehospitalization.

We conclude that respiratory tract infections and structural defects, such as inguinal hernia, have great impact on the rehospitalization rate, especially in the period directly after the initial discharge. After the first year of life, the rehospitalization rate diminished considerably from 28% to 13%. Especially in the "non-handicapped" children a rehospitalization rate during their second year of life was found, similar to that of children from the general population.

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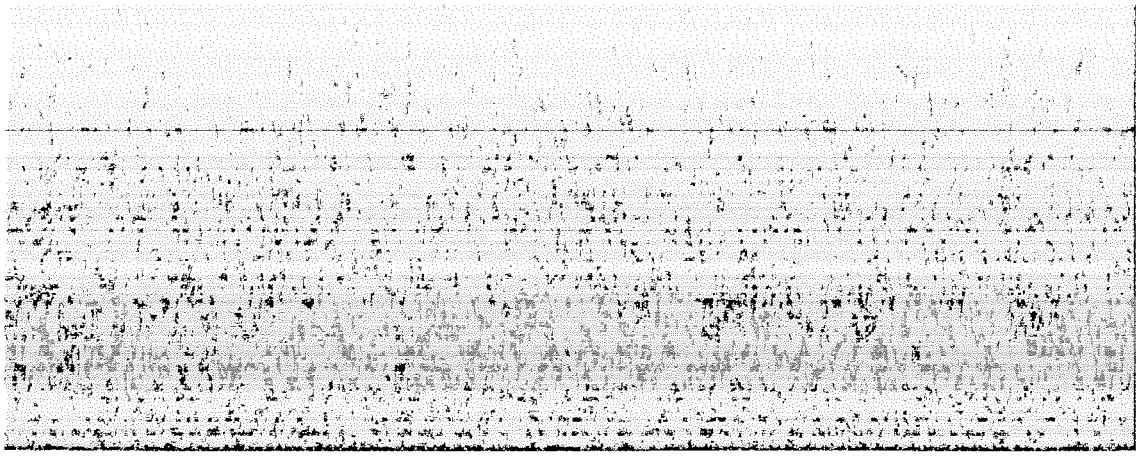

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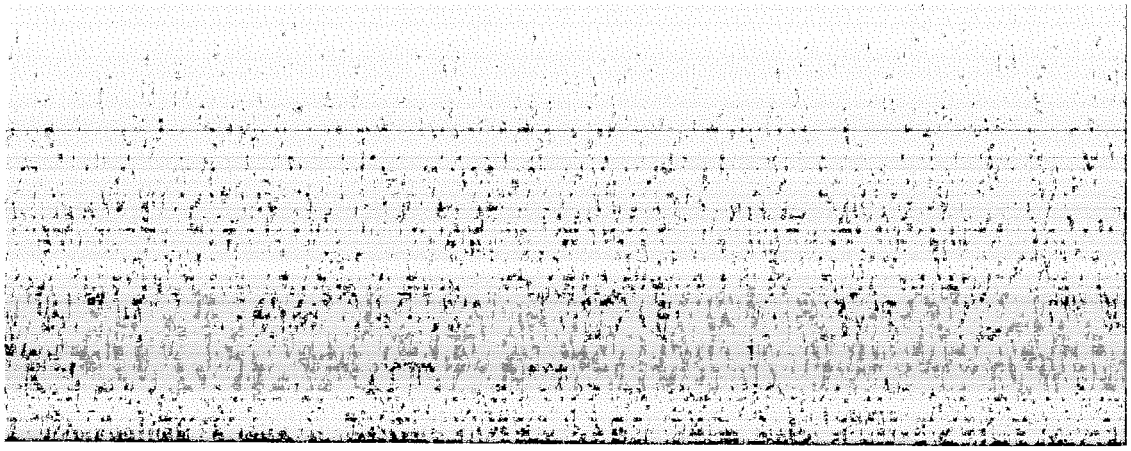

CHAPTER 9

USE OF HEALTH SERVICES IN THE FIRST TWO YEARS OF LIFE IN A NATIONWIDE COHORT OF VERY PRETERM AND /OR VERY LOW BIRTHWEIGHT INFANTS IN THE NETHERLANDS

II: OUTPATIENT CARE

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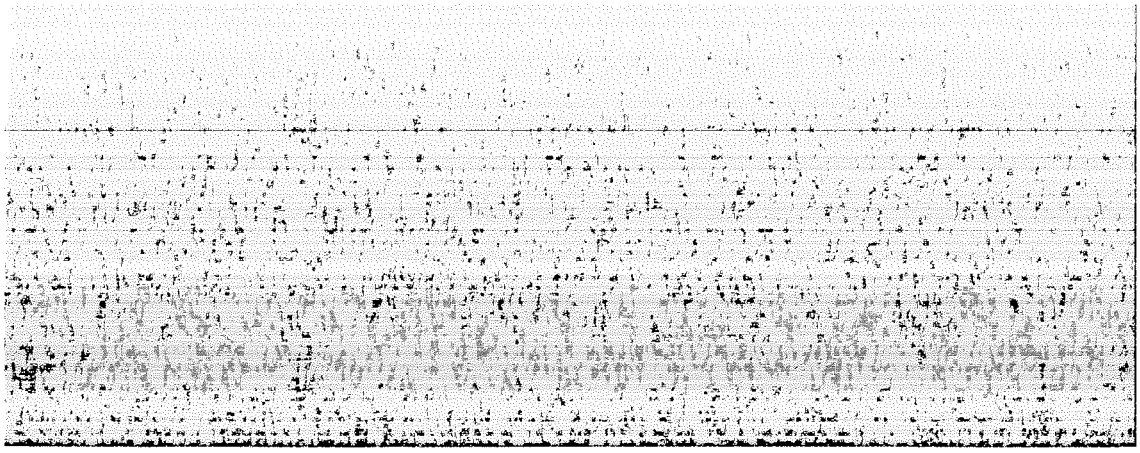
Submitted for publication



SUMMARY

In a prospective collaborative study on very preterm (<32 weeks) and/or very low birthweight infants (<1500 g) in the Netherlands, we studied the use of outpatient services, i.e. visits to medical specialists and physical therapists.

During the period between discharge from the initial hospital stay and the age of 24 months corrected for preterm birth, 671 children (67%) attended a medical specialist other than their paediatrician and 313 children (31%) attended a physical therapist.

The use of outpatient services as a whole was higher in the first year than in the second year and depended very much on the neurodevelopmental outcome of the child. In the second year of life the use of outpatient care by the "normal" children from our study population was similar to that of the general Dutch population.

INTRODUCTION

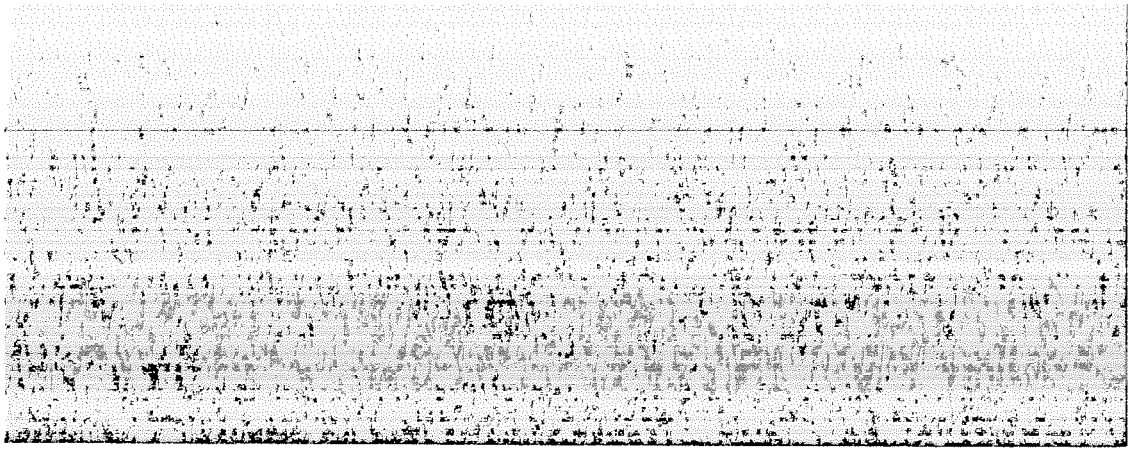
In the last ten years a downward trend was noted not only in mortality but also in morbidity in very preterm and very low birthweight infants.[1,2] Even for extremely low birthweight infants better survival chances emerged.[3,4] Reports upon morbidity are mainly dealing with disabilities and handicaps such as cerebral palsy, visual and hearing disturbances and cognitive problems. Still, one may query the extent of the continuing morbidity in this group of children resulting in rehospitalization and outpatient medical consumption.

Therefore, as part of a collaborative survey on mortality and morbidity in very preterm and/or very low birthweight infants in the Netherlands, we prospectively studied rehospitalization and the use of outpatient services by these infants during the period after discharge from the initial hospital stay till the age of two years corrected for preterm birth. By further describing the extend of the ongoing "lesser" morbidity, the aftermath of neonatal intensive care may become clearer. Such an approach is likely to provide an understanding of the requirements of health care after the initial perinatal hospital stay.

PATIENTS AND METHODS

In 1983, from January 1 till December 31, 1338 infants in the Netherlands, liveborn after a gestational age of less than 32 completed weeks and/or with a birthweight of less than 1500 g were enrolled in the prospective survey: Project On Preterm and Small for gestational age infants (POPS).[5] The compliance rate was 94%.

All infants discharged home alive after the initial hospital stay were enrolled in the follow-up study. At the age of 3, 6, 12 and 24 months corrected for preterm birth follow-up examinations were scheduled at the outpatient department by the local paediatrician or at the referral hospital. To study changes in time,



the follow-up period was divided into 4 intervals. For each follow-up interval, discharge -3 months, 3-6, 6-12 and 12-24 months, data were recorded separately concerning growth, physical disturbances, psychomotor development, psycho-social problems and the use of health services other than the paediatric follow-up.

The incidence of and reasons for rehospitalization have been described in chapter 8. Outpatient visits to medical specialists other than the paediatrician were divided into routine health checks and visits on medical grounds; physical therapy was divided into periodical advice to the parents concerning handling and caretaking of their child or regular (neurodevelopmental) treatment. The number of visits to the specialist or the physical therapist during a follow-up interval was not recorded. Visits to the ophthalmologist, otorhinolaryngologist, (paediatric)neurologist, orthopaedic surgeon, rehabilitation specialist and (paediatric)cardiologist were recorded as such, to other medical specialists as "others".

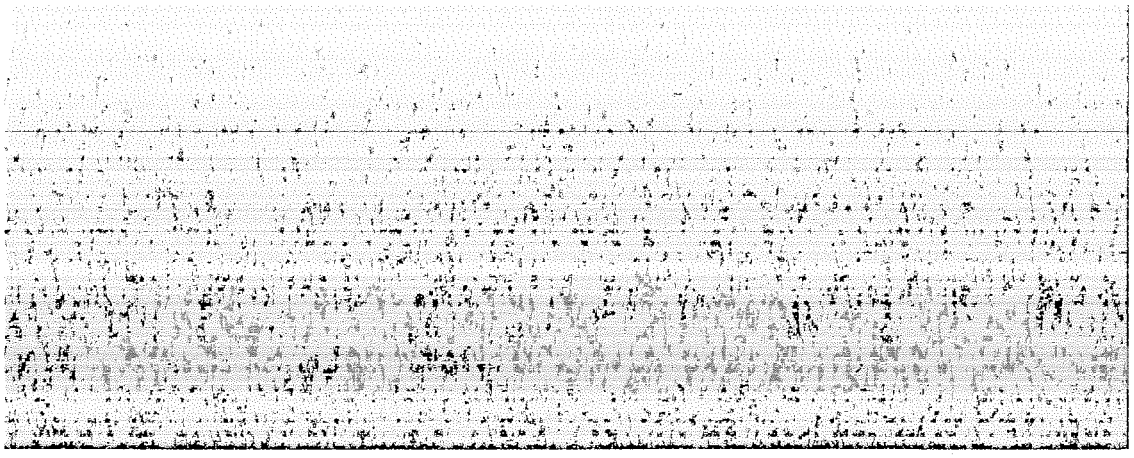
We studied the total number of children that visited a certain specialist as a routine health check or on medical grounds during the 1st and 2nd year of life, the total follow-up period, and for each follow-up interval separately. The same procedure was used regarding visits to the physical therapist.

In the surviving children neurodevelopmental outcome was assessed at the age of two years corrected for preterm birth by the attending paediatrician or in some cases at the community child health centre. An overall developmental level was assessed using the Gesell test adapted for Dutch children[6] and supplemented by neurological, visual and hearing examinations, when necessary performed by a multidisciplinary team. The children were divided by outcome into three groups: "major handicapped", "minor handicapped" and "normal".[7]

The relationship between outcome and medical consumption (visits to medical specialists and physical therapist separately) was studied. Furthermore, the Netherlands Health Interview Survey, performed by the Central Bureau of Statistics,[8] provided us with data on medical consumption from the general Dutch population (Central Bureau of Statistics, Heerlen, the Netherlands 1988, personal communication). As a result, a comparison could be made between the medical consumption in this selected group of surviving high-risk infants and children from the general Dutch population.

RESULTS

Of the 1338 infants originally enrolled in the study, 998 infants were discharged home alive and included in the follow-up programme. Up to the age of 2 years corrected for preterm birth, 29 infants died and 25 infants (2.5% of the infants under study) were lost to follow-up: 12 families moved abroad, 6 children were lost because further cooperation was refused, and 7 children could not be traced. Data on medical consumption of these children are included for the time they participated in the follow-up programme.



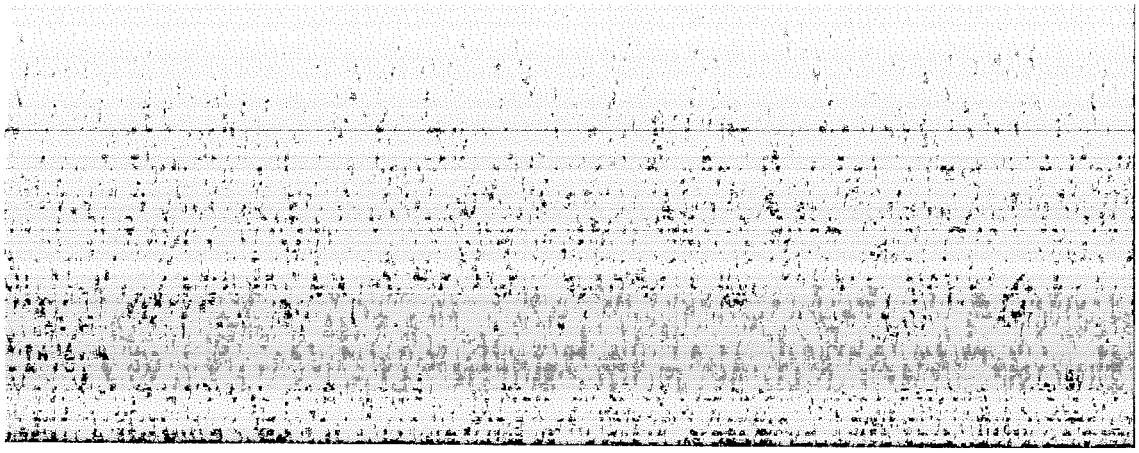
A total of 671 children (67% of the infants surviving the initial hospital stay), visited a medical specialist during the total follow-up period, in addition to their paediatrician: during the first year 605 children (60%) and during the second year 368 (37%). A total of 550 children (55%) made visits as a health check (426 and 151 children in the first and second year respectively) while 483 (48%) were seen on medical grounds (359 and 267 in the first and second year respectively).

The number of children that visited a certain medical specialist, as a routine health check or on medical grounds, is shown in table 1 for each interval separately, together with the total numbers. Most visits were made to the ophthalmologist; during the first two follow-up intervals these visits were mostly made as a health check (n=210 and n=165 respectively) for the possible occurrence of retinopathy of prematurity, whereas in the second year of life visits on medical grounds increased, often because of strabismus.

Table 1. Number of children visiting a medical specialist, as a health check or on medical grounds, divided by specialist and follow-up interval

medical specialist		follow-up interval (in months)				total* from discharge	
		discharge-3	3-6	6-12	12-24	till-12	till-24
grand total*		393	371	419	368	605	671
total*	health check	283	242	221	151	426	550
	medical grounds	157	171	253	267	359	483
ophthalmologist	health check	210	165	146	98		361
	medical grounds	32	41	69	74		142
otorhinolaryngologist	health check	1	0	7	12		20
	medical grounds	16	0	77	111		165
neurologist	health check	36	34	24	22		73
	medical grounds	23	26	32	41		77
orthopaedic surgeon	health check	4	4	3	5		11
	medical grounds	8	13	18	40		58
rehabilitation specialist	health check	52	58	58	34		86
	medical grounds	12	21	37	53		73
cardiologist	health check	4	6	8	2		14
	medical grounds	22	13	10	17		42
"other"	health check	19	17	16	11		53
	medical grounds	76	72	87	50		181

*the total number does not equal the sum of the separate numbers because of overlap



An increase in the number of visits to the otorhinolaryngologist appeared during the second year of life, due to upper and lower respiratory tract infections.

Orthopaedic surgeons and rehabilitation specialists were increasingly consulted on medical grounds during the second year of life, mostly by handicapped children with cerebral palsy in view of evaluation and treatment by a multi-disciplinary team.

In the category "other" medical specialist, consultations by a surgeon were included. Many of these visits preceded readmission to hospital for a herniorrhaphy.

At two years of age corrected for preterm birth neurodevelopmental outcome was assessed in 944 children (97.4% of the survivors). A major handicap was diagnosed in 59 children and a minor handicap in 111 children (6% and 12% of the assessed children respectively), 774 children were considered "normal".[9]

The total numbers and percentages of children that visited a medical specialist are shown in table 2, according to the character of medical visit, neurodevelopmental outcome and year of follow-up. As one might expect, all but 1 major handicapped child (98%) visited a medical specialist apart from their paediatrician. On the other hand still 500 (65%) of the 774 children considered "normal" at the corrected age of 2 years had visited a medical specialist on any occasion.

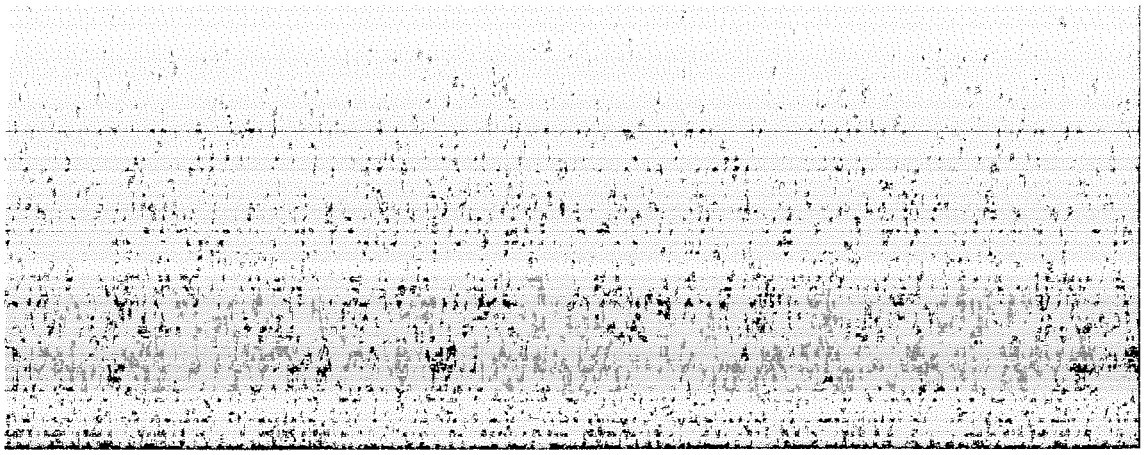
Table 2. Numbers and percentages of children visiting a medical specialist, according to the character of medical visit, neurodevelopmental outcome and year of follow-up

visits to a medical specialist	normal n=774				handicapped minor n=111				handicapped major n=59			
	total*		1st	2nd	total*		1st	2nd	total*		1st	2nd
	n	(%)	n	n	n	(%)	n	n	n	(%)	n	n
as a health check	409	(53)	330	100	79	(71)	55	32	46	(78)	26	19
on medical grounds	337	(44)	243	166	77	(69)	58	52	58	(98)	48	49
total*	500	(65)	454	246	97	(87)	83	67	58	(98)	52	55

*the total number does not equal the sum of the separate numbers because of overlap

The results reveal a clear decrease in the percentage of "normal" children visiting a medical specialist during the second year of follow-up. This is to some extend also seen for the minor handicapped children but not for the major handicapped ones.

In many cases the same child attended more than one specialist. This was related to the condition of the child; major handicapped children visited most specialists, because of the higher number of visits on medical grounds.



The number of infants attending a physical therapist, expressed as periodical advice to the parents or as regular (neurodevelopmental) treatment of the child, and split up into the various follow-up intervals, is shown in table 3.

Table 3. Number of children according to the character of physical therapy and per follow-up interval

physical therapy	follow-up interval (in months)				total* from discharge	
	discharge-3	3-6	6-12	12-24	till-12	till-24
periodical advice	87	84	55	51	160	182
regular treatment	74	108	120	88	170	191
total	161	192	175	139	281	313

*the total number does not equal the sum of the separate numbers because of overlap

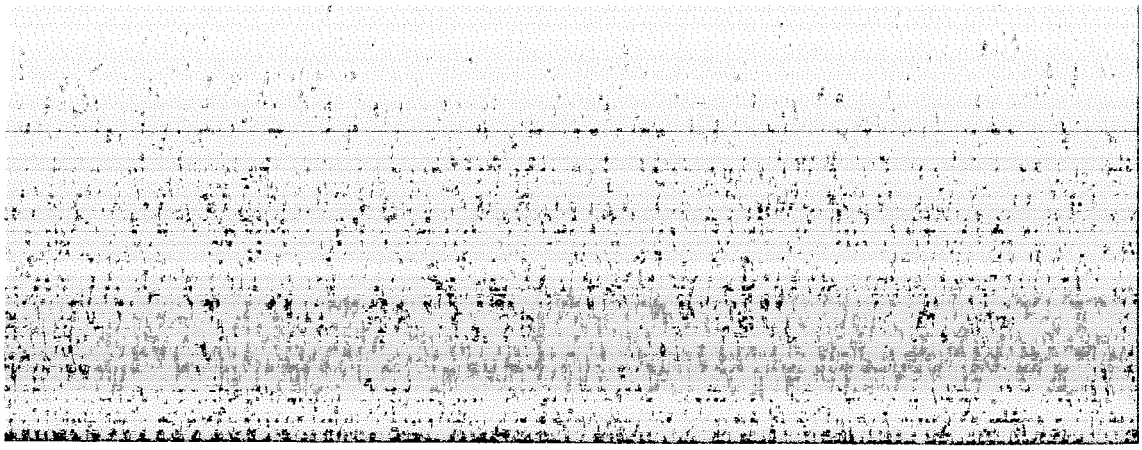
Already 281 children attended a physical therapist in their first year of life, i.e. 90% of all children receiving physical therapy in the total follow-up period. The relationship with neurodevelopmental outcome at the corrected age of two years is shown in table 4. The total numbers of children are given together with the numbers for the two years separately. Obviously, a much higher percentage of major handicapped children received physical therapy than of the normal or minor handicapped.

The same pattern as described in table 2 emerges from the data for the two years separately in table 4. A decrease in visits of "normal" children to a physical therapist in the second year of life, while minor and major handicapped children continue to visit physical therapists at the same rate.

Table 4. Numbers and percentages of children visiting a physical therapist, according to the character of physical therapy, neurodevelopmental outcome and year of follow-up

physical therapy	normal n=774				handicapped minor n=111				handicapped major n=59			
	total*		1st	2nd	total*		1st	2nd	total*		1st	2nd
	n	(%)	n	n	n	(%)	n	n	n	(%)	n	n
periodical advice	131	(19)	118	33	34	(36)	26	14	13	(20)	12	4
regular treatment	88	(11)	84	14	48	(43)	37	32	50	(84)	44	42
total*	180	(23)	169	47	71	(64)	56	46	53	(89)	47	46

*the total number does not equal the sum of the separate numbers because of overlap



Children receiving physical therapy were very often also attending medical specialists such as a neurologist (24%) and rehabilitation specialist (27%).

As described previously, 320 infants (32% of infants discharged home alive) were readmitted 481 times during the follow-up period. Respiratory tract disorders and surgical procedures, mainly inguinal herniorrhaphy, accounted together for more than 60% of the reasons for rehospitalization. The rehospitalized children also visited the hospital more often as an outpatient than the non-rehospitalized ones: 86% versus 58%. Visits on medical grounds occurred 2-5 times more often in the rehospitalized group. The percentage of children receiving physical therapy on any occasion was twice as high in rehospitalized children compared to non-rehospitalized children (46% versus 24%).

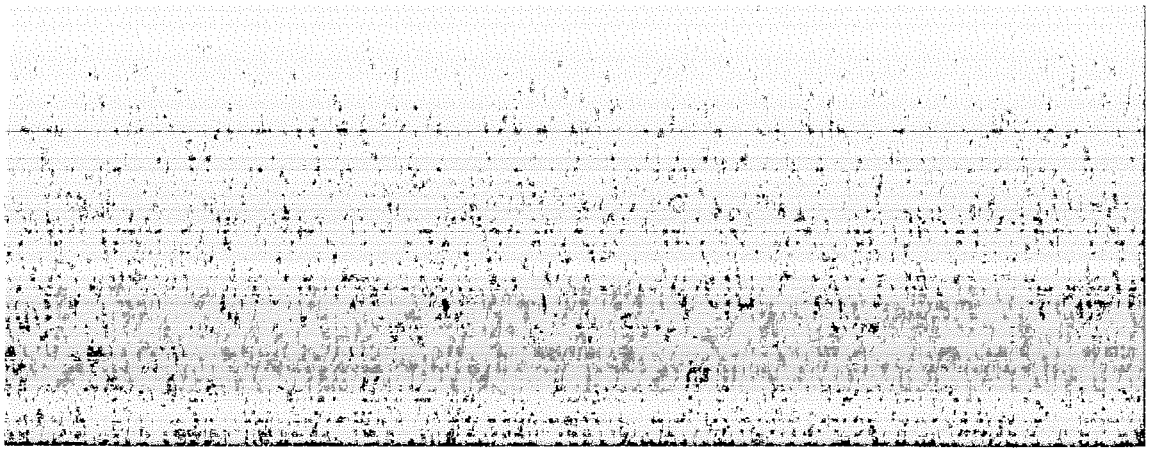
DISCUSSION

Very low birthweight and very preterm infants require substantial outpatient care rendered by various medical specialists and physical therapists, even if they survive the neonatal period apparently without any problem.

The later morbidity of these children has only been occasionally described in terms of their need of outpatient care. Mostly, the rehospitalization-rate is used as a measure of the so-called ongoing morbidity. Morgan,[10] however, mentioned that 36% of the very low birthweight infants in her follow-up study visited the hospital as an outpatient in the first year of life compared to 16% of the group of term infants used as control. Skeoch et al.[11] came to the conclusion that rehospitalization-rate alone was not a good measure of morbidity. During a 15 months follow-up period of very low birthweight infants, they found severe morbidity in 46% of the children resulting in rehospitalization in 73% of these cases. The others were treated as outpatient.

In 1983-1987, annually around 34% of a general population of Dutch children in their first and second year of life visited a medical specialist.[8] In the first year of life more than half of these visits were to a paediatrician, in the second year half of them. After exclusion of the visits to the paediatrician, 20% and 17% of the children in their first and second year of life, respectively, visited a non-paediatric medical specialist, compared to 60% and 37% of the children under study. Visits to a (paediatric) neurologist or (paediatric) cardiologist are considered as non-paediatric visits. However, the use of outpatient services (non-paediatric, on medical grounds) by the children under study considered "normal" at the corrected age of two years is, especially in their second year of life, comparable to the general population.

Less than 2% of the children in the general Dutch population visits a physical therapist up to the age of two years.[8] In our study, however, even as many as 23% of the children considered normal at the corrected age of two years attended one. Figures for the first and second year separately showed that during their second year of life only 6% of these "normal" children attended a physical therapist. The percentages of minor and major handicapped children visiting



a physical therapist remained high during the first as well as second year of follow-up.

It is still a matter of debate whether physical therapy may alter the pattern of motordevelopment.[12,13,14,15] However, as a result of physical therapy, one can expect easier way of handling and caretaking of the child and prevention of secondary handicaps, such as contractures.[16]

The continuing morbidity of very preterm and very low birthweight infants, as measured by the use of outpatient services as described here, is considerable. Moreover, it is an underestimation of the real use of health services, because visits to the family doctor and community child health centre were not included. Nonetheless the nationwide data show that after the first year of life with its numerous outpatient visits and probably a hospital readmission (in 28% of our patients), the use of health services of the "normal" children i.e. the majority of the surviving children, decreases to a level similar to that of the general population.

These results on the one hand emphasize the need for a systematic programme of follow-up and well organized continuing care after discharge of these high-risk infants especially in the first years of life; on the other hand, they illustrate the gradual "normalization of life" for the majority of survivors.

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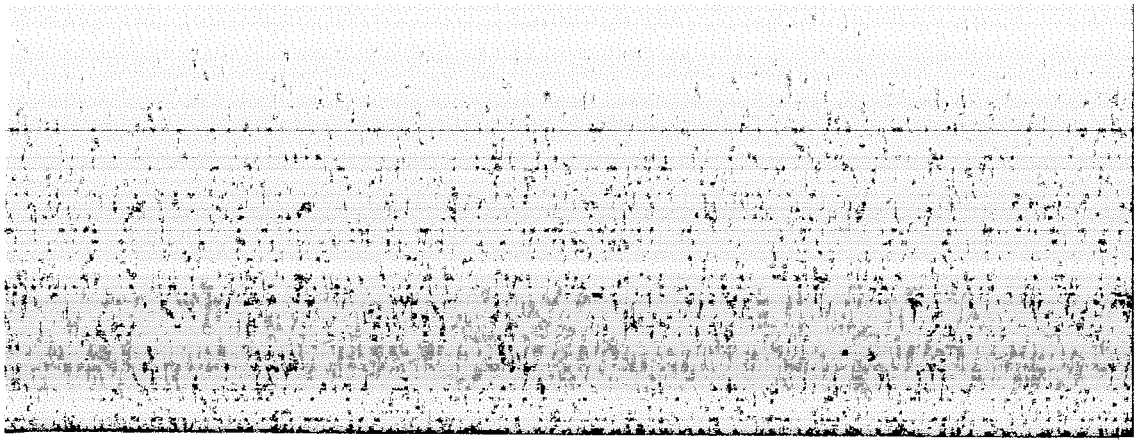

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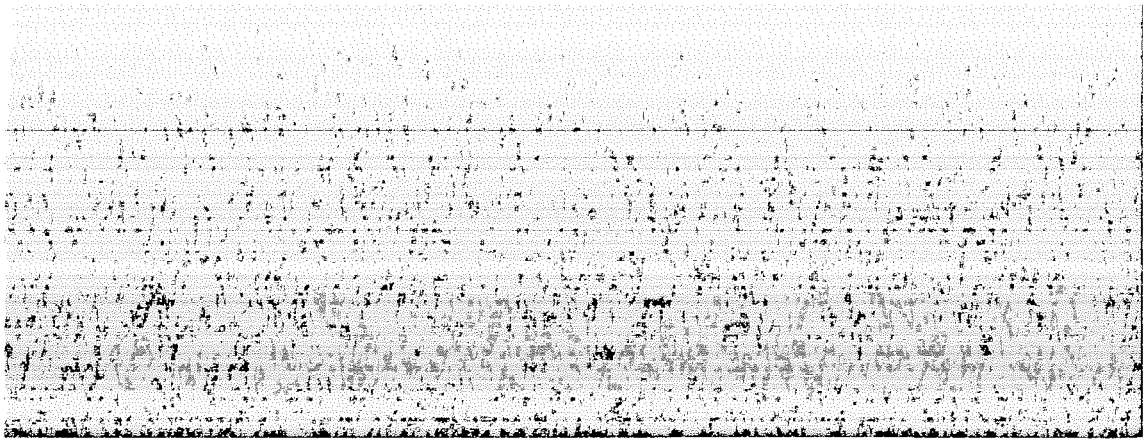
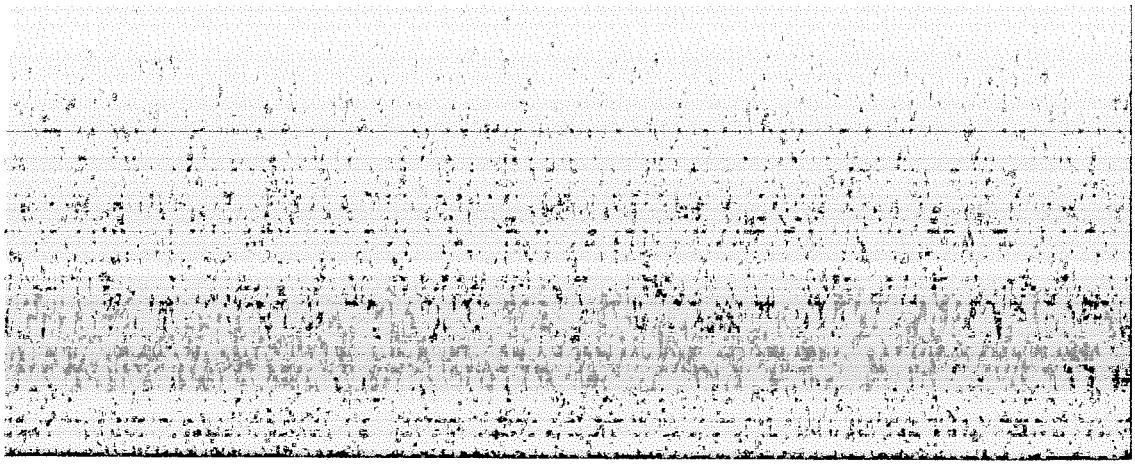




CHAPTER 10

RELATIONSHIP BETWEEN VARIOUS PERINATAL FACTORS, MORTALITY AND HANDICAP

INTRODUCTION

Two of the main objectives of the Project On Preterm and Small for gestational age infants were to determine the neonatal and postneonatal mortality rates as well as the handicap rate up to the age of two years corrected for preterm birth. Together with information collected during the perinatal and follow-up period, these outcome data might elucidate relationships between perinatal factors and outcome.

However, it is very difficult to single out the influence of one such perinatal factor. To study this influence, correction has to be made for differences in the distribution of other variables associated with the outcome. Therefore, multivariate statistical methods have to be used, such as a logistic regression analysis.

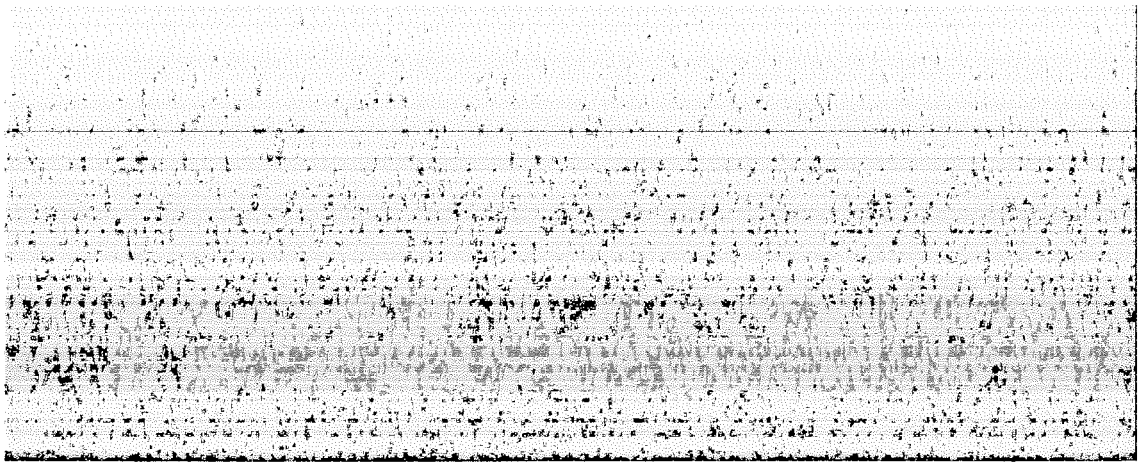
METHODOLOGY

The relationships between various perinatal factors and the sequelae of very preterm birth were studied applying logistic regression analyses.

As measures of outcome were used: "major adverse outcome" (= total deaths plus major handicaps) and "total adverse outcome" (= total deaths plus major and minor handicaps), both in liveborn infants; and "total handicaps" (= major and minor handicaps) in surviving children. The number of children with a major or with a minor handicap was too small to allow separate analyses with these outcome measures. Furthermore, allocating the children into the categories major or minor handicap may be subject to inter-observer variability in this kind of survey. Therefore, analysis of handicaps in surviving infants in relation to perinatal factors was done irrespective of severity of the handicap.

Some general remarks have to be made regarding the methodology. Each perinatal factor was considered in turn as an exposure (independent variable), with all others included as potential confounders for the outcome-exposure relationship.

As a measure of the association between any factor and an outcome, crude odds ratios (OR) were calculated. That way, a first impression was obtained of the influence of the exposure on the outcome measure. Thereafter, adjusted odds ratios and 95% confidence intervals were calculated indicating the overall effect of one perinatal factor (as exposure) while adjusting for the possible confounding effect of the other factors included in the analyses. An odds ratio



is significantly different from 1 at the 5% level if, and only if, its (exact) 95% confidence interval does not include 1. An odds ratio greater than 1 indicates a higher risk; an odds ratio smaller than 1 indicates a lower risk for the exposed infants compared to the non-exposed infants.

Because of the number of children with a handicap, the number of perinatal factors to be included in the analyses had to be limited for methodological reasons. A total of 22 factors were selected to be used in the various outcome analyses. The factors were chosen because of their generally accepted or disputed influence on handicaps. They were divided into 4 distinct categories based on a chronological order of events:

1. pre-pregnancy and pregnancy related factors
2. delivery related factors
3. factors emerging immediately after birth
4. factors related to the neonatal period

These 4 sequential time-categories were installed to avoid adjustment for any factor which could not be a confounder in the true sense.[1] Within each time-category no further sequence in time of factors can be indicated.

The following rules were maintained analysing the effect of the various exposures:

1. In order to analyse the effect of an exposure in time-category 1 (pre-pregnancy and pregnancy related factors), a logistic regression equation containing only the category 1 factors as potential confounders was fitted.
2. To analyse time-category 2 factors (delivery related factors), a logistic regression equation containing all factors from categories 1 and 2 was fitted.
3. In the third sequential category (factors emerging after birth), the factors have been analysed by fitting a logistic regression equation including all factors from time-categories 1, 2 and 3.
4. The factors in time-category 4 (related to the neonatal period) have been analysed by fitting a logistic regression equation including all perinatal factors.

The definition of each of the 22 factors used in the logistic regression analyses is shown in table 1. Apart from bilirubin, all other factors were used in the previously described analyses on mortality and neonatal morbidity.[1] Bilirubin was included because of the possible influence of the serum bilirubin level on the outcome handicap.

Perinatal factors used in previous (mortality) analyses but omitted from the present logistic regression analyses were: maternal age, parity, history of preterm birth or abortion, smoking during pregnancy, medication and intoxication, hospital admission during pregnancy, prolonged duration of ruptured membranes, chorioamnionitis, cardiotocography during pregnancy and elective delivery. Omitting them from the analyses was done because no confounding effect of these factors in the here described analyses was to be expected and restriction of the number of factors was necessary for methodological reasons.

The factors socio-economic status, fetal presentation and Apgar score had a considerable number of missing data. An extra (dummy) variable was included,

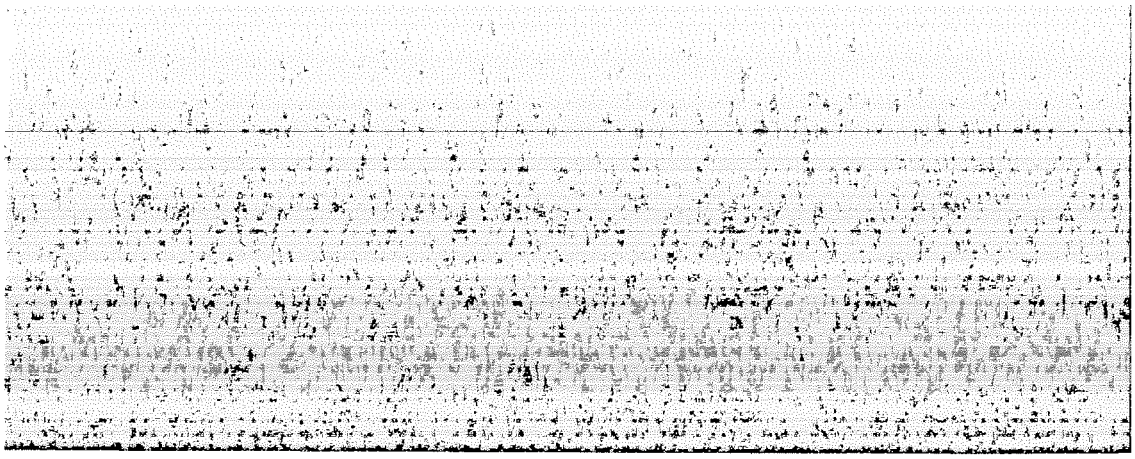
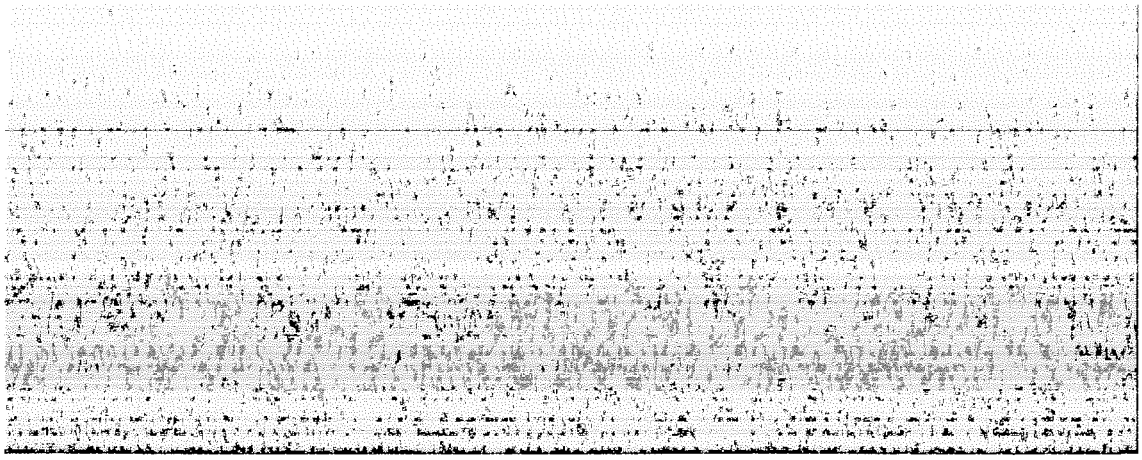


Table 1. Definition of 22 factors used in the logistic regression analyses (in chronological order of occurrence and in categories of concurrent factors)

Time-category 1		
1.	socio-economic class	1 (low) to 6 (high)[2]
2.	pre-existing maternal disease	including heart disease, epilepsy, diabetes mellitus, renal disease, hypertension (diastolic blood pressure 90 mmHg) versus none
3.	infants' sex	male versus female
4.	maternal hypertensive disorders during pregnancy	diastolic blood pressure $\geq$90 mmHg, measured at least twice versus none
5.	congenital malformation	any versus none
6.	multiple pregnancy	yes versus no
7.	antenatal transport	to a perinatal intensive care centre (level 3) versus no
8.	tocolysis	$\geq$24 h. suppression of uterine contractions versus none or <24 h.
9.	glucocorticoid administration	to the pregnant mother, yes versus no
10.	fetal presentation	breech and transverse presentation versus vertex
11.	gestational age	in days
12.	birthweight	in grams
13.	small for gestational age (SGA)	<10th percentile versus $\geq$10th percentile[3]
Time-category 2		
14.	hospital of birth:	
	level 1 (low)	level 1 versus level 3 (high)
	level 2 (intermediate)	level 2 versus level 3 (high)
15.	mode of delivery	caesarean section versus vaginal
Time-category 3		
16.	Apgar score 5 min.	<7 versus $\geq$7
Time-category 4		
17.	neonatal transport	to level 2, 3; yes versus no
18.	idiopathic respiratory distress syndrome (IRDS)	clinical diagnosis (based on extra O_2 >24 h., expiratory grunting, tachypnoea, sternal and intercostal retractions and nasal flaring) and /or typical x-ray versus none
19.	intracranial haemorrhage (ICH)	clinical diagnosis (based on rapid or saltatory deterioration, fall in haematocrit) and /or confirmation by ultrasound or computerized tomography versus none
20.	septicaemia	haematological findings (typical white blood cell count) and /or positive bloodculture versus none
21.	seizures	clinical versus none
22.	bilirubin	maximal total serum bilirubin level

indicating for each child whether or not the factor was known. By including the factors with an extra variable, "known versus unknown", all infants could be retained in the analysis. At the same time, the potential confounding effect of such a factor was accounted for as much as possible.



Due to the large number of missing data, however, no OR was calculated for the factor socio-economic status.

For the factor fetal presentation, the crude rates are shown for three groups of infants: breech or transverse, vertex and unknown. The crude and adjusted odds ratios are calculated only for the infants with known fetal presentation.

For the factor Apgar score at 5 minutes, the crude rates are shown for three groups of infants; Apgar score <7, Apgar score $\geqslant 7$, and Apgar score unknown. The crude and adjusted odds ratios are calculated only for the infants with known Apgar score.

In the analyses on liveborn infants no odds ratios were calculated for gestational age, birthweight and small for gestational age (SGA). This was too complicated because these factors were included not only linearly in the model, but also as products and squares. In the analysis on surviving children odds ratios were calculated for gestational age (per week of gestational age), birthweight (per 100 g birthweight) and for small for gestational age (without adjusting for birthweight); here the factors were only included as linear terms, because the number of factors in the model had to be kept to a minimum.

Tests for interaction were performed for those factors where interaction had been shown to be present in the mortality analyses.[1] Practical considerations precluded extensive search for other interactions.

RESULTS

The adjusted odds ratios (OR) and 95% confidence intervals associated with the various perinatal factors used in the logistic regression analyses are summarized in two tables. Table 2 presents the analyses with the outcome measures: "major adverse outcome" and "total adverse outcome", and table 3 the analyses with the outcome measure: "total handicaps in survivors".

Some of the perinatal factors and their relationships with the various outcome measures have been described in the previous chapters. They are included in the tables for completeness sake, but will not be discussed here further. These factors were: maternal hypertensive disorders (chapter 3), infants' sex (chapter 4), seizures (chapter 6) and bilirubin (chapter 7).

A description of the other perinatal factors used as an exposure in the analyses is given in the remainder of this chapter (tables 4-21). For each exposure separately, the in-hospital mortality is shown together with the major and total adverse outcome in liveborn infants and total handicaps in surviving children. Neonatal mortality is shown only if necessary to elucidate the various outcomes. The numbers of children used in the tables may be lower than those mentioned in the text, because in performing an analysis cases with missing data on the adverse outcome or on any of the factors in a model (if not included as a separate category) were omitted.

Next to the crude and adjusted odds ratios, the 95% confidence intervals are presented. Extreme care has to be taken in the interpretation of the (non-)-

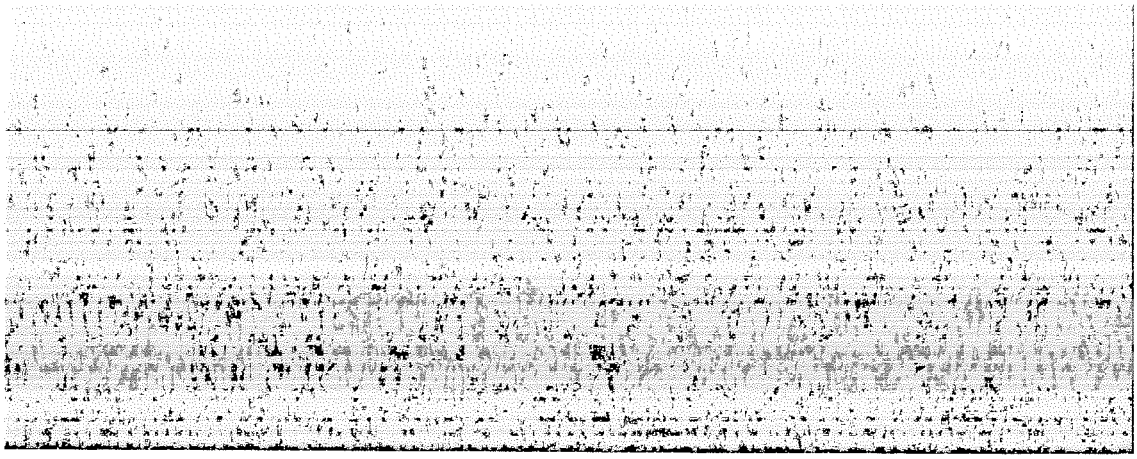


Table 2. Adjusted odds ratios (OR) and 95% confidence intervals (CI) for major adverse outcome (= total deaths plus major handicaps) and total adverse outcome (= total deaths plus major and minor handicaps) in liveborn infants

		major adverse outcome		total adverse outcome	
		OR	CI	OR	CI
Time-category 1					
1.	socio-economic class	-	-	-	-
2.	pre-existing mat. disease	1.26	[0.67-1.95] n.s.	1.95	[1.13-3.37]**
3.	infants' sex	1.59	[1.18-2.13]**	1.54	[1.18-2.01]**
4.	maternal hypertension	0.51	[0.33-0.79]**	0.56	[0.38-0.81]**
5.	congenital malformation	3.14	[2.05-4.81]**	3.56	[2.36-5.38]**
6.	multiple pregnancy	1.73	[1.24-2.40]**	1.28	[0.94-1.74] n.s.
7.	antenatal transport	0.93	[0.65-1.34] n.s.	1.08	[0.77-1.52] n.s.
8.	tocolysis	0.93	[0.68-1.28] n.s.	0.96	[0.72-1.29] n.s.
9.	glucocorticoid administration	0.67	[0.44-1.04] n.s.	0.80	[0.54-1.17] n.s.
10.	fetal presentation	1.04	[0.76-1.42] n.s.	1.09	[0.82-1.45] n.s.
11.	gestational age	-	-	-	-
12.	birthweight	-	-	-	-
13.	SGA	-	-	-	-
Time-category 2					
14.	hospital of birth: level 1	1.70	[1.12-2.58]**	1.63	[1.11-2.06]**
	level 2	1.48	[0.95-2.30] n.s.	1.23	[0.83-1.84] n.s.
15.	mode of delivery	0.89	[0.62-1.29] n.s.	1.16	[0.84-1.61] n.s.
Time-category 3					
16.	Apgar score 5 minutes	3.90	[2.71-5.60]**	3.64	[2.56-5.19]**
Time-category 4					
17.	neonatal transport	0.76	[0.49-1.16] n.s.	0.96	[0.66-1.40] n.s.
18.	IRDS	1.53	[1.09-2.15]**	1.52	[1.12-2.06]**
19.	ICH	2.53	[1.75-3.66]**	1.97	[1.40-2.77]**
20.	septicaemia	0.96	[0.69-1.34] n.s.	0.95	[0.71-1.28] n.s.
21.	seizures	5.05	[2.62-9.73]**	3.29	[1.73-6.26]**

** $p < 0.05$

significance of the OR associated with the outcome measures: "major adverse outcome" and "total adverse outcome". A non-significant OR for one of these two outcome measures should never be interpreted as if there would be no difference between the exposed and non-exposed groups with respect to the risk on either death ór a major (ór a minor) handicap. It only means that if we combine various outcomes such as death, major and minor handicap to a composite outcome measure, the two groups can not be statistically distinguished with respect to their respective risks on that composite outcome. A non-significant

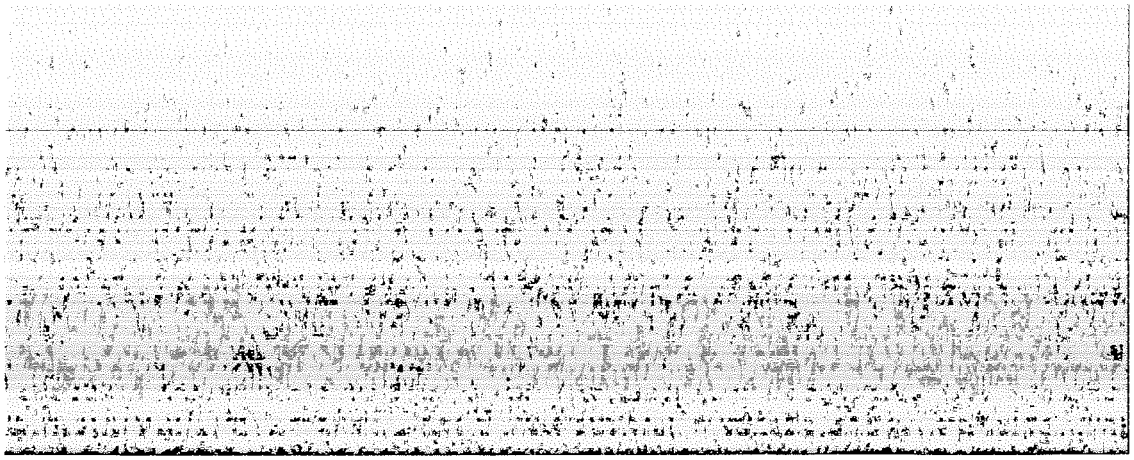


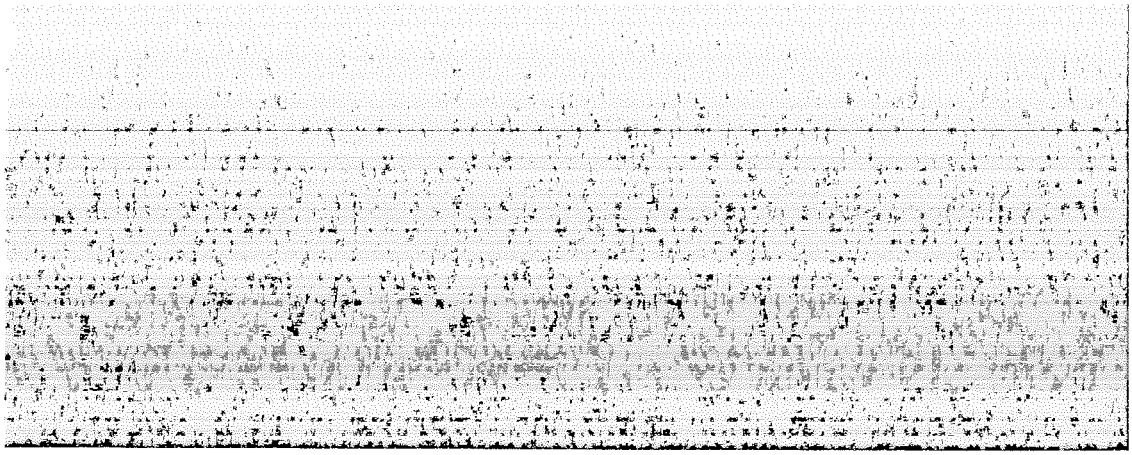
Table 3. Adjusted odds ratios (OR) and 95% confidence intervals (CI) for total handicaps (= major and minor handicaps) in surviving children

	total handicaps	
	OR	CI
Time-category 1		
1. socio-economic class	-	-
2. pre-existing mat. disease	2.54	[1.32-4.88]**
3. infants' sex	1.68	[1.17-2.42]**
4. maternal hypertension	0.74	[0.46-1.21] n.s.
5. congenital malformation	3.23	[1.91-5.46]**
6. multiple pregnancy	0.91	[0.58-1.42] n.s.
7. antenatal transport	1.70	[1.09-2.67]**
8. tocolysis	1.16	[0.77-1.75] n.s.
9. glucocorticoid administration	1.10	[0.67-1.79] n.s.
10. fetal presentation	0.93	[0.62-1.40] n.s.
11. gestational age	0.97	[0.86-1.08] n.s
12. birthweight	0.98	[0.90-1.08] n.s.
13. SGA	1.06	[0.65-1.73] n.s.*
Time-category 2		
14. hospital of birth: level 1	1.58	[0.94-2.65] n.s.
level 2	0.88	[0.49-1.57] n.s
15. mode of delivery	1.52	[0.99-2.35] n.s.
Time-category 3		
16. Apgar score 5 minutes	2.04	[1.23-3.37]**
Time-category 4		
17. neonatal transport	1.26	[0.75-2.13] n.s.
18. IRDS	1.03	[0.68-1.56] n.s.
19. ICH	1.37	[0.84-2.23] n.s.
20. septicaemia	1.10	[0.74-1.64] n.s.
21. seizures	2.89	[1.24-6.76]**
22. bilirubin (per 50 μmol /L)	1.33	[1.07-1.66]**

*adjusted for the potential confounding effect of all other factors from time-category 1 except birthweight

**$p < 0.05$

difference e.g. for the outcome measure "major adverse outcome" simply states that the total number of infants either dead or severely handicapped does not differ statistically in the two groups; this does not preclude that both the number of deaths and the number of handicapped children do differ significantly or at least appreciably. In turn this can be interpreted as follows: the difference between the two groups with respect to the chance of "staying alive without a major handicap", can be explained by chance fluctuations alone.



To prevent any misinterpretation (regarding to the tables 2, 4-21), the reader is strongly urged to keep the following in mind:

The odds ratio (OR) associated with the outcome:	measures the difference between the two groups with respect to the chance of:
neonatal mortality	staying alive after the neonatal period
in-hospital mortality	staying alive after the initial hospital stay
death plus major handicap ("major adverse outcome")	staying alive without a major handicap
death plus major and minor handicap ("total adverse outcome")	staying alive without any handicap
total handicaps	after surviving, being without any handicap

Pre-existing maternal disease

From the 86 infants born to mothers with pre-existing maternal disease 20 died, 4 developed a major and 13 a minor handicap; in the group of 1252 infants born to mothers without a pre-existing disease these numbers were 349, 55 and 98 respectively.

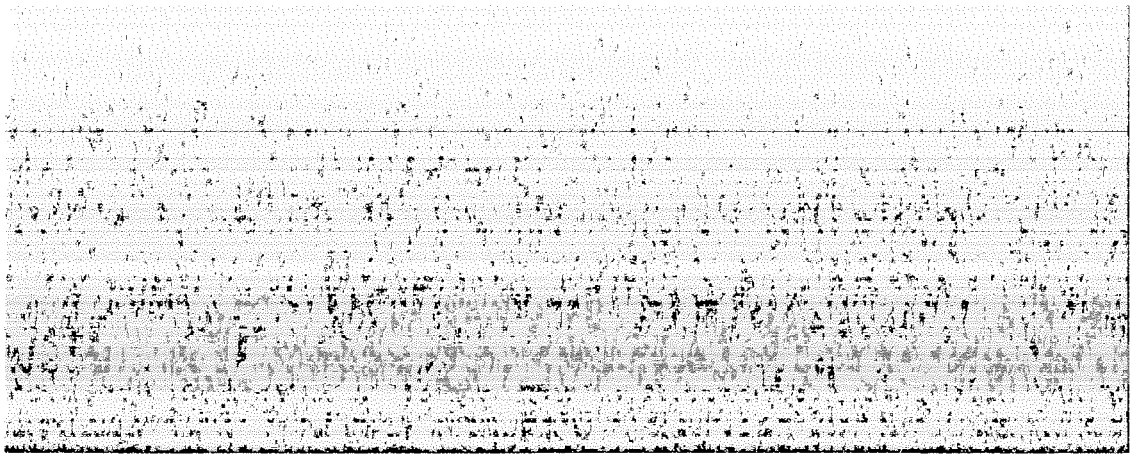
The crude rates and crude odds ratios of the various outcomes in liveborn infants (table 4) reveal similar risks on an adverse outcome in the two groups.

After adjusting for the other perinatal factors in time-category 1, however, there is a significantly higher odds on neonatal mortality for the exposed versus

Table 4. Crude rates, crude odds ratios, and adjusted odds ratios for exposure: pre-existing maternal disease

outcome	crude rates pre-existing mat.dis. present n	%	absent n	%	crude OR	adjusted OR* and 95% CI	
neonatal mortality	20/86	23.3	292/1252	23.3	1.00	2.55	[1.22-5.34]**
in-hospital mortality	20/86	23.3	320/1252	25.6	0.88	1.83	[0.88-3.82]n.s.
death plus major handicap	24/82	29.3	404/1231	32.8	0.85	1.26	[0.67-2.37]n.s.
death plus major and minor handicap	37/82	45.1	502/1231	40.8	1.19	1.95	[1.13-3.37]**
total handicaps in survivors	17/62	27.4	153/ 882	17.3	1.80	2.54	[1.32-4.88]**

* adjusted for the potential confounding effect of all other factors from time-category 1
** $p < 0.05$



the non-exposed infants. The odds on an adverse outcome diminishes after including the post neonatal deaths and major handicaps in the outcome measures. In the adjusted odds ratio on total adverse outcome the influence of the frequent occurrence of minor handicaps in the exposed group is reflected.

In the surviving children a higher risk to develop a handicap is present, as expressed in the higher crude rate and odds ratio. The adjusted odds ratio is significantly higher as well.

The difference in crude and adjusted odds ratios for all outcome measures is due to the fact that the infants born to mothers with pre-existing diseases belong mostly to higher gestational age groups.[1] The mean gestational age in infants with and without pre-existing maternal disease is 31.0 and 30.2 weeks respectively. Thus, although the crude odds ratio for neonatal mortality is 1, after adjusting for factors such as gestational age a significantly higher risk emerges for the exposed infants.

These results show that in our population the presence of a pre-existing maternal disease not only contributes significantly to the risk on neonatal mortality, but in the surviving children also to the risk to develop a handicap.

Congenital malformation

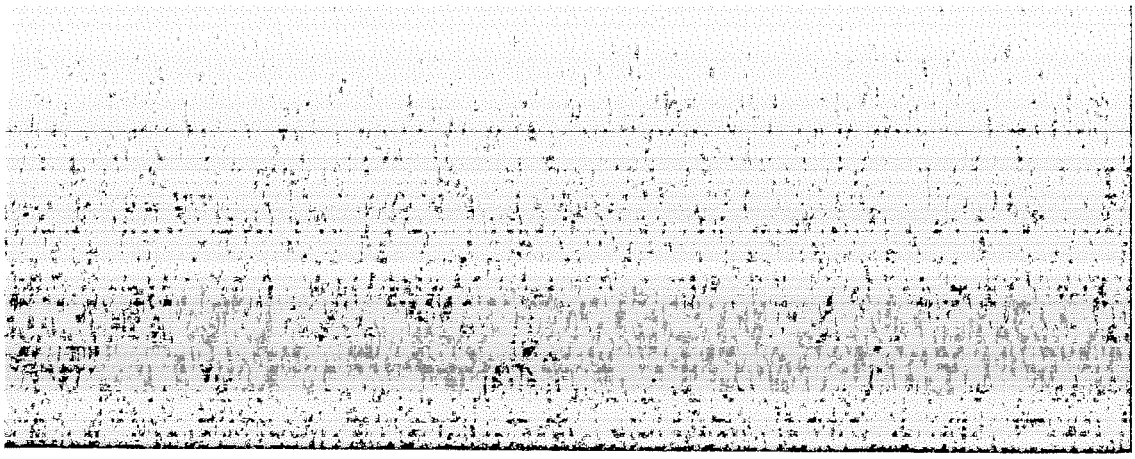
From the 1338 infants originally enrolled in the survey 146 had a congenital malformation: 28 were considered lethal, a total of 61 died, 12 developed a major and 18 a minor handicap; in the group of 1192 infants without a congenital malformation these numbers were 308, 47, and 93 respectively.

As shown in the crude rates and crude odds ratios (table 5a) the infants with

Table 5a. Crude rates, crude odds ratios, and adjusted odds ratios for exposure: congenital malformation

outcome	crude rates congenital malformation				crude OR	adjusted OR* and 95% CI	
	malformed		normal				
	n	%	n	%			
in-hospital mortality	53/146	36.3	287/1192	24.1	1.80	2.20	[1.3- 3.6]**
death plus major handicap	73/146	50.0	355/1167	30.4	2.29	3.14	[2.05-4.81]**
death plus major and minor handicap	91/146	62.3	448/1167	38.4	2.65	3.56	[2.36-5.38]**
total handicaps in survivors	30/ 85	35.3	140/ 859	16.3	2.80	3.23	[1.91-5.46]**

* adjusted for the potential confounding effect of all other factors from time-category 1
** $p < 0.05$



a congenital malformation have a greater risk to die or to develop a handicap; in the surviving children the crude handicap rate is twice as high as in the children without a congenital malformation. After adjusting for other factors in time-category 1 a significantly higher odds for mortality as well as handicap was found also in the malformed group.

As described previously,[1] testing for interaction revealed a significant (1%-level) modification of the effect of congenital malformation on mortality by the factor gestational age. In the higher gestational age categories, infants with congenital malformations have a higher mortality risk than infants without. In the lower gestational age categories the opposite is found: infants with congenital malformations have a lower mortality risk than normal infants. This is to be expected because as a result of the entry criteria of our study, lethal congenital malformations associated with small for gestational age were more frequent in the higher gestational age categories. This same interaction is found for the outcome measures major and total adverse outcome. Some examples of adjusted odds ratios for different gestational age categories are shown in table 5b. In the surviving children testing for interaction shows no effect modification by gestational age.

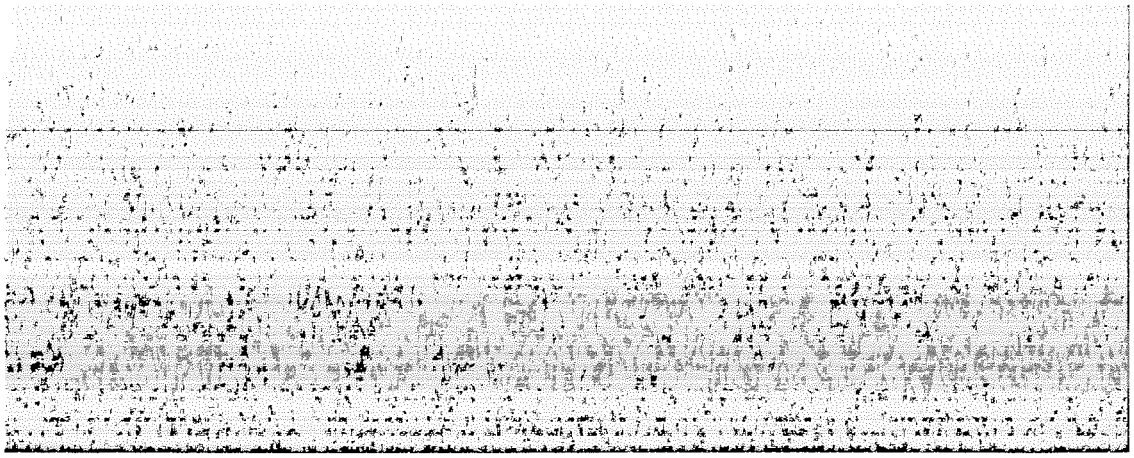
Table 5b. Adjusted odds ratios for congenital malformation by gestational age

major adverse outcome	adjusted OR*	total adverse outcome	adjusted OR*
death plus major handicap	3.14	death plus major and minor handicap	3.56
gestational age (weeks)		gestational age (weeks)	
26	0.6	26	1.1
28	1.2	28	1.8
30	2.4	30	2.8
32	4.9	32	4.5

* adjusted for the potential confounding effect of all other factors from time-category 1

In 50% (15 /30) of the children, the congenital malformation is the main cause of the handicap; the other children have a handicap in addition to their congenital malformation.

A more thorough study of the infants with a congenital malformation in this study population is currently undertaken at the Clinical Genetics Centre, Leiden University Hospital.



Multiple pregnancy

From the 312 infants born as a result of a multiple pregnancy 111 died, 16 developed a major and 18 a minor handicap; for the 1026 infants born singleton these numbers were 258, 43 and 93 respectively.

The risk to die is significantly higher for infants born as a result of a multiple pregnancy than for infants born as a singleton (table 6).

Table 6. Crude rates, crude odds ratios, and adjusted odds ratios for exposure: multiple pregnancy

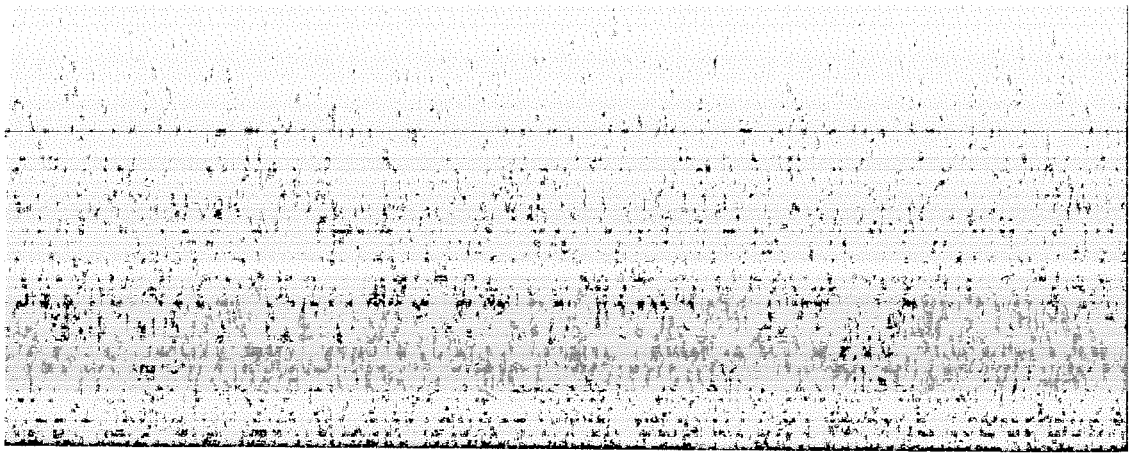
outcome	crude rates multiple pregnancy				crude OR	adjusted OR* and 95% CI	
	multiple		singleton				
	n	%	n	%			
in-hospital mortality	103/312	33.0	237/1026	23.1	1.64	1.83	[1.23-2.73]**
death plus major handicap	127/310	40.1	301/1003	30.0	1.62	1.73	[1.24-2.40]**
death plus major and minor handicap	145/310	46.8	394/1003	39.3	1.36	1.28	[0.94-1.74]n.s.
total handicaps in	34/199	17.1	136/ 745	18.2	0.92	0.91	[0.58-1.42]n.s.

* adjusted for the potential confounding effect of all other factors from time-category 1
** $p < 0.05$

In the crude OR this might be attributed to the difference in gestational age in the two groups: the median gestational age in multiple births is one week shorter than in singletons, causing a significantly higher neonatal and in-hospital mortality risk[1]. However, in the adjusted OR, with correction for differences in gestational age, still a significantly higher odds for multiple births is present. This may be partly explained by the increased risk of IRDS in infants of multiple pregnancy. In the adjusted OR for major adverse outcome the strong influence of multiple pregnancy on mortality is still shown. This influence has faded after including the occurrence of minor handicaps in the total adverse outcome.

In surviving children no difference is found in the crude rates, crude odds ratio and adjusted odds ratio between those born from a multiple pregnancy and singletons. Thus, multiple pregnancy does not contribute to the risk on a handicap in the surviving children.

The relationship of multiple pregnancy with an adverse outcome seems to be restricted to mortality as reflected in the described adverse outcomes in liveborn infants.



Antenatal transport

From the 245 infants born after antenatal transport to a level 3 hospital, 77 died, 14 developed a major and 22 a minor handicap; for the 1093 infants in the non-transported group these numbers were 292, 45 and 89 respectively.

The crude rates and crude odds ratios suggest an increased number of deaths and handicapped children after maternal transport (table 7). The adjusted odds ratios, however, show on the one hand a significantly lower mortality risk and on the other hand a significantly higher handicap risk in the survivors.

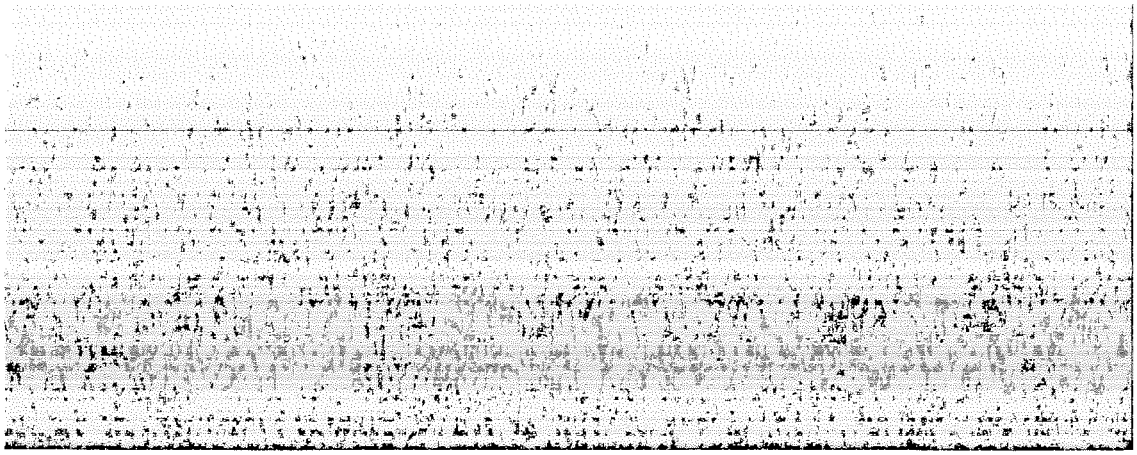
Table 7. Crude rates, crude odds ratios, and adjusted odds ratios for exposure: antenatal transport

outcome	crude rates antenatal transport present n	%	absent n	%	crude OR		adjusted OR* and 95% CI
neonatal mortality	63/245	25.7	249/1093	22.8	1.17	0.60	[0.39-0.94]**
in-hospital mortality	72/245	29.4	268/1093	24.5	1.28	0.68	[0.44-1.04]**
death plus major handicap	91/238	38.2	337/1075	31.3	1.35	0.93	[0.65-1.34]n.s.
death plus major and minor handicap	113/238	47.5	426/1075	39.6	1.38	1.08	[0.77-1.52]n.s.
total handicaps in survivors	35/161	22.4	134/ 783	17.1	1.39	1.70	[1.09-2.67]**

* adjusted for the potential confounding effect of all other factors from time-category 1
** $p < 0.05$

The decision to effectuate antenatal transport is influenced by many factors, such as capacity in tertiary centres, parents' preference and the character of maternal as well as infant's pathology. The limited capacity in tertiary centres causes careful selection of cases for maternal transport. This is reflected in the fact that in the antenatally transported infants the gestational age was one week less and the mean birthweight was 100 g less than in the non-transported infants. After adjusting for various confounding factors such as gestational and birthweight, the significantly lower mortality risk for antenatally transported infants appears.

A significantly higher risk on a handicap is found in children surviving after antenatal transport. Considerations leading to the decision of antenatal transport of the pregnant mother and resulting in a significantly better survival chance of the infants, at the same time bring about a significantly higher handicap odds. In these considerations various hard to define factors may be involved, causing selection bias.



This complex problem of antenatal transport and outcome, as far as mortality is concerned, was analysed in a separate part of the "Project", where the problem of selection bias has at least partially been solved.[4,5] Further analysis of antenatal transport and handicap is in progress.

Tocolysis

From the 591 infants born to mothers with tocolytic drug therapy for more than 24 hours, 167 died, 30 developed a major and 53 a minor handicap. In the 747 infants born to non-treated mothers these numbers were 202, 29 and 58 respectively.

No different crude rates, crude odds ratios or adjusted odds ratios for the 4 outcome measures are found in the two groups (table 8).

The objective of tocolysis is to increase gestational age, and thereby increasing the infant's chance of survival. Adjusting for perinatal factors such as gestational age shows that tocolytic drug treatment itself has no effect on the risk on the adverse outcomes described here.

Table 8. Crude rates, crude odds ratios, and adjusted odds ratios for exposure: tocolysis

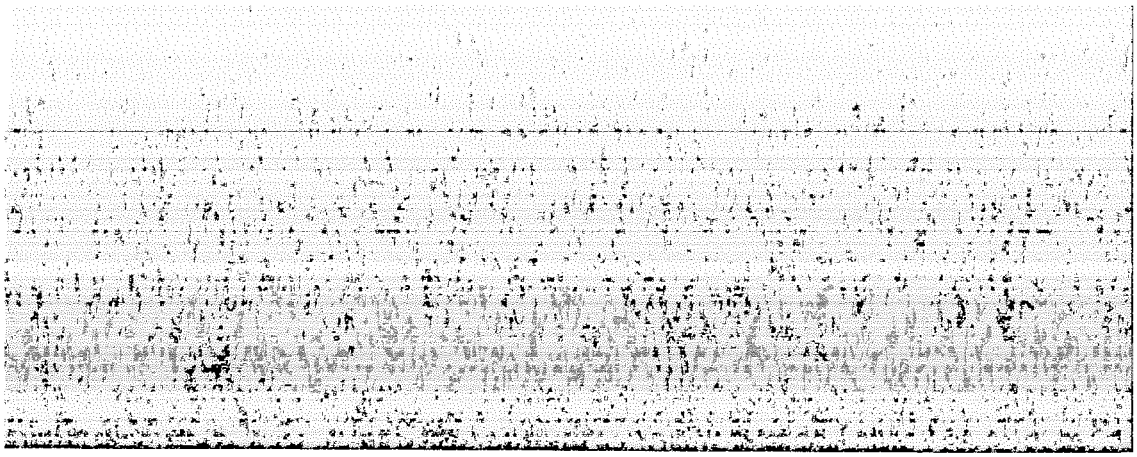
outcome	crude rates tocolysis present n	%	absent n	%	crude OR	adjusted OR* and 95% CI	
in-hospital mortality	155/591	26.2	185/747	24.8	1.08	1.02	[0.67-1.5]n.s.
death plus major handicap	197/578	34.1	231/735	31.4	1.12	0.93	[0.68-1.28]n.s.
death plus major and minor handicap	250/578	43.2	289/735	39.3	1.18	0.96	[0.72-1.29]n.s.
total handicaps in survivors	83/411	20.2	87/533	16.3	1.30	1.16	[0.77-1.75]n.s.

* adjusted for the potential confounding effect of all other factors from time-category 1

Administration of glucocorticoids

From the 190 infants born to mothers after the administration of glucocorticoids 38 died, 13 developed a major and 20 a minor handicap; for the 1143 infants in the non-exposed group these numbers are 328, 46 and 91 respectively.

Glucocorticoids are administered to the mother to accelerate fetal lung maturation, a procedure associated with a significantly lower in-hospital mortality risk.[1] A lower risk on a major and total adverse outcome is shown in the crude



rates and odds ratios of these outcome measures as well (table 9). These odds ratios, however, are greatly influenced by the significantly lower mortality odds for the exposed infants. This influence diminishes after including the occurrence of major and afterwards minor handicaps in the outcome: the odds ratios come closer to 1. From the adjusted odds ratio on the adverse outcome in surviving children is clear that glucocorticoid administration has no effect on the development of handicaps in the surviving children.

Nonetheless, considering the discussion regarding the use of glucocorticoids and the fear for long term ill-effects on the infants,[6] further follow-up of this group of children remains advisable.

Table 9. Crude rates, crude odds ratios, and adjusted odds ratios for exposure: administration of glucocorticoids

outcome	crude rates glucocorticoids present		absent		crude OR		adjusted OR* and 95% CI
	n	%	n	%			
in-hospital mortality	34/190	17.9	303/1143	26.5	0.60	0.49	[0.29-0.83]**
death plus major handicap	51/188	27.1	374/1120	33.4	0.74	0.67	[0.44-1.04]n.s.
death plus major and minor handicap	71/188	37.8	465/1120	41.5	0.85	0.80	[0.54-1.17]n.s.
total handicaps in survivors	33/150	22.0	137/ 792	17.3	1.35	1.10	[0.67-1.79]n.s.

* adjusted for the potential confounding effect of all other factors from time-category 1
** $p < 0.05$

Fetal presentation

From the 921 infants in vertex presentation 239 died, 45 developed a major and 75 a minor handicap. In the group of 362 infants in non-vertex presentation these numbers were 120, 12 and 33 respectively. In the group of 55 infants where fetal presentation was unknown, 10 infants died, 2 had a major and 3 a minor handicap.

The crude rates and odds ratios show a higher mortality risk for infants born in non-vertex presentation (table 10). This is confirmed in the significantly higher adjusted neonatal mortality odds for infants born in non-vertex than for infants born in vertex presentation.

This higher mortality odds influences to some extent also the other adverse outcomes in liveborn infants. The results of the handicap analyses on surviving infants, however, show a similar risk on an adverse outcome in both groups.

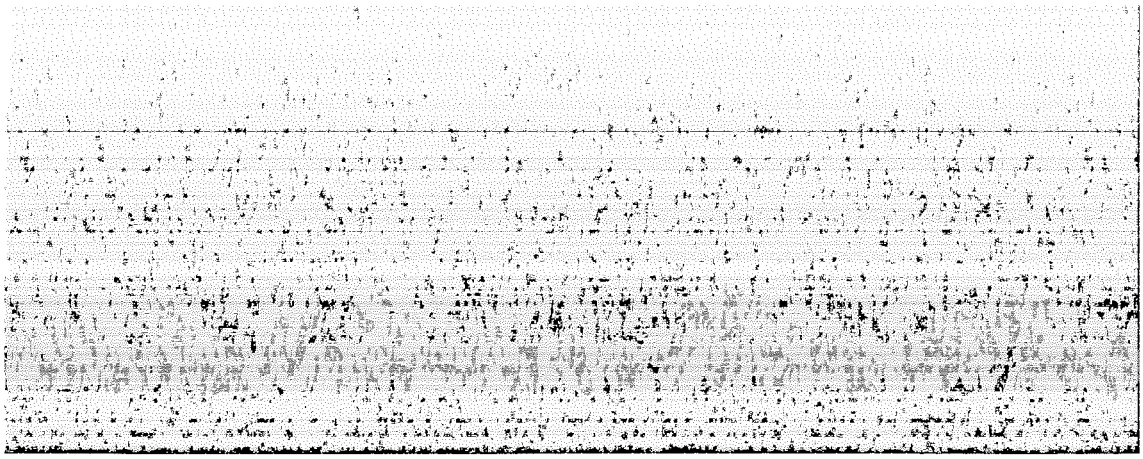


Table 10. Crude rates, crude odds ratios, and adjusted odds ratios for exposure: fetal presentation

outcome	crude rates fetal presentation breech and transverse		vertex		crude OR	adjusted OR* and 95% CI	
	n	%	n	%			
neonatal mortality	107/362	29.6	198/921	21.5	1.53	1.57	[1.09-2.26]**
in-hospital mortality	112/362	30.9	216/921	23.4	1.46	1.38	[0.96-1.97]n.s.
death plus major handicap	132/362	36.5	284/909	31.2	1.26	1.04	[0.76-1.42]n.s.
death plus major and minor handicap	165/362	45.6	359/909	39.3	1.28	1.09	[0.82-1.45]n.s.
total handicaps in survivors	45/242	18.6	120/670	17.9	1.05	0.93	[0.62-1.40]n.s.

* adjusted for the potential confounding effect of all other factors from time-category 1
** $p < 0.05$

Because fetal presentation is closely related to the mode of delivery, adjusted odds ratios were calculated according to mode of delivery. The mortality odds for fetal presentation were significantly higher in vaginal deliveries, comparing non-vertex and vertex presentation, but similar in caesarean sections.[1] In the analyses on major and total adverse outcome and total handicaps no odds ratios significantly different from 1 by mode of delivery were found.

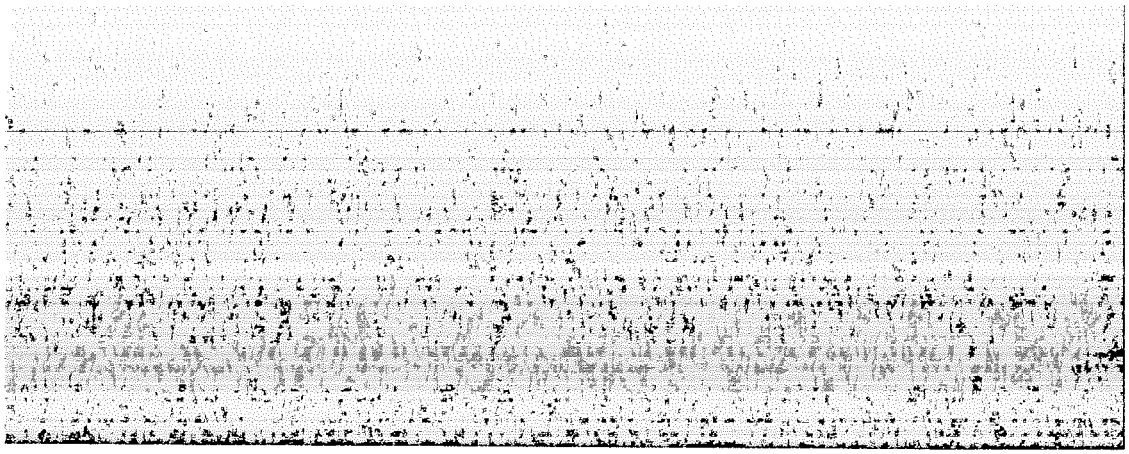
Gestational age and birthweight

The importance of gestational age and birthweight in relation to mortality in this study poplation has been described elsewhere.[7] Gestational age as well as birthweight were inversely associated with mortality.

In the outcome analyses on liveborn infants gestational age and birthweight are only included as potential confounders.

In the analysis on total handicaps in surviving children, gestational age and birthweight are included as linear terms only. An adjusted odds ratio is calculated per additional week of gestational age or additional 100 gram birthweight, as shown in table 11. With this analysis no systematically increasing or decreasing relationship between an adverse outcome in the survivors and gestational age or birthweight emerged.

The numbers and percentages of surviving, assessed and handicapped children for each gestational age category is shown in table 12, and for each birthweight category in table 13.



The handicap rates calculated per gestational age and birthweight category do not show a systematic relationship between these two factors and an adverse outcome either.

Table 11. Adjusted odds ratios for the exposures gestational age and birthweight

outcome: total handicaps in survivors	adjusted OR* and 95% CI	
exposure:		
gestational age (per additional week)	0.97	[0.86-1.08]
birthweight (per additional 100 g)	0.98	[0.90-1.08]

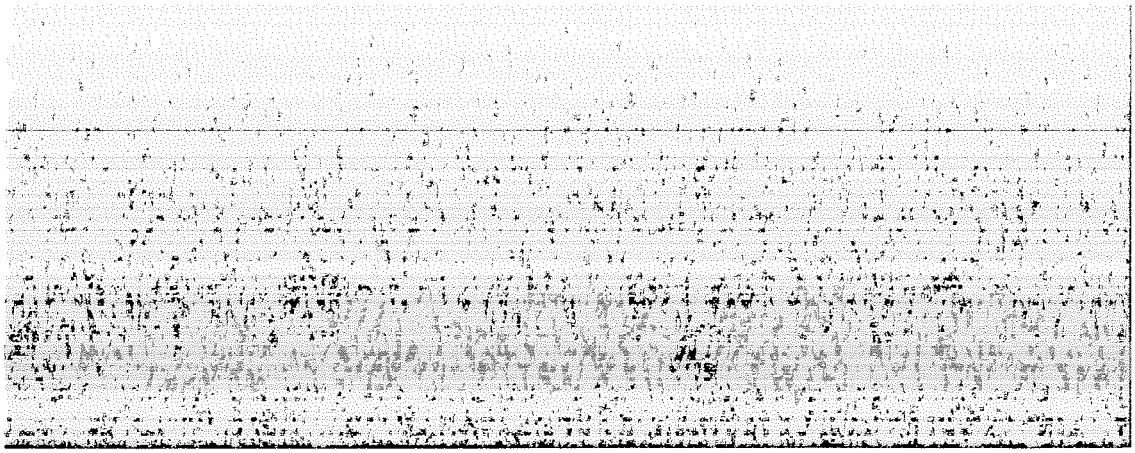
* adjusted for the potential confounding effect of all other factors from time-category 1

Table 12. Number of surviving, assessed and handicapped children in the various gestational age categories (weeks)

gestational age (weeks)	surviving children n	children assessed n	major and minor handicap n	(%)
25	5	4	3	
26	28	27	4	(14.8)
27	56	52	10	(19.2)
28	88	86	21	(24.4)
29	130	126	29	(23.0)
30	159	155	24	(15.5)
31	212	206	32	(15.5)
⩾32	289	286	47	(16.4)
unknown	2	2		
total	969	944	170	(18.0)

Table 13. Number of surviving, assessed and handicapped children in the various birthweight categories (100 g)

birthweight (weeks)	surviving children n	children assessed n	major and minor handicap n	(%)
500	1	1	0	
600	11	11	4	(36.4)
700	16	15	2	(13.3)
800	36	34	7	(20.6)
900	66	64	10	(15.6)
1000	80	79	16	(20.3)
1100	105	102	14	(13.7)
1200	116	116	21	(18.1)
1300	160	153	32	(20.9)
1400	179	176	31	(17.6)
⩾1500	199	193	33	(17.1)
total	969	944	170	(18.0)



Small for gestational age

All infants were categorized as small for gestational age (SGA) or appropriate /large for gestational age (AGA /LGA) in accordance with the Amsterdam growth charts.[3] Infants with a birthweight below the 10th percentile were considered small for gestational age.

From the 454 SGA infants 91 died, 27 developed a major and 35 a minor handicap. From the 851 infants in the AGA /LGA group these numbers were 247, 32 and 76 respectively.

The crude rates (table 14), show a lower risk on an adverse outcome in the liveborn SGA infants in comparison with the AGA /LGA infants.

Small for gestational age infants surviving the neonatal period have similar crude risks to develop a handicap as AGA /LGA infants.

In view of the way birthweight was incorporated in the logistic model for mortality and adverse outcome in liveborn infants, it is very difficult to attach a meaning to the estimated adjusted OR's of SGA in these cases. We therefore refrain from stating these OR's.

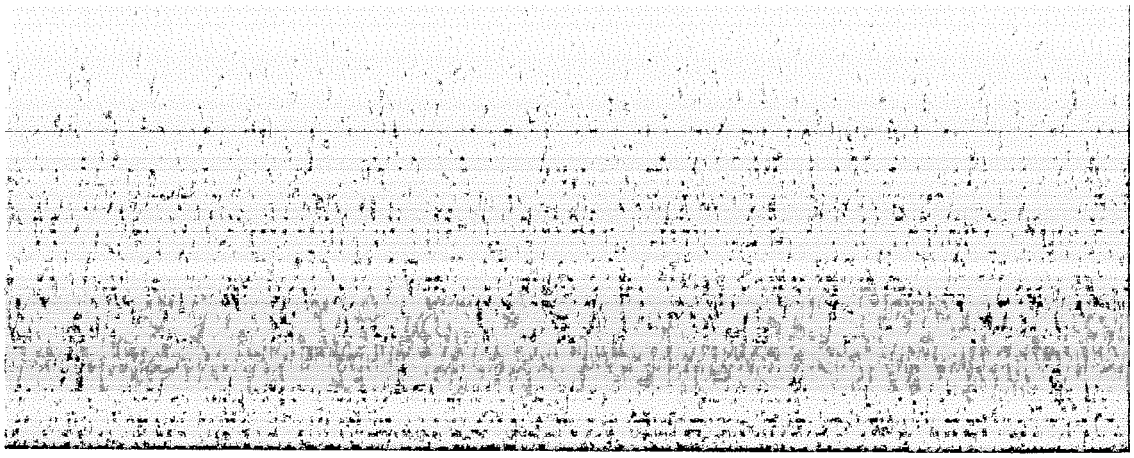
In children surviving the neonatal period the model used was simpler. This enabled us to interpret the OR of SGA in a meaningful way after adjustment for all factors from time-category 1 except for birthweight. Hence for any specific gestational age no effect of SGA can be demonstrated in these infants, which is in accordance to our finding that birthweight itself was not significantly associated with the outcome in surviving children.

Table 14. Crude rates, crude odds ratios, and adjusted odds ratios for exposure: small for gestational age

outcome	crude rates				crude OR	adjusted OR* and 95% CI	
	SGA		AGA /LGA				
	n	%	n	%			
in-hospital mortality	82 /454	18.1	227 /851	26.7	0.61	-	-
death plus major handicap	118 /450	26.2	279 /831	33.6	0.70	-	-
death plus major and minor handicap	153 /450	34.0	355 /531	42.7	0.70	-	-
total handicaps in survivors	62 /359	17.2	108 /584	18.5	0.92	1.06	[0.65-1.73]n.s.

* adjusted for the potential confounding effect of all other factors from time-category 1 except for birthweight

** $p < 0.05$



Hospital level of care

All 133 hospitals where study infants have been born were classified into one of three levels of care according to a scoring system. Based on the scoring system by Paneth et al[8] our own scoring system was devised.

The items scored included staffing, specialization of medical and nursing staff, teaching qualification (obstetrics/gynaecology and paediatrics) and round-the-clock availability of medical staff of both the obstetric and the neonatal department, as well as the measure of cooperation between these departments (e.g. regular staff meetings about high risk cases, perinatal conferences, formal and informal consultations). Moreover, the equipment of the neonatal unit and the standard policies and procedures regarding delivery and management immediately after birth of high risk infants were included in the scoring system.[9]

From the 498 infants born in a level 1 hospital 134 died, 27 developed a major and 45 a minor handicap. In the group of 359 infants born in a level 2 hospital these numbers were 96, 10 and 24 respectively. From the 481 infants born in a level 3 hospital 139 died and 22 and 42 had a major or minor handicap respectively.

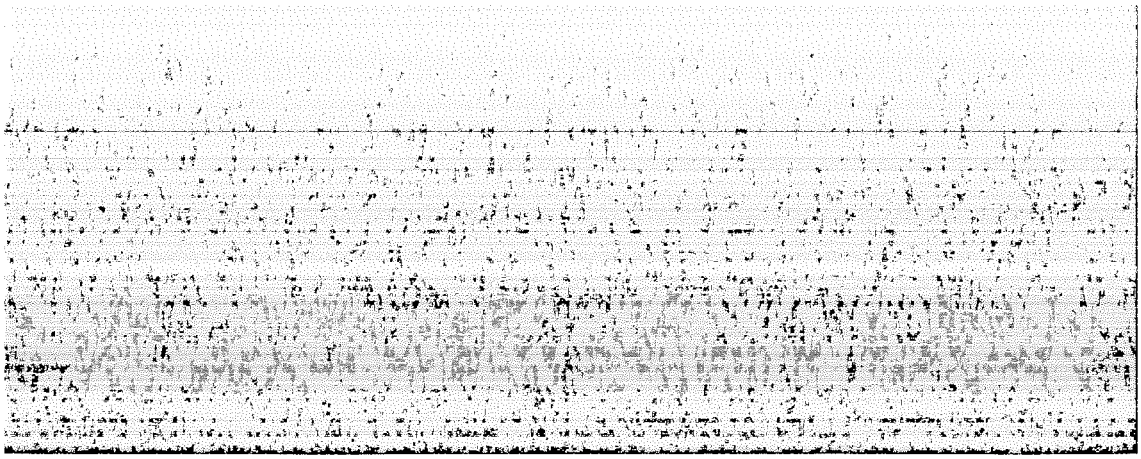
The crude rates and crude odds ratios for infants liveborn in a level 1 hospital versus infants born in level 3 hospitals are similar (table 15a), indicating a similar crude risk to die or to develop a handicap.

Table 15a. Crude rates, crude odds ratios, and adjusted odds ratios for exposure: hospital of birth, level of care (level 1 versus level 3)

outcome	crude rates				crude OR	adjusted OR* and 95% CI	
	level 1		level 3				
	n	%	n	%			
in-hospital mortality	129/498	25.9	127/481	26.4	0.97	1.80	[1.09-2.95]**
death plus major handicap	161/486	33.1	161/427	34.1	0.82	1.70	[1.12-2.58]**
death plus major and minor handicap	206/486	42.4	203/472	43.0	0.97	1.63	[1.11-2.37]**
total handicaps in survivors	72/352	20.5	64/333	19.2	1.08	1.58	[0.94-2.65]n.s.

* adjusted for the potential confounding effect of all other factors from time-category 1 and 2
** $p < 0.05$

After adjusting for the other factors in time-category 1 and 2 the odds ratio for in-hospital mortality is significantly higher for the infants born in a level 1 hospital. This shift in odds ratio from similar crude odds to a significantly higher adjusted odds ratio is mainly caused by the confounding effect of gestational age on the crude OR in the various groups of infants. The mean gestational



age of infants born in a level 1 hospital is 30.6 weeks, while this is 29.6 weeks for infants born in a level 3 hospital.

The significantly higher mortality odds are also reflected in the higher major and total adverse outcome odds ratios.

Comparing the adverse outcomes of infants born in a level 2 hospital to infants born in a level 3 hospital, lower crude rates and odds ratios for the level 2 infants emerge (table 15b).

Table 15b. Crude rates, crude odds ratios, and adjusted odds ratios for exposure: hospital of birth, level of care (level 2 versus level 3)

outcome	crude rates				crude OR	adjusted OR* and 95% CI	
	level 2		level 3				
	n	%	n	%			
in-hospital mortality	84/359	23.4	127/481	26.4	0.85	1.90	[1.13-3.20]**
death plus major handicap	106/355	29.9	161/472	34.1	0.82	1.48	[0.95-2.30]n.s.
death plus major and minor handicap	130/355	36.6	203/472	43.0	0.77	1.23	[0.83-1.84]n.s.
total handicaps in survivors	34/259	13.1	64/333	19.2	0.64	0.88	[0.49-1.57]n.s.

* adjusted for the potential confounding effect of all other factors from time-category 1 and 2
** $p < 0.05$

After adjusting, the odds ratios for the infants born in the level 2 hospital indicate a higher risk on an adverse outcome. This change in odds ratio from <1 to >1 is again mainly caused by correction for the difference in gestational age in the two groups. The mean gestational age of the infants born in a level 2 hospital is 30.7 weeks.

The influence of the higher mortality odds of infants born in a level 1 and 2 hospital is not present in the adverse outcome of surviving children. In the analyses on surviving children the relationship between level of care and outcome is no longer present.

Mode of delivery

From the 566 infants born after caesarean section 104 died, 29 developed a major and 58 a minor handicap. In the 772 infants born vaginally these numbers were 265, 30 and 53 respectively.

In the outcome measures on liveborn infants the crude rates and odds ratios indicate a better outcome for infants born after caesarean section (table 16).

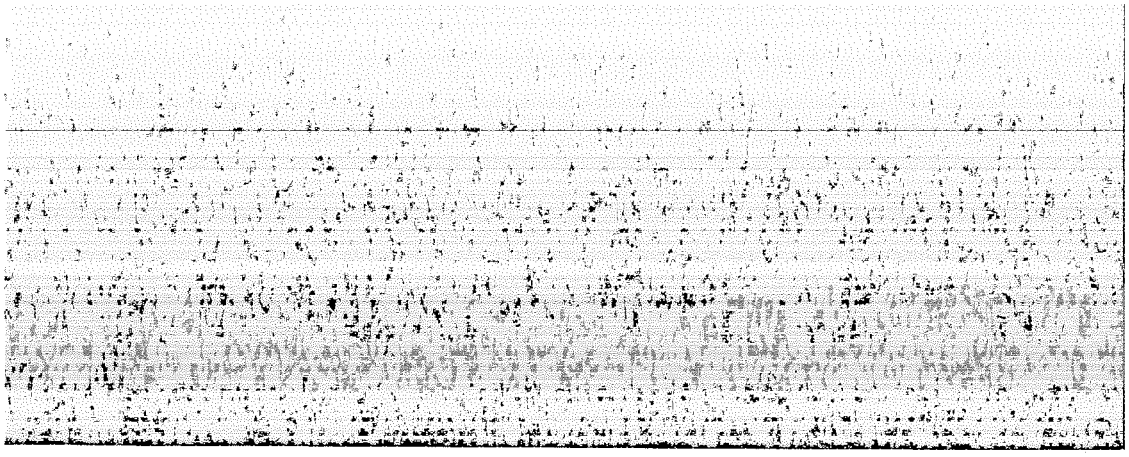


Table 16. Crude rates, crude odds ratios, and adjusted odds ratios for exposure: mode of delivery

outcome	crude rates				crude OR		adjusted OR* and 95% CI
	caesarean section		vaginal				
	n	%	n	%			
in-hospital mortality	97/566	17.1	243/772	31.5	0.45	0.86	[0.53-1.39]n.s.
death plus major handicap	133/562	23.7	295/751	39.3	0.48	0.89	[0.62-1.29]n.s.
death plus major and minor handicap	191/562	34.0	348/751	46.3	0.60	1.16	[0.82-1.61]n.s.
total handicaps in survivors	87/458	19.0	83/486	17.1	1.14	1.52	[0.99-2.35]n.s.

* adjusted for the potential confounding effect of all other factors from time-category 1 and 2

The adjusted odds ratios point to similar risks on mortality and handicap in both groups.

The exposure "mode of delivery" is biased by many factors, such as differences in indication and an uneven distribution of gestational age over mode of delivery. The mean gestational age of infants born after caesarean section is 31.6 weeks, of infants born vaginally 29.3 weeks. In the multivariate analysis, after adjusting for various confounding factors such as gestational age no effect of caesarean section as such is revealed.

Therefore, the relationship between mode of delivery and the various outcomes is very difficult to assess mainly because of problems in chosing the clinically correct confounding factors involved. Speculations on the relation between mode of delivery and the risk to develop a handicap should only be made after more extensive analyses of this subject.

For completeness sake the results on total handicap in surviving children are included. No conclusions may be attached to it.

Apgar score

From the 971 infants born with an Apgar score at 5 minutes $\geqslant 7$, 166 died, 45 developed a major and 84 a minor handicap. In the group of 251 infants with an Apgar score at 5 minutes <7 these numbers were 148, 11 and 20 respectively. Of 116 infants the Apgar score was unknown: in this group 55 infants died, 3 developed a major and 7 a minor handicap.

As illustrated in the crude rates and odds ratios, the infants with an Apgar score at 5 minutes after birth lower than 7 have a far greater risk to die or to develop a handicap than infants with an Apgar score higher than or equal to 7 (table 17).

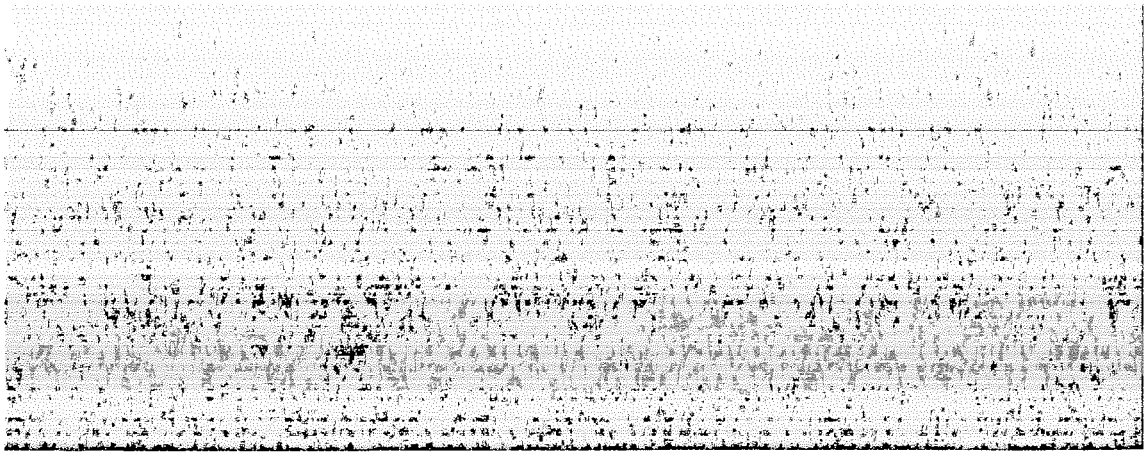


Table 17. Crude rates, crude odds ratios, and adjusted odds ratios for exposure: Apgar score at 5 minutes after birth

outcome	crude rates				crude OR	adjusted OR* and 95% CI	
	AS <7		AS ≥7				
	n	%	n	%			
in-hospital mortality	142 /251	56.6	148 /971	15.2	7.2	4.58	[3.04-6.89]**
death plus major handicap	159 /249	63.8	211 /953	22.1	6.2	3.90	[2.71-5.60]**
death plus major and minor handicap	179 /249	71.9	295 /953	31.0	5.7	3.64	[2.56-5.19]**
total handicaps in survivors	31 /101	30.7	129 /787	16.4	2.26	2.04	[1.23-3.37]**

* adjusted for the potential confounding effect of all other factors from time-category 1, 2, 3
** $p < 0.05$

The adjusted odds ratios for the outcome measures in liveborn infants, show a significantly higher risk on mortality in the infants with a low Apgar score at 5 minutes. The risk diminishes only slightly after including the risk on a major and minor handicap in the outcome measure. This is caused by the fact that a low Apgar score is also associated with a significantly higher handicap risk in the surviving children.

Drage in 1966[10] described the 5 minutes Apgar score as a useful predictor of neurological impairment. In an recent editorial in the Lancet,[11] the use of the Apgar score as a scientific assessment of babies immediately after birth has been discussed. Especially for infants at risk, the Apgar score is no longer used in the decision to resuscitate nor in the counseling of parents about survival. Moreover, inaccuracies in its calculation reduce the usefulness of attempts to correlate it with more subtle outcomes.

Although uncertainty exists about what clinical status is exactly assessed in the 5 minutes Apgar score, it appears to be significantly associated with an adverse outcome in liveborn as well as surviving children.

Neonatal transport

From the 407 infants transported in the neonatal period 129 died, 17 developed a major and 40 a minor handicap. In the group of 931 non-transported infants these numbers were 240, 42 and 71 respectively.

The crude rates and odds ratios show a higher risk to die or to develop a handicap for the transported infants. In the adjusted odds ratios no significantly different risk on an adverse outcome is present for the two groups(table 18).

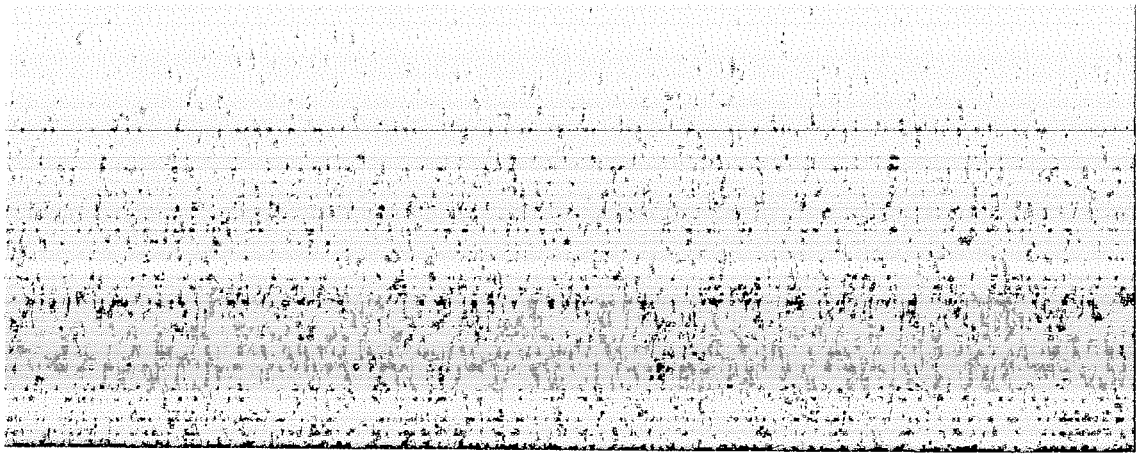


Table 18. Crude rates, crude odds ratios, and adjusted odds ratios for exposure: neonatal transport

outcome	crude rates neonatal transport present n	%	absent n	%	crude OR	adjusted OR* and 95% CI
in-hospital mortality	118/407	29.0	222/931	23.8	1.30	0.69 [0.4 -1.1]n.s.
death plus major handicap	146/397	36.8	282/916	30.8	1.31	0.76 [0.49-1.16]n.s.
death plus major and minor handicap	186/397	46.8	353/916	38.5	1.40	0.96 [0.66-1.40]n.s.
total handicaps in survivors	57/268	21.3	113/676	16.7	1.34	1.26 [0.75-2.13]n.s.

* adjusted for the potential confounding effect of all other factors in the 4 time-categories

In the mortality analyses testing for interaction revealed a significant (1%-level) modification of the effect of neonatal transport by gestational age.[1] At lower gestational ages neonatal transport was associated with lower mortality risks in otherwise similar infants compared to non-transport, while at more advanced gestational ages a higher mortality risk existed in this group of infants. This same interaction by gestational age is also found for the outcome measures: major and total adverse outcome. Testing for interaction in the group of surviving children revealed no effect modification by gestational age.

The problem of neonatal transport, however, is a very complicated one and very much depending on referral policy and organization. The results described here are a reflection of many of these non-medical influences. Other analyses are necessary to reveal the real influence neonatal transport could have on the various outcome measures.

Therefore, as a continuation of previous studies on maternal and neonatal transport,[4,5] this complex problem will be further analysed in a separate part of the "Project", where the problem of selection bias has at least partially been solved.

Idiopathic respiratory distress syndrome

From the 621 infants with an idiopathic respiratory distress syndrome (IRDS), 246 died, 22 developed a major and 54 a minor handicap. In the group of 717 infants without IRDS these numbers were 123, 37 and 57 respectively.

The crude rates and odds ratios reveal a higher risk on an adverse outcome in the liveborn infants. A significantly higher mortality odds is found in infants with IRDS (table 19a).

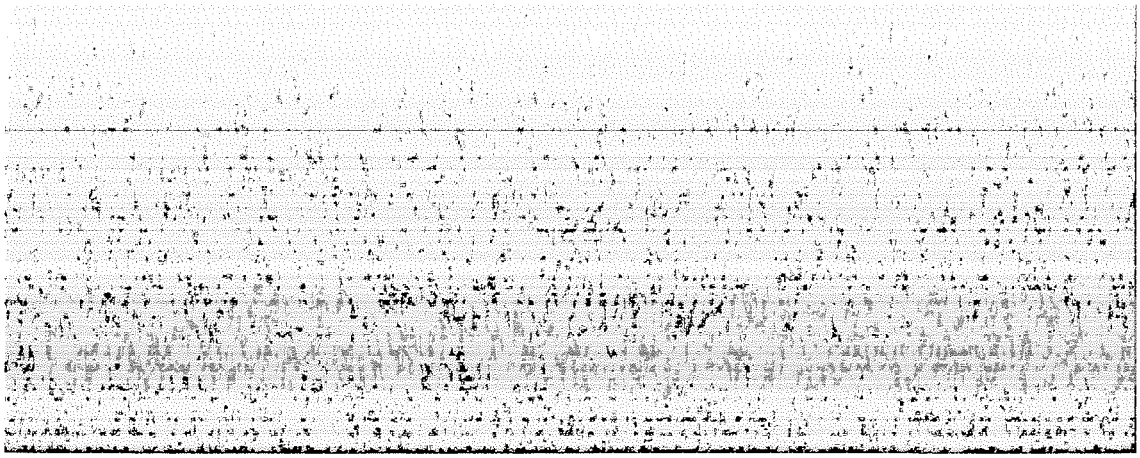


Table 19a. Crude rates, crude odds ratios, and adjusted odds ratios for exposure: idiopathic respiratory distress syndrome

outcome	crude rates IRDS present n	%	absent n	%	crude OR		adjusted OR* and 95% CI
in-hospital mortality	232/621	37.4	108/717	15.1	3.36	2.64	[1.8- 4.0]**
death plus major handicap	268/612	43.8	160/701	22.8	2.63	1.53	[1.09-2.15]**
death plus major and minor handicap	322/612	52.6	217/701	30.9	2.48	1.52	[1.12-2.06]**
total handicaps in survivors	57/268	21.3	113/676	16.7	1.34	1.03	[0.68-1.56]n.s.

* adjusted for the potential confounding effect of all other factors in the 4 time-categories
** $p < 0.05$

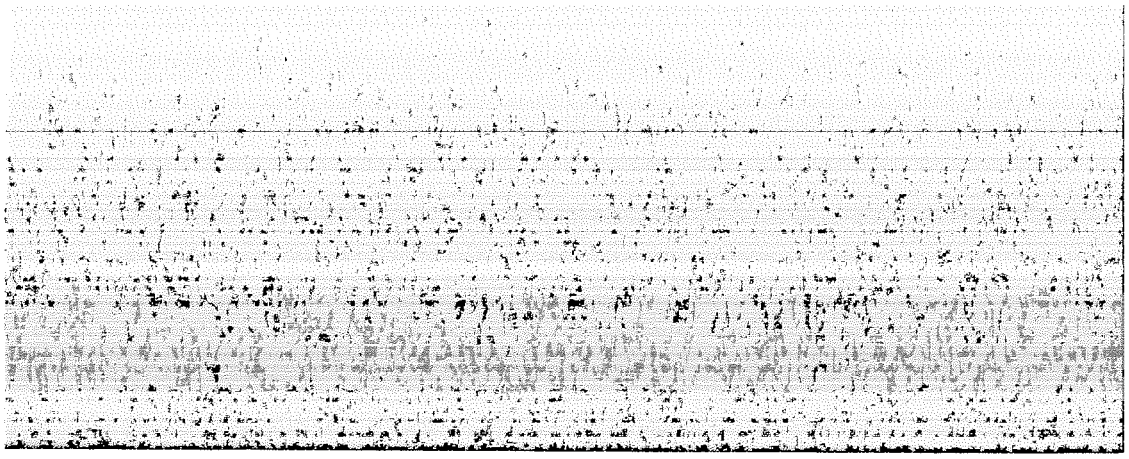
Since IRDS is one of the major causes of death in the study population this result was not unexpected.[1] This strong association between IRDS and mortality is also reflected in the other outcome measures of liveborn infants. Similar to the interaction by the factor Apgar score in the mortality analyses, this interaction was also present in the analysis on a major adverse outcome in liveborn infants as shown in table 19b. In infants with a low Apgar score the fact whether or not IRDS ensued was irrelevant for the outcome, in infants with a high Apgar score it was.

Table 19b. Adjusted odds ratios for IRDS by Apgar score at 5 minutes

major adverse outcome	adjusted OR*
death plus major handicap	1.53
Apgar score:	
unknown	1.3
≥7	1.9
<7	0.9

* adjusted for the potential confounding effect of all other factors in the 4 time-categories

Idiopathic respiratory distress syndrome itself is not associated with the risk on a handicap in the surviving children and no interaction with Apgar score was found.



Intracranial haemorrhage

From the 333 infants with an intracranial haemorrhage (ICH), 167 died, 22 developed a major and 22 a minor handicap. In the group of 1005 infants without ICH these numbers were 202, 37 and 89 respectively.

ICH itself is closely associated with mortality and handicap.[12,13] A part of the effect of ICH on the various outcomes becomes evident through the perinatal factor seizures. Because seizures are included as a counfounder, the effect of ICH itself may have been underestimated. Therefore, the association between ICH itself and the adverse outcomes may be even stronger. A further description of ICH in relation with the occurrence of seizures is given in chapter 6.

The crude rates and crude odds ratios reveal a much higher risk on an adverse outcome for children with the clinical diagnosis ICH (table 20). In the adjusted odds ratios a significantly higher mortality odds appears for children with a clinical intracranial haemorrhage. This strong association is also reflected in the results of the other outcome measures of liveborn infants.

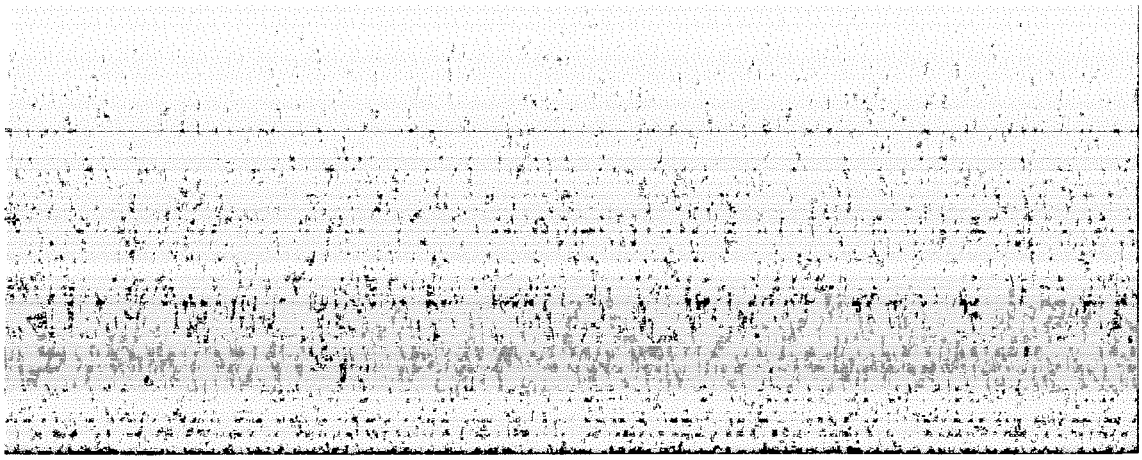
Table 20. Crude rates, crude odds ratios, and adjusted odds ratios for exposure: intracranial haemorrhage

outcome	crude rates ICH present n	%	absent n	%	crude OR		adjusted OR* and 95% CI
in-hospital mortality	158/333	47.4	182/1005	18.1	4.08	2.37	[1.56-3.59]**
death plus major handicap	189/329	57.4	239/ 984	24.8	4.21	2.53	[1.75-3.66]**
death plus major and minor handicap	211/329	64.1	328/ 984	33.3	3.58	1.97	[1.40-2.77]**
total handicaps in survivors	44/162	27.2	126/ 782	16.2	1.94	1.37	[0.84-2.23]n.s.

* adjusted for the potential confounding effect of all other factors in the 4 time-categories
** $p < 0.05$

The results of the handicap analysis of surviving children show that according to the confidence interval the 5% level of significance is not reached for this outcome measure, partly due to overcorrection for the factor seizures.

In a selected part of our study population, treated in 6 of the eight NICU's in our country, significantly more handicaps are found in children with ICH (grade I-IV). In this analysis seizures were included as confounding factor as well.[13]



Septicaemia

From the 469 infants with septicaemia 122 died, 28 developed a major and numbers were 240, 31 and 72 respectively.

The occurrence of septicaemia is not associated with a higher risk on an adverse outcome in liveborn or surviving children (table 21a).

Table 21a. Crude rates, crude odds ratios, and adjusted odds ratios for exposure: septicaemia

outcome	crude rates septicaemia present n	%	absent n	%	crude OR	adjusted OR* and 95% CI	
in-hospital mortality	111/469	23.7	222/869	25.5	0.90	0.86	[0.6 -1.3]n.s.
death plus major handicap	150/436	34.4	271/869	31.2	1.16	0.96	[0.69-1.34]n.s.
death plus major and minor handicap	189/436	43.3	343/869	39.5	1.17	0.95	[0.71-1.28]n.s.
total handicaps in survivors	67/314	21.3	103/629	16.4	1.38	1.10	[0.74-1.64]n.s.

* adjusted for the potential confounding effect of all other factors in the 4 time-categories

In the mortality analyses, testing for interaction showed a significant modification of the effect of septicaemia by birthweight: in infants with a relatively low birthweight the mortality risk was lower in septicaemia cases, while in the higher birthweight categories the mortality risk was higher.

As described elsewhere,[14,15] in infants with birthweights below 1000 g, over 80% was treated with total parental nutrition (TPN). The duration of TPN was significantly associated with a lower mean birthweight and with clinical sepsis. The effect modification of septicaemia by birthweight may be explained by this frequent occurrence of TPN in lower birthweight categories. The causative organisms in these cases of septicaemia were mainly staphylococci, and the associated mortality was low. This same interaction was also present in the outcome measures, major and total adverse outcome. To illustrate this effect some adjusted OR's for septicaemia in several birthweights are shown in table 21b. No interaction with birthweight was found in the analysis on surviving children.

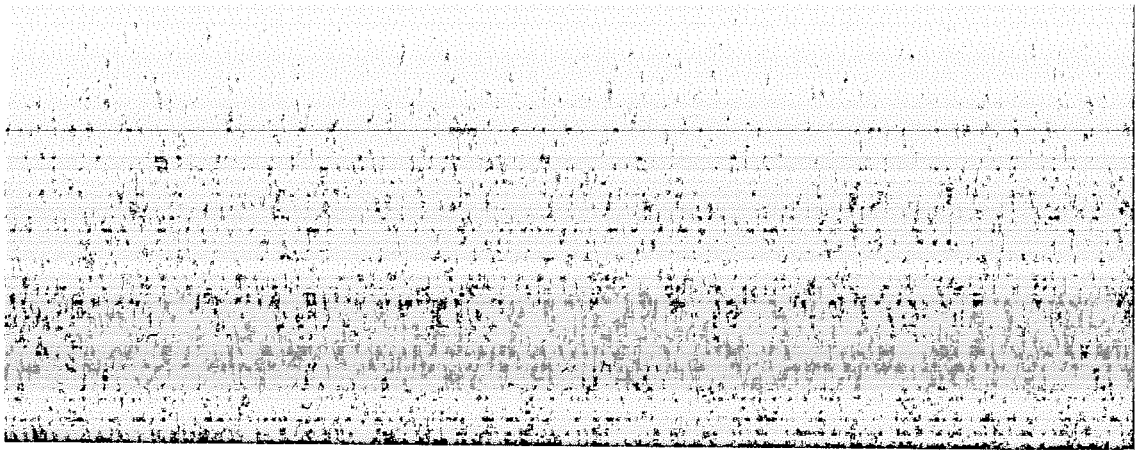


Table 21b. Adjusted odds ratios for septicaemia by birthweight

major adverse outcome	adjusted OR*	total adverse outcome	adjusted OR*
death plus major handicap	0.96	death plus major and minor handicap	0.95
birthweight (g)		birthweight (g)	
750	0.4	750	0.4
1000	0.7	1000	0.7
1500	1.5	1500	1.4
2000	3.5	2000	2.9

* adjusted for the potential confounding effect of all other factors in the 4 time-categories

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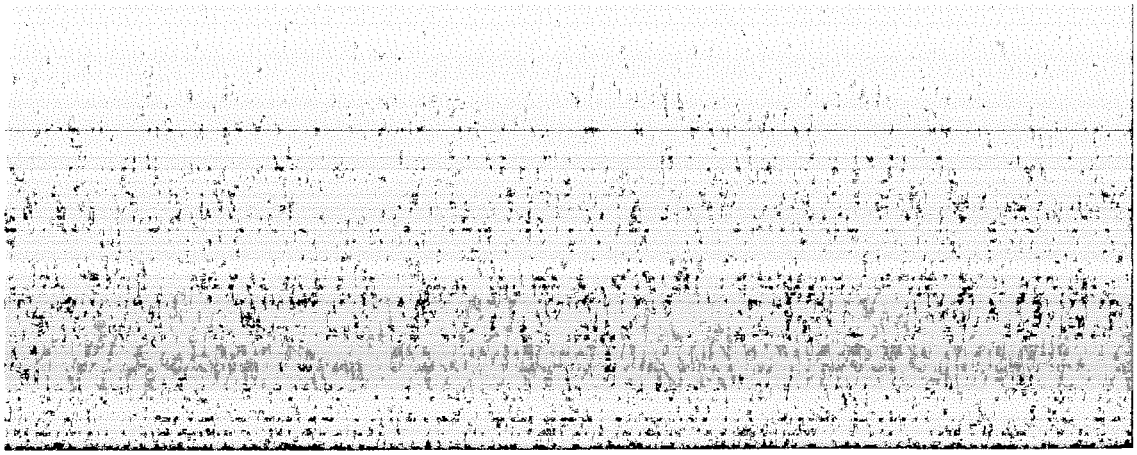

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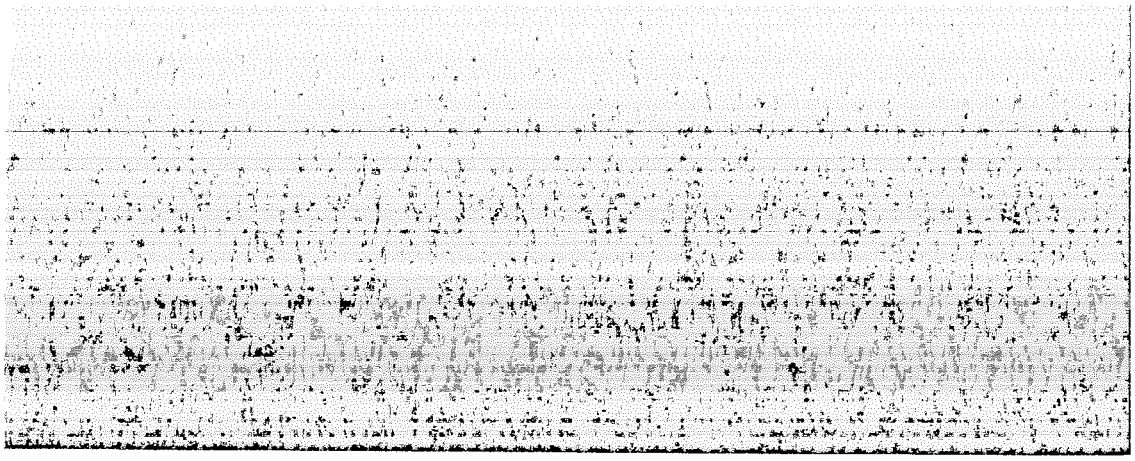


CHAPTER 11

GENERAL DISCUSSION

Over the last decades the prognosis and outcome of high-risk newborns such as preterm and small for gestational age infants has been the focus of extensive medical as well as occasional political attention. Besides a decrease in neonatal morbidity and mortality an improvement in later outcome has occurred; both aspects have been described elaborately.[1]

Most reports, however, are based on single hospital populations from paediatric wards in general hospitals or from neonatal intensive care units (NICU's) in university hospitals.

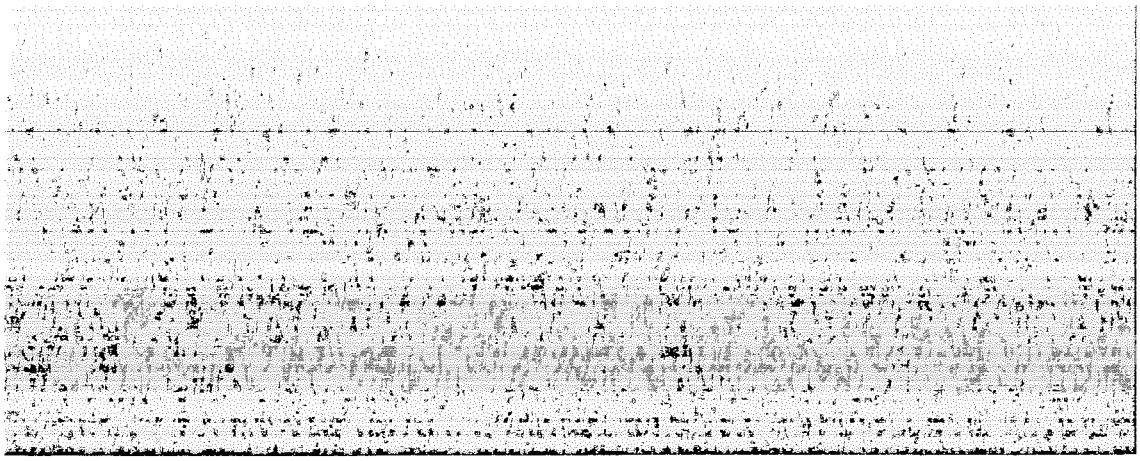
In the Netherlands single hospital based studies were performed regularly.[2-14] These hospitals provide follow-up for their graduates of neonatal intensive care as part of the continuing care offered to them and as an audit for their own patterns of care.

Studies from single hospital populations, however, are not of great value in determining the prognosis of other infants at risk, if they lack information about the population from which the study samples are drawn and about the reasons for hospital admission.[15] The outcome will also depend on the pattern of referral; if only the less critically ill infants, who can tolerate transport, are selected, the results will appear to be much better than if the situation is reversed.

Predicting the prognosis of other infants at risk can only be done by following-up all babies born to residents of a defined geographical area.[16] In such surveys the numbers would be larger, inferences would be more secure, selection bias by the hospital would not be operative, and there would be the opportunity for inter-hospital comparison.[17]

Such large, long lasting and widespread surveys may give rise to various problems regarding organizational, scientific and financial aspects. Notwithstanding these problems such a study design was considered suitable for the Netherlands, being a small densely populated country (14,255 square miles, 14,3 million inhabitants).

Therefore, in 1983 in the Netherlands the "Project On Preterm and Small for gestational age infants"(POPS) was started as a nationwide, prospective survey on infants born after a gestational age less than 32 weeks and /or with a birthweight less than 1500 grams. Altogether 1338 infants were enrolled in the survey, i.e. 94% of the infants meeting the entry criteria born in 1983. All surviving infants were enrolled in a follow-up programme up to the age of two years corrected for preterm birth. Paediatricians in 101 neonatal departments collaborated in recording the necessary data and through their enthousiastic participation it was possible to attain a 97.4% compliance rate for the follow-up programme.



The main results concerning mortality, handicaps and loss to follow-up are summarized in table 1, while a further subdivision of these results according to birthweight and gestational age is shown in table 2.

Table 1: Outcome at the corrected age of 2 years

	n		(%)
deaths	369		(27.6)
in-hospital		340	
neonatal		312	
> 28 days		28	
after discharge	29		
discharge-1 yr		23	
1-2 yr		6	
survivors - 2 yr	969		
assessed - 2 yr	944		
major handicap		59	(4.4)
minor handicap		111	(8.3)
no handicap		774	(57.8)
lost to follow-up	25		(1.9)
total liveborn, < 32 wks and /or < 1500 g	1338		(100.0)

To enable evaluation of the present perinatal care for these infants in the Netherlands and to evaluate trends in morbidity and mortality we compared our data with data derived from studies in other geographically defined populations. In such studies the intake criteria, definition of major handicap and moment of assessment should be similar. Furthermore they should provide sufficient data on the number of infants originally enrolled in the survey, on deceased and surviving infants and on loss to follow-up, to calculate the percentages necessary to actually compare the data.

Data of 6 studies on populations from geographically defined areas were suitable to use in a comparison with our study (table 3). All populations contained infants with a birthweight less than 1500 g. Data on neonatal and postneonatal mortality were available, and the major handicap rate was given as a percentage of liveborn and assessed infants.

In all studies the definition of "major handicap" was based on Stewart's definition,[18] that a major handicap is a disability that is likely to prevent the child from going to a normal school, or causes serious interference with normal function in society.

Horwood used as outcome criteria to measure morbidity: major neurologic sequelae (cerebral palsy, hydrocephaly and mental retardation, blindness and deafness).[19] Saigal reported handicap in terms of neurologic and functional status. Neurologic handicaps were taken into account such as cerebral palsy, hydrocephaly, mental retardation, blindness and deafness. These dysfunctions were

Table 2. Numbers of death, surviving and assessed children at the corrected age of 2 years, divided by several birthweight and gestational age categories

	total population		< 1500 g		< 32 wkn		SGA		< 1000 g		< 30 wkn	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
deaths	369	(27.6)	327	(29.8)	332	(32.9)	91	(20.0)	162	(55.5)	255	(45.4)
in-hospital	340		306		310		82		157		246	
discharge-2yr	29		21		22		9		5		9	
survivors-2yr	969		770		678		363		130		307	
assessed-2yr	944		751		656		359		125		295	
major handicap	59	(4.4)	47	(4.3)	42	(4.1)	27	(5.9)	10	(3.4)	23	(4.1)
minor handicap	111	(8.3)	90	(8.2)	81	(8.0)	35	(7.7)	13	(4.4)	44	(7.8)
no handicap	774	(57.8)	614	(56.0)	533	(52.8)	297	(65.4)	102	(34.9)	228	(40.6)
lost to follow-up	25	(1.9)	19	(2.2)	22	(2.2)	4	(0.9)	5	(1.7)	12	(2.1)
total	1338	(100)	1097	(100)	1010	(100)	454	(100)	292	(100)	562	(100)

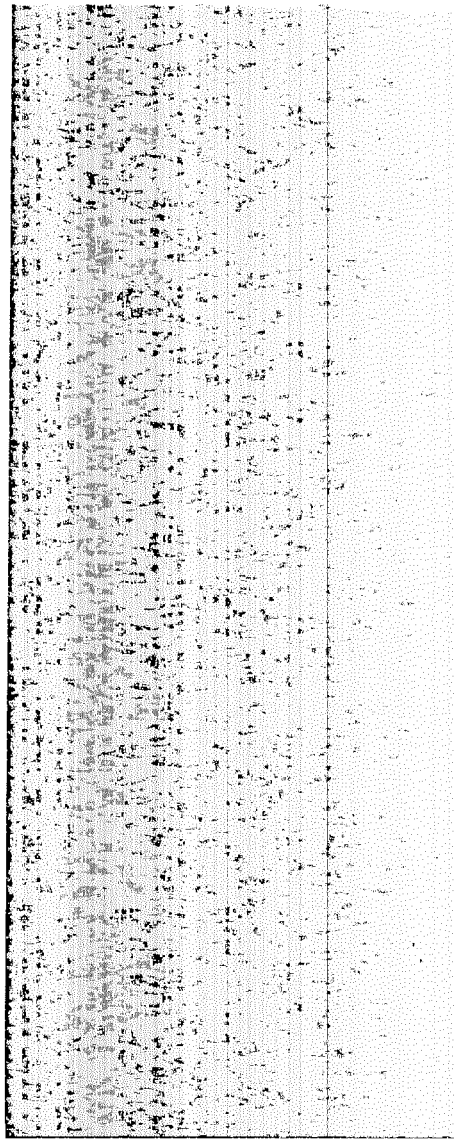
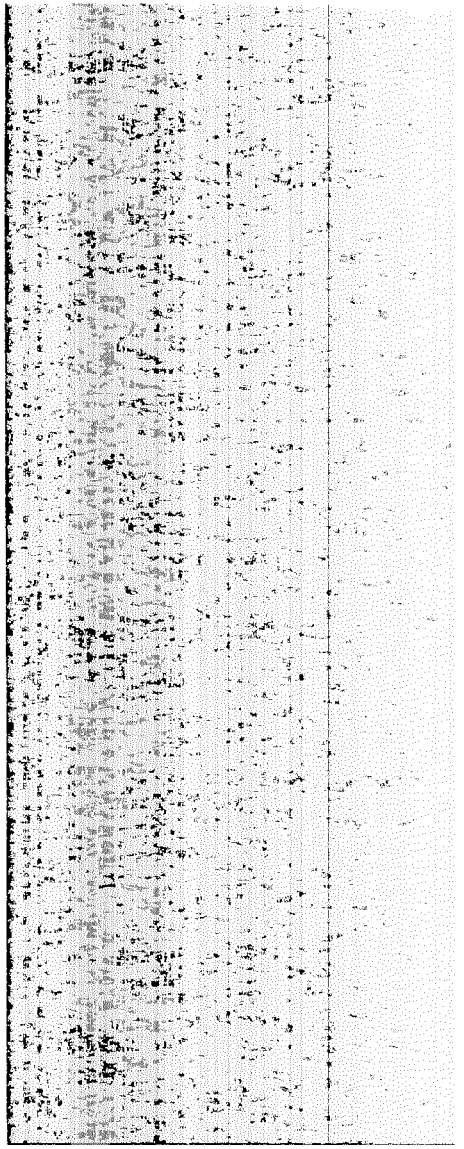
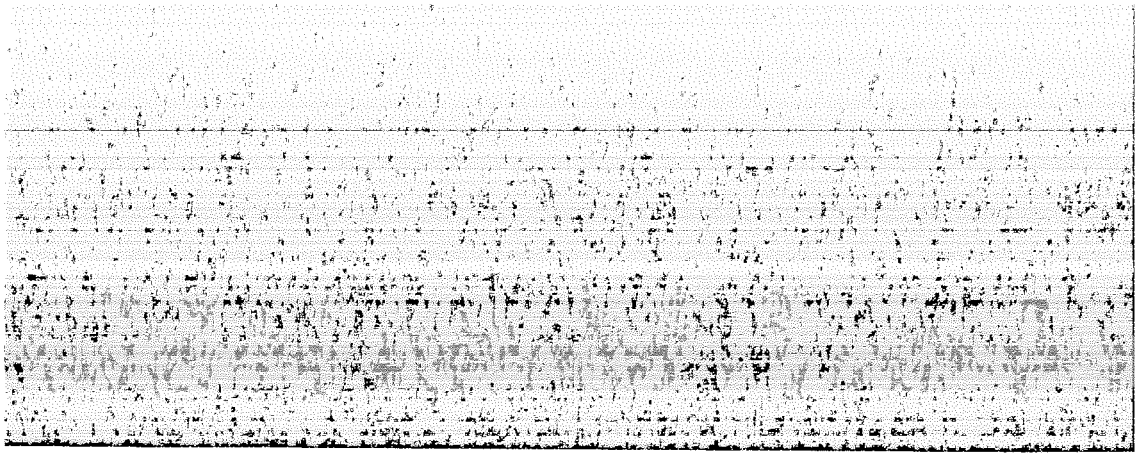


Table 3. Handicap rate in VLBW infants, as a percentage of liveborn, surviving and assessed infants in 7 studies performed in geographically defined areas

author, year of publication	area, (country)	study sample	sample criteria	liveborn infants n	surviving infants			major handicaps			duration follow-up (years)
					n	% of liveborn	n assessed	n	% of liveborn	% of assessed	
Horwood, 1982	Ham.Wentworth	1964-69	500-1499	373	143	38.3	121	13	3.5	10.7	9-14
	(Canada)	1973-77	500-1499	265	147	55.5	134	18	6.8	13.4	1.5- 6
Saigal, 1982	Ham.Wentworth (Canada)	1973-78	501-1500	294	179	60.9	170	30	10.2	17.6	2- 5
Powell, 1986	Mersey region (England)	1979-81	<1500	603	331	54.9	322	23	3.8	7.1	2.9- 4.4
Johnson, 1987	New Foundland (Canada)	1980-81	500-1499	143	82	57.3	79	8	5.6	10.1	1.5- 3
Piekkala, 1988	Turku (Finland)	1981-82	500-1499	28	16	57.1	16	1	3.6	6.3	2
POPS, 1989	Netherlands	1983	<1500	1097	770	70.2	751	47	4.3	6.3	2





considered major when a child required significant/unusual adult caretaking or help, far beyond what is usually expected for corrected age.[20] Powell focused on neurological impairments, vision and hearing loss. To measure the impairment quantitatively, the need for special schooling was used as a criterion.[21] Johnson used three outcome categories, normal, mild, or major dysfunction. Children with a major handicap had a central motor deficit and persisting neurologic signs, with or without associated sensory impairment.[22] Piekkala had only 16 surviving infants comparable with our population. A major handicap occurred in 2 infants.[23]

In all but one, the moment of assessment was in the pre-school period. Only in Horwood's first cohort under study, the children were much older at the moment of assessment: between 9-14 years old. Nonetheless, the handicap rate in this study population was low.

In table 3 the main results are presented from 7 studies in geographically defined areas, including the comparable weight category (< 1500 g) in the present study.

In the past decades the survival rate has increased impressively. Consequently the focus of outcome studies has shifted from mere survival to sequelae such as major handicaps. It is of utmost importance to demonstrate, whether the improved survival has occurred at the cost of an increase in major handicaps. That way the major adverse outcome (= total deaths plus major handicaps) would have remained at the same level. In all 7 studies sufficient data on mortality were available to calculate the mortality up to the age of two years in each of them. As a result the total mortality in the studies can be compared. The total mortality, major handicap rate and the major adverse outcome was calculated for each study (table 4). Moreover, in figure 1 the total mortality and the major adverse outcome from the various studies are shown in a diagram.

Table 4. Total mortality, major handicaps and major adverse outcome as a percentage of liveborn infants in 7 studies performed in geographically defined areas

author, year of publication	study sample	liveborn infants	total mortality		major handicaps		major adverse outcome	
			n	%	n	%	n	%
Horwood, 1982[19]	1964-69	373	230	61.6	13	3.5	243	65.1
	1973-77	265	118	44.5	18	6.8	136	51.3
Saigal, 1982[20]	1973-78	294	115	39.1	30	10.2	145	49.3
Powell, 1986[21]	1979-81	603	272	45.1	23	3.8	295	48.9
Johnson, 1987[22]	1980-81	143	61	42.6	8	5.6	69	48.2
Piekkala, 1988[23]	1981-82	28	12	42.8	1	3.6	13	46.4
POPS, 1989[P]	1983	1097	327	29.8	47	4.3	374	34.1

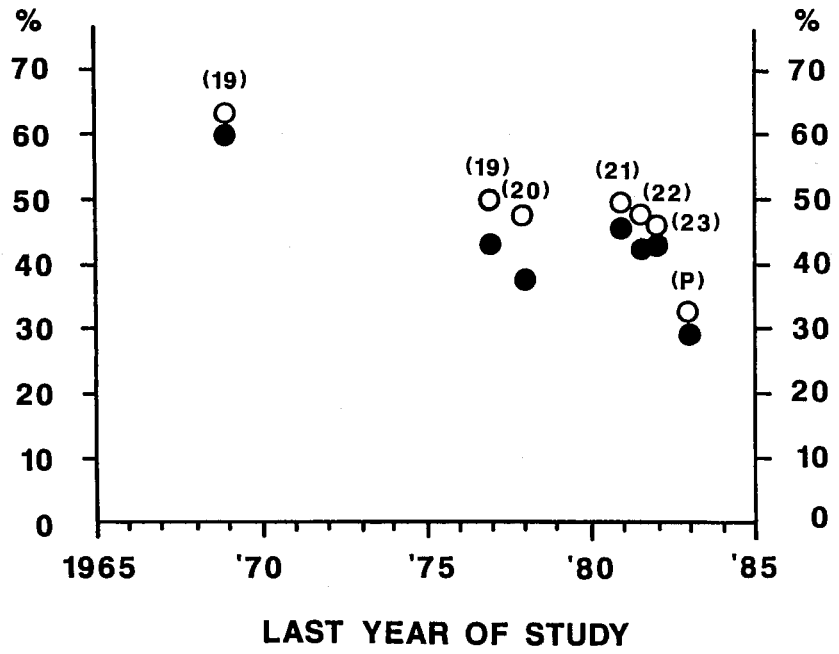


Figure. Mortality (●) and major adverse outcome (○) (total deaths plus major handicaps) as a percentage of liveborn infants in 7 regional studies including the present study.[19,20,21,22,23,P]

These data show that in the mid seventies the decrease of mortality was accompanied by a relatively high major adverse outcome due to an increased handicap rate. In later years this phenomenon disappeared at the cost of a somewhat higher mortality rate. From the POPS-survey it seems as if the mortality rate decreased further again while the low handicap rate remained low, resulting in the lowest major adverse outcome rate reported so far. The results of the follow-up assessment at 5 years of age will reveal whether the low handicap rate at 2 years reflects reality; preliminary data do not show a need to believe otherwise.

A comparison with data from future studies from populations in geographically defined areas will reveal whether this decrease is going to continue.

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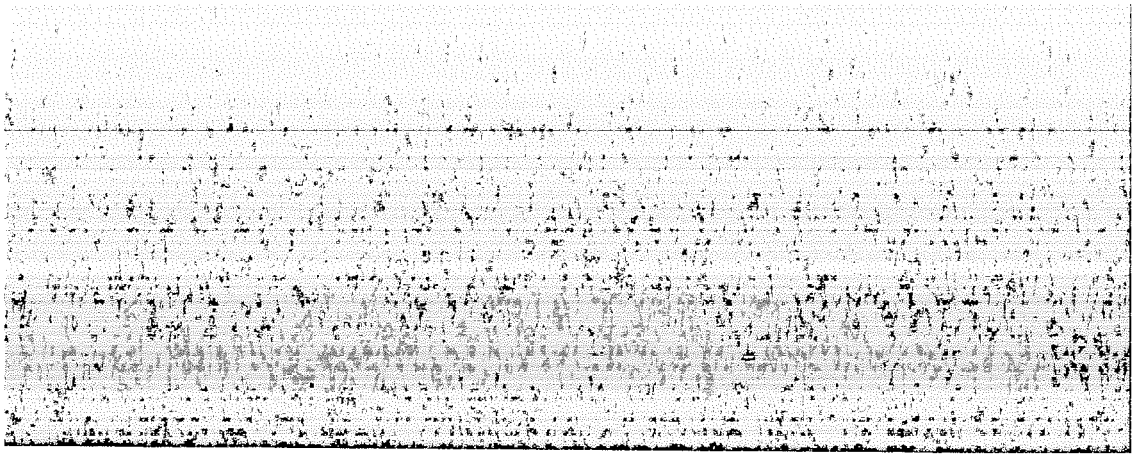

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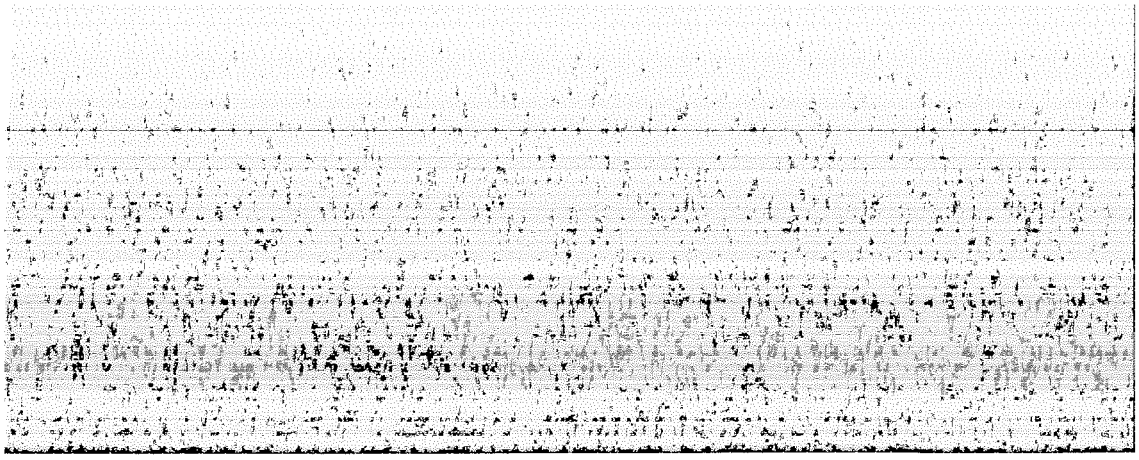
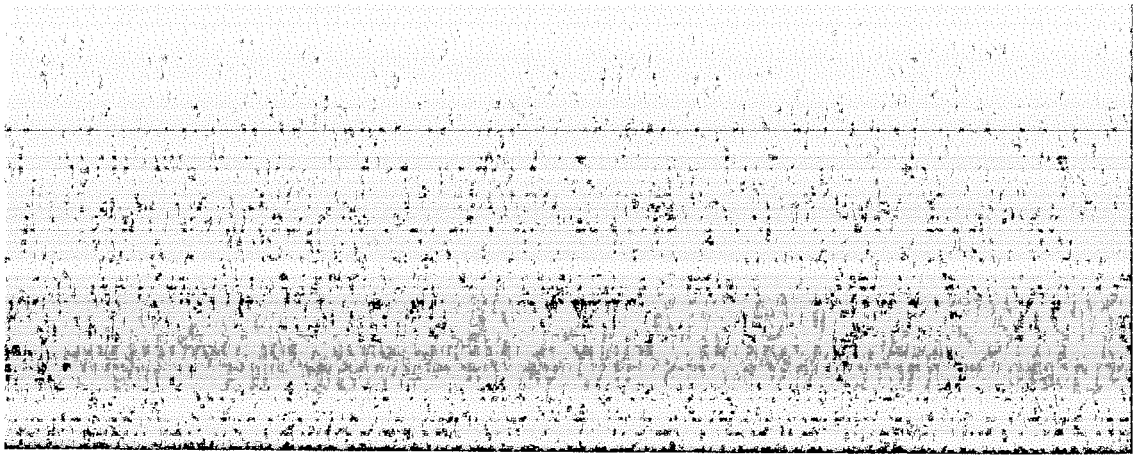




SUMMARY AND CONCLUSIONS

In *chapter 1* the original objectives and the study design of the "Project On Preterm and Small for gestational age infants" (POPS) are described. In a prospective, collaborative, longitudinal survey data were collected on infants, born in 1983 with a gestational age of less than 32 completed weeks and/or with a birthweight of less than 1500 g. A total of 1338 infants was included, representing 94% of all infants born in the Netherlands in 1983 and meeting the entry criteria.

Neonatal mortality and morbidity were studied. Nowadays, however, these are generally considered insufficient measures to assess the care offered to these high-risk infants. The necessity to report on postneonatal mortality and outcome in terms of later handicaps in order to assess this care is discussed.

A follow-up programme up to the age of 2 years with health examinations at the age of 3, 6, 12 and 24 months corrected for preterm birth was scheduled for all infants surviving the initial hospital stay. Finally, at the age of two years, corrected for preterm birth, all infants were divided into one of three categories according to neurodevelopmental assessment: major handicapped, minor handicapped or normal. The word handicap implies a disturbance of normal life and as such it places the underlying impairment or disability in a social context. As measures of adverse outcome were chosen: "major adverse outcome" (= total deaths and major handicaps) and "total adverse outcome" (= total deaths plus major and minor handicaps), both in liveborn infants and "total handicaps" (= major and minor handicaps) in surviving children.

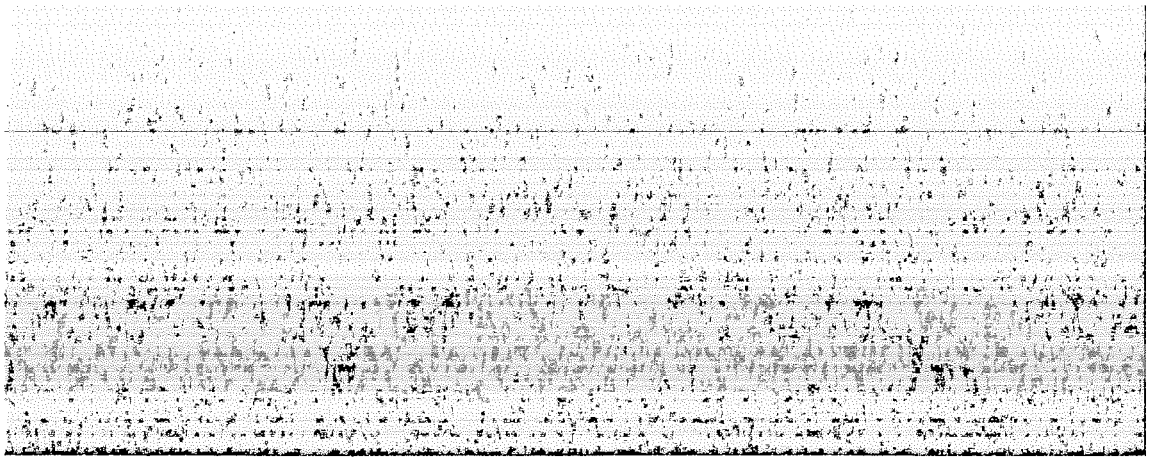
The study was performed in a decentralized way by the local paediatrician or the paediatrician at the referral hospital in accordance with the parents' preference. Data processing and analysing were performed at the coordinating study centre.

Analysis of the collected data involved descriptive statistics, such as frequency tables, and inferential statistics. The use of multivariate statistical techniques enabled analysis of the relationship between various perinatal factors and the three previously defined adverse outcomes while controlling (adjusting) for the possible uneven distribution of confounding factors.

In *chapter 2* the outcome of the study population at the age of two years corrected for preterm birth is presented in a descriptive way. From the 1338 infants originally enrolled in the survey, 369 died (27.6%), 59 children (4.4%) developed a major and 111 children (8.3%) a minor handicap.

Unlike mortality, handicap was apparently unrelated to gestational age or birthweight.

With great effort a 97.4% follow-up rate was achieved. The handicap rate in the children whose follow-up data were most difficult to collect was similar



to that in the remainder of the population under study. Therefore, we concluded that in a decentralized study-design as used in this survey a follow-up rate of 90% may be sufficient to describe the outcome without introducing a bias because of loss to follow-up.

In *chapter 3* the relationship between mortality, handicaps and maternal hypertensive disorders during pregnancy is discussed.

The in-hospital mortality in infants born to mothers with hypertensive disorders during pregnancy was significantly lower than in infants born to mothers without (11% and 30% respectively). The handicap rate in both groups was similar (16.2% and 18.7% respectively).

Intra-uterine growth, as expressed in the confounding factors birthweight and small for gestational age is probably related to maternal hypertensive disorders during pregnancy. Therefore, two different multiple regression analyses were performed with and without these two factors as confounders. Comparing the results of the two analyses the conclusion remained that there is an independent effect of maternal hypertension as such on mortality and handicap, regardless of intra-uterine growth.

In *chapter 4* the relation between mortality, handicaps and female infants' sex is described. The in-hospital mortality risk for infants of both sexes in this population was similar. The risk on a handicap in the surviving children, however, was significantly higher for boys than for girls: 15% of the male children was handicapped at the age of two years compared to 10% of the girls. This difference in handicap rates was apparent throughout most gestational age categories.

The consequences of the well-known delay in lungmaturation in male infants, such as IRDS and need of assisted ventilation did not explain this male disadvantage. The etiology remains unclear and further study is necessary.

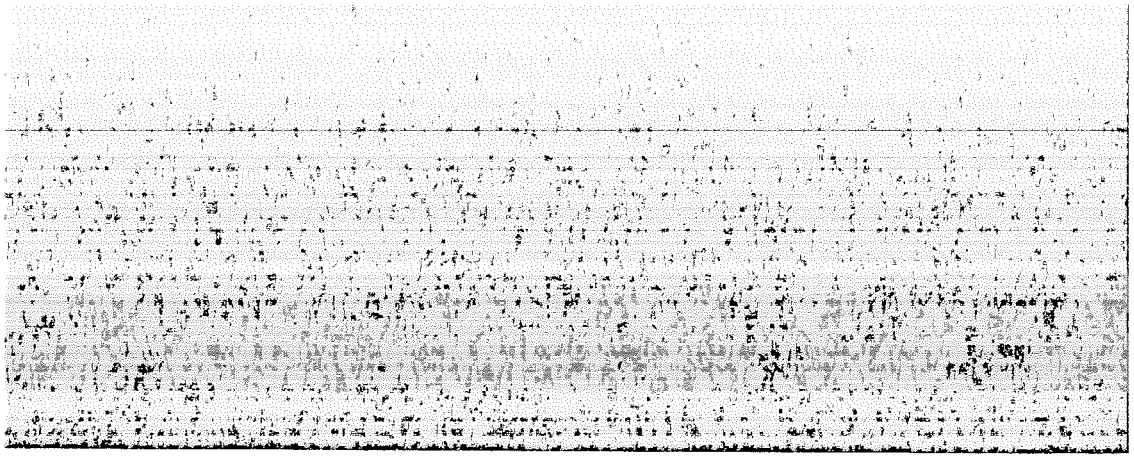
In *chapter 5* the occurrence of neurological dysfunction (ND) in the neonatal period is described.

The attending paediatricians throughout all levels of care diagnosed, by routine neurological examination, neurological dysfunction in the neonatal period in only 8% of the infants. The mortality and handicap rate in these infants, however, was extremely high: 81% and 50% respectively. A mortality and handicap rate of 18% and 4% was found in neurologically normal survivors.

It is stated that although obvious neonatal neurological dysfunction occurred in relatively few infants in this population, mortality was high and a normal outcome exceptional.

Using routine physical examination, a quarter of the very preterm or VLBW infants with later neurological disturbances may be identified. A more standardized neurological examination, incorporated in the routine examination of newborns in all levels of care, may improve the early identification of infants at risk for handicaps.

In *chapter 6* the adverse outcome of children with seizures in the neonatal period is shown. Neonatal seizures were recorded in 72 infants (5.4%): 44 died and 12 developed a handicap. In almost all of the handicapped children the



seizures occurred at the 5th day of life or later. Nevertheless, 16 of the 28 survivors with neonatal seizures were considered normal at the corrected age of two years. Clinical data of the surviving children reveal a difference in severity of their neonatal complications.

In nearly all surviving children an ICH as well as IRDS was diagnosed in the neonatal period. The neonatal complications were more severe in the children surviving with a handicap, for instance necessitating assisted ventilation for a longer period. Moreover, in 6 out of the 11 children with a major handicap a hydrocephalus was diagnosed.

In *chapter 7* the relation between maximal serum total bilirubin concentration in the neonatal period (TBmax) and neurodevelopmental outcome at the corrected age of 2 years is described.

Children with minor and major handicaps had significantly higher TBmax than children with a normal neurodevelopmental outcome. A consistent increase in prevalence of handicaps was found for each 50 μmol/l (2.9 mg/dl) increase of TBmax. With logistic regression analysis an odds ratio of 1.3 was found. This indicates that, on a multiplicative scale, the risk of a handicap increased by 30% for each 50 μmol/l (2.9 mg/dl) increase of TBmax. Further analysis treated bilirubin as a categorized exposure. A striking systematic increase was found, suggesting a causal relationship between TBmax and neurodevelopmental outcome. Only a randomized clinical trial, however, can test the effect of decreased serum biblirubin concentrations on neurologic outcome and therefore, altering current clinical practice is not justified until such a trial has been carried out.

In *chapter 8* the use of health services as expressed in the frequency of and reasons for rehospitalization is described. During the period between discharge home from the initial hospital stay and the age of 2 years corrected for preterm birth 320 infants (34%) were readmitted 481 times.

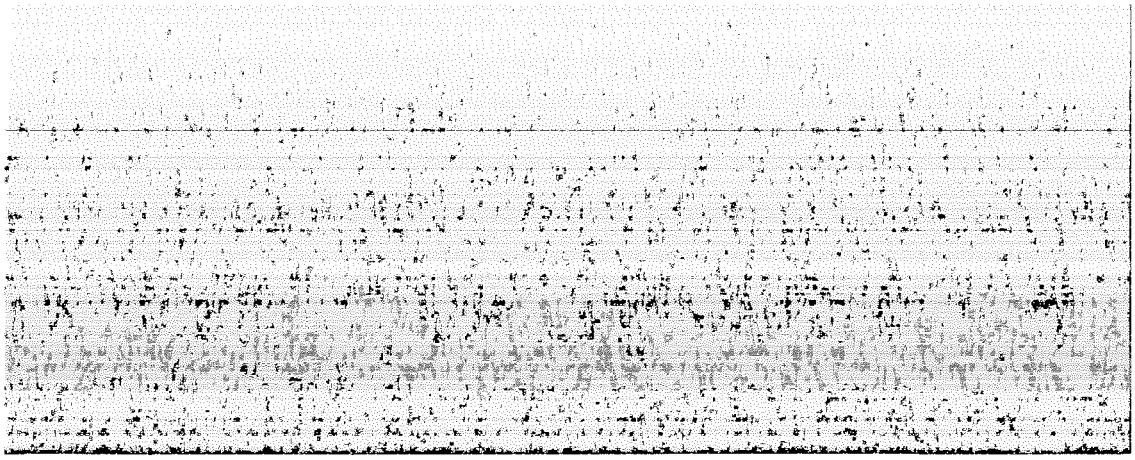
The main reasons for rehospitalization were surgical procedures, of which inguinal herniorrhaphy was the most prominent, and respiratory tract disorders: 149 admissions (31%) and 147 (31%) admissions respectively.

In a multivariate analysis sex and the length of the initial hospital stay was shown to be significantly associated with an increased risk of rehospitalization.

The Netherlands Central Bureau of Statistics provided data from the general Dutch population as recorded in the Netherlands Health Interview Survey. A comparison with our data showed a higher rehospitalization rate in our population in the first as well as second year of follow-up. The surviving children with a normal outcome, however, had a rehospitalization rate during their second year of life, similar to that of children from the general population.

In *chapter 9* the use of health services as expressed in outpatient visits to medical specialists and physical therapists is described. During the period between discharge from the initial hospital stay and the age of 2 years corrected for preterm birth, 671 children (67%) attended a medical specialist other than their paediatrician and 313 children (31%) attended a physical therapist.

The use of outpatient services as a whole was higher in the first year than



in the second year and was clearly related to the neurodevelopmental outcome of the child. Comparison of the use of outpatient care in surviving children with a normal outcome and in children from the general Dutch population revealed a similar use in both groups.

In *chapter 10* a description is given of the relationship between various perinatal factors used as an exposure and mortality and handicap. As outcome measures were used: "major adverse outcome" (= total deaths plus major handicaps) and "total adverse outcome" (= total deaths plus major and minor handicaps), both in liveborn infants and "total handicaps" (= major and minor handicaps) in surviving children. The crude rates, crude odds ratios and adjusted odds ratios were calculated for the various perinatal factors and presented together with the results on in-hospital mortality. For each perinatal factor separately, a short comment was given on the results of the analyses.

In addition to the perinatal factors already described in the previous chapters (chapter 4: infants'sex, chapter 6: seizures, chapter 7: bilirubin), the factors pre-existing disease of the mother, congenital malformations, antenatal transport and Apgar score at 5 minutes were significantly associated with an adverse outcome in surviving children.

In *chapter 11* the numbers of deaths, surviving and assessed children are summarized for several gestational age and birthweight categories. Furthermore, a comparison is shown between the results of this study and six previously published studies performed in populations from geographically defined areas.

In the past decades the survival rate of infants meeting our entry criteria has increased impressively. Consequently the focus of outcome studies has shifted from mere survival to sequelae such as major handicaps. It is of the utmost importance to demonstrate whether the improved survival has or has not been accompanied by an increase in major handicaps. That way the major adverse outcome would have remained at the same level.

Therefore, the "major adverse outcome" was calculated in the various studies as a measure of decrease of adverse outcome. These data showed that in the mid seventies the decrease of mortality was accompanied by a relatively high major adverse outcome due to an increased handicap rate. In later years this phenomenon disappeared at the cost of a somewhat higher mortality rate. In the present studie it seems as if the mortality rate decreased further again while the handicap rate remained low, resulting in the lowest major adverse outcome rate reported so far.

Preliminary data from the follow-up assessment at 5 years reveal that so far the low handicap rate at 2 years reflects reality. A comparison with data from future studies from populations in geographically defined areas will reveal whether this decrease is going to continue.

SAMENVATTING EN CONCLUSIES

In *hoofdstuk 1* worden de oorspronkelijke doelstellingen en de studieopzet van het "Project Onderzoek Prematuritas Small for gestational age" (POPS) beschreven. In een prospectief, beschrijvend, longitudinaal onderzoek werden gegevens verzameld van kinderen, geboren in 1983 na een zwangerschapsduur van minder dan 32 weken en (of) met een geboortegewicht van minder dan 1500 g. Een totaal van 1338 kinderen werd in het onderzoek opgenomen, wat betekent 94% van alle kinderen die in 1983 in Nederland werden geboren en aan deze eisen voldeden.

De neonatale sterfte en morbiditeit werden bestudeerd. Echter deze uitkomsten worden momenteel in het algemeen onvoldoende geacht om de zorg die aan deze high-risk kinderen werd geboden te beoordelen. De noodzaak om ook te rapporteren over post-neonatale sterfte en latere handicaps met het doel deze zorg te toetsen wordt besproken.

Voor alle kinderen die na de eerste ziekenhuisopname nog in leven waren, werd een schema opgesteld met na-controle onderzoeken op de leeftijd van 3, 6, 12 en 24 maanden, gecorrigeerd voor de preterme geboorte. Tenslotte werden alle kinderen op de, voor de vroeggeboorte gecorrigeerde leeftijd van twee jaar gebaseerd op de uitslag van een psychomotorisch onderzoek, ingedeeld in drie categorieën: ernstig gehandicapt, licht gehandicapt of normaal. Het begrip handicap duidt op een verstoring van het dagelijks functioneren en als zodanig plaatst het de onderliggende stoornis ("impairment") of beperking ("dysability") in een sociale kontekst. Als ongewenste uitkomst werden gedefinieerd: "major adverse outcome" (= totale sterfte plus ernstige handicaps") en "total adverse outcome" (= totale sterfte plus ernstige en lichte handicaps), beide in levend geboren kinderen en "total handicaps" (= ernstige en lichte handicaps) in overlevende kinderen.

Het onderzoek werd gedecentraliseerd uitgevoerd door de plaatselijke kinderarts of door de kinderarts in het perinatologisch centrum, al naar gelang de voorkeur van de ouders. De verwerking en analyse van de gegevens vond in het coördinerend studiecentrum plaats.

Analyse van de gegevens gebeurde met behulp van beschrijvende statistiek, zoals frequentietabellen, en inferentiële statistiek. De relatie tussen verschillende perinatale factoren en de drie eerder gedefinieerde ongewenste uitkomsten werd geanalyseerd met behulp van multivariate statistische technieken. Zodoende kon worden gecorrigeerd voor de mogelijk ongelijke verdeling van storende factoren (confounders).

In *hoofdstuk 2* wordt een beschrijving gegeven van de uitkomst van de studiepopulatie op de leeftijd van twee jaar gecorrigeerd voor de vroeggeboorte. Van de 1338 kinderen, die oorspronkelijk in het onderzoek waren opgenomen,

overleden er 369 (27,6%), 59 kinderen (4,4%) ontwikkelden een ernstige handicap en 111 kinderen (8,3%) een lichte.

In tegenstelling tot de sterfte, bleek het optreden van een handicap niet samen te hangen met zwangerschapsduur of geboortegewicht.

Het gelukte, na veel inspanning, een follow-up percentage van 97.4% te behalen. In de groep kinderen waarvan het zeer moeilijk was gegevens te bemachtigen, was het percentage handicaps gelijk aan het percentage dat gevonden werd in de rest van de studie-populatie. Hieruit werd geconcludeerd dat in een gedecentraliseerde studie opzet, zoals hier gebruikt, een follow-up percentage van 90% waarschijnlijk voldoende is om de uitkomst te beschrijven zonder een bias ten gevolge van loss to follow-up te introduceren.

In *hoofdstuk 3* wordt de relatie beschreven tussen sterfte, handicaps en hypertensie tijdens de zwangerschap.

De sterfte tijdens de eerste ziekenhuisopname van kinderen van moeders met hypertensie tijdens de zwangerschap was significant lager dan van kinderen van moeders zonder hypertensie (respectievelijk 11% en 30%). Het percentage handicaps in beide groepen was gelijk (respectievelijk 16,2% en 18,7%).

Intra-uteriene groei, uitgedrukt in de confounders geboortegewicht en small for gestational age, hangt waarschijnlijk samen met hypertensie van de moeder tijdens de zwangerschap. Daarom werden twee verschillende multiple regressie analyses gedaan, namelijk mét en zónder deze twee factoren als confounders. Bij het vergelijken van de resultaten van de twee analyses bleef de conclusie gehandhaafd dat hypertensie van de moeder een eigen effect heeft op sterfte en handicap, ongeacht de intra-uteriene groei.

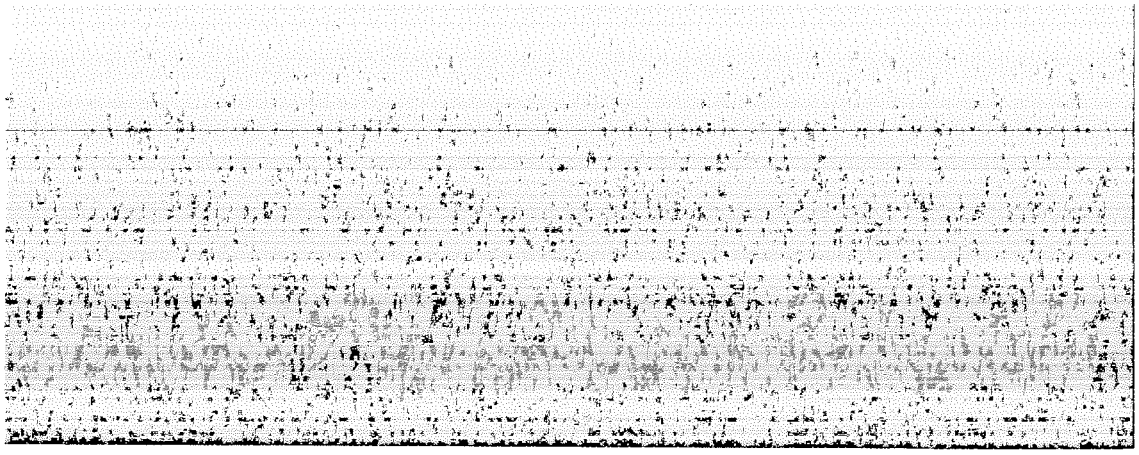
In *hoofdstuk 4* worden sterfte en handicaps beschreven bij kinderen van verschillend geslacht. De kans op sterfte tijdens de eerste ziekenhuisopname was voor jongens en meisjes in deze populatie gelijk. Bij de overlevende kinderen was de kans op een handicap echter voor jongens significant hoger dan voor meisjes: 15% van de jongens was op de leeftijd van twee jaar gehandicapt in tegenstelling tot 10% van de meisjes. Dit verschil in handicap percentages was duidelijk zichtbaar in vrijwel alle zwangerschapsduurcategorieën.

Deze significant hogere kans op een ongewenste uitkomst voor de jongens kon niet verklaard worden uit de gevolgen van de bekende vertraagde longrijping bij jongens, zoals IRDS en de behoefte aan kunstmatige ventilatie. De oorzaak blijft onduidelijk en verder onderzoek hiernaar is gewenst.

In *hoofdstuk 5* wordt het vóórkomen beschreven van neurologische dysfunctie (ND) in de neonatale periode.

Bij routine neurologisch onderzoek door de behandelende kinderartsen (alle niveau's van zorg), werd slechts bij 8% van de kinderen in de neonatale periode een neurologische dysfunctie vastgesteld. Het percentage van deze kinderen dat overleed of een handicap bleek te hebben was echter extreem hoog: respectievelijk 81% een 50%. Bij de overlevende kinderen die neurologisch normaal waren, werd een sterfte- en handicap percentage van respectievelijk 18% en 4% gevonden.

Gesteld wordt dat bij slechts weinig kinderen een duidelijke neonatale



neurologische dysfunctie werd gevonden, maar dat de sterfte in deze groep hoog was en een normale uitkomst uitzonderlijk.

Met dergelijk routine lichamelijk onderzoek, kan een kwart van de ernstig preterm geboren of very low birthweight (VLBW) kinderen met latere neurologische afwijkingen geïdentificeerd worden. Een meer gestandaardiseerd neurologisch onderzoek, opgenomen in het routine onderzoek van pasgeborenen in alle niveau's van zorg, zou het vroeg opsporen van kinderen met de kans op een handicap kunnen vergroten.

In *hoofdstuk 6* wordt de uitkomst beschreven van kinderen met convulsies gedurende de neonatale periode. Neonatale convulsies werden waargenomen bij 72 kinderen (5,4%): 44 kinderen overleden en 12 ontwikkelden een handicap. Bij vrijwel alle gehandicapte kinderen traden de convulsies gedurende de vijfde levensdag op of later. Desalniettemin werden 16 van de 28 overlevende kinderen met neonatale convulsies als normaal beschouwd op de gecorrigeerde leeftijd van 2 jaar.

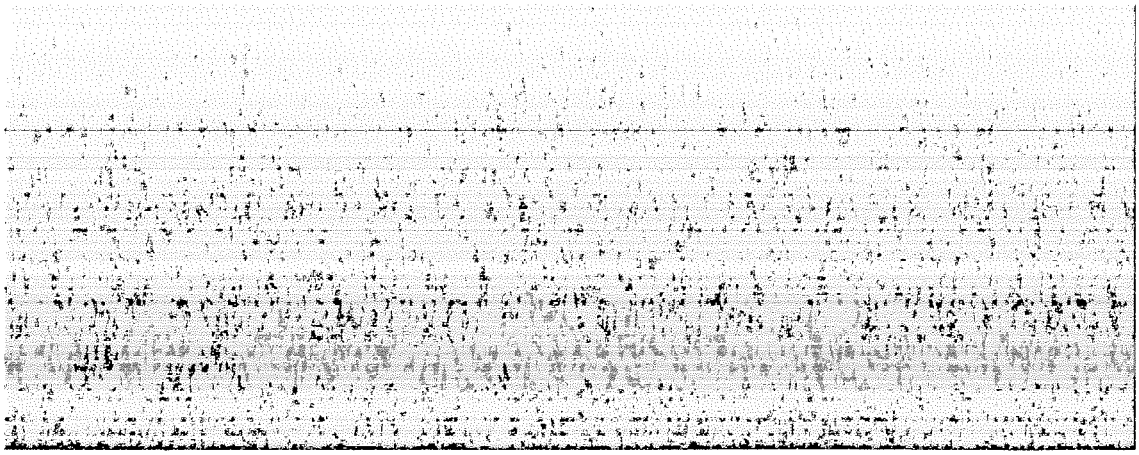
Klinische gegevens van de overlevende kinderen toonden een verschil in ernst van de neonatale complicaties in deze twee groepen. Bij bijna alle overlevende kinderen werd in de neonatale periode zowel een ICH als IRDS gediagnostiseerd. Bij de kinderen die overleefden met een handicap waren deze problemen echter ernstiger. Vaak was hierdoor een langere periode van kunstmatige beademing noodzakelijk; bovendien werd bij 6 van de 11 kinderen met een ernstige handicap een hydrocephalus gevonden.

In *hoofdstuk 7* wordt de relatie beschreven tussen de maximale totaal serum bilirubine concentratie in de neonatale periode (TBmax) en de psychomotore ontwikkeling op de gecorrigeerde leeftijd van 2 jaar. Kinderen met een lichte en ernstige handicap hadden een significant hogere TBmax dan kinderen met een normale psychomotore uitkomst. Een constante stijging in het vóórkomen van handicaps werd gevonden voor iedere 50 μmol/L (2,9 mg/dl) stijging van TBmax.

Met logistische regressie analyse werd een odds ratio van 1.3 gevonden, wat betekent dat, op een multiplicatieve schaal, de kans op een handicap toenam met 30% voor iedere stijging van de TBmax met 50 μmol/l (2,9 mg/dl). Voor een verdere analyse werd de mogelijke risicofactor bilirubine verdeeld in een aantal catgeorieën. Een opvallende systematische stijging werd gevonden, hetgeen wijst op een oorzakelijk verband (dosis-respons relatie) tussen TBmax en de psychomotore uitkomst. Alleen een gerandomiseerde klinische trial echter, kan het effect van een lagere bilirubine concentratie in het serum op de uiteindelijke uitkomst aantonen. Het is daarom niet juist het huidige klinische beleid te veranderen voordat een dergelijk onderzoek heeft plaatsgevonden.

In *hoofdstuk 8* wordt het gebruik van gezondheidszorgvoorzieningen beschreven, weergegeven in de frequentie van en redenen voor ziekenhuisheropnames. In de periode tussen ontslag naar huis na de eerste ziekenhuisopname en de gecorrigeerde leeftijd van 2 jaar werden 320 kinderen (34%) 481 keer opgenomen.

De belangrijkste redenen voor opname waren chirurgische ingrepen, waarbij



inguinale herniotomie het vaakst voorkwam, en aandoeningen van de tractus respiratorius: respectievelijk 149 (31%) en 147 (31%) opnames.

In een multivariate analyse bleek er een significant verband te bestaan tussen geslacht, de lengte van de eerste ziekenhuisopname en een verhoogde kans op heropname.

Het Nederlands Centraal Bureau voor de Statistiek verschafte gegevens over de doorsnee Nederlandse bevolking, zoals die zijn verzameld in de Gezondheidszorgenquête. Een vergelijking met onze gegevens toonde aan dat, zowel in het eerste als tweede jaar van nacontrole, een hoger percentage van de kinderen uit de studie-populatie in een ziekenhuis werd opgenomen. Bij de overlevende kinderen met een normale ontwikkeling werd echter in het tweede levensjaar een opname percentage gevonden dat genormaliseerd was tot dezelfde waarde als bij de kinderen uit de doorsnee bevolking.

In *hoofdstuk 9* wordt het gebruik van gezondheidszorgvoorzieningen beschreven, weergegeven in poliklinische consulten van medische specialisten en fysiotherapeutische behandeling.

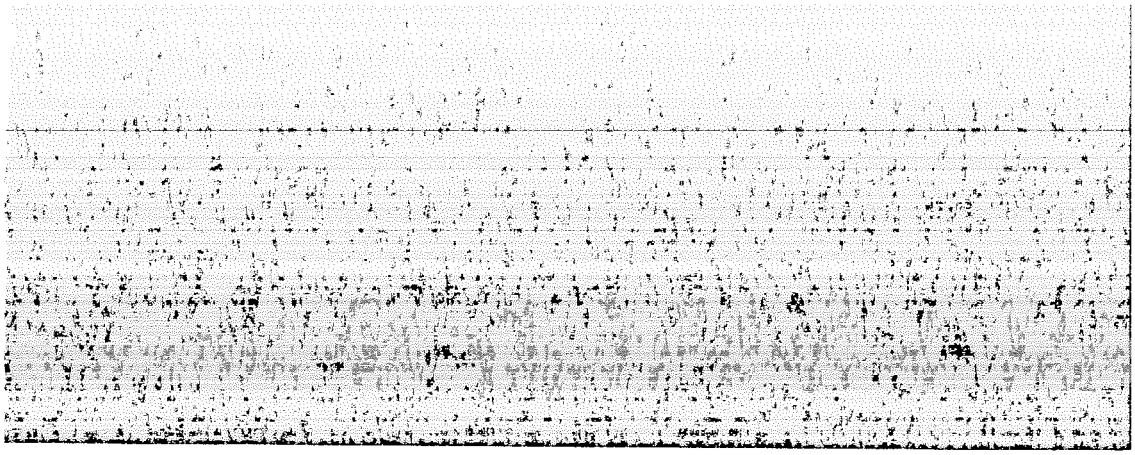
Gedurende de periode tussen ontslag na de eerste ziekenhuisopname en de gecorrigeerde leeftijd van 2 jaar bezochten 671 kinderen (67%) een medisch specialist (anders dan hun kinderarts) en bezochten 313 kinderen (31%) een fysiotherapeut.

In het algemeen was het polikliniek bezoek in het eerste jaar hoger dan in het tweede jaar en erg afhankelijk van de psychomotore ontwikkeling van het kind. Een vergelijking van het gebruik van poliklinische voorzieningen door kinderen met een normale uitkomst en kinderen uit de doorsnee Nederlandse bevolking toonde een gelijk gebruik in beide groepen.

In *hoofdstuk 10* wordt een beschrijving gegeven van de relatie tussen verschillende perinatale risicofactoren, sterfte en handicap. Als maat voor een ongewenste uitkomst werden gebruikt: "major adverse outcome" (= totale sterfte plus ernstige handicaps") en "total adverse outcome" (= totale sterfte plus ernstige en lichte handicaps), beide in levend geboren kinderen en "total handicaps" (= ernstige en lichte handicaps) in overlevende kinderen. Voor de verschillende perinatale factoren werden de ruwe percentages en de ruwe en gecorrigeeerde odds ratios berekend en samen met de uitkomsten van de sterfte tijdens de eerste ziekenhuisopname in één tabel getoond. Deze uitkomsten van de analyses werden voor iedere perinatale factor afzonderlijk in een korte beschrijvng toegelicht.

Naast de reeds in eerdere hoofdstukken beschreven perinatale factoren (hoofdstuk 4: geslacht, hoofdstuk 6: convulsies, hoofdstuk 7: bilirubine), waren de factoren: reeds bestaande ziekte van de moeder, aangeboren afwijkingen, antenataal transport en Apgar score op de leeftijd van 5 minuten significant geassocieerd met een ongewenste uitkomst bij de overlevende kinderen.

In *hoofdstuk 11* wordt een overzicht gegeven van de aantallen kinderen die tijdens de onderzoeksperiode zijn overleden, in leven bleven en werden naonderzocht, ingedeeld in verschillende categorieën van zwangerschapsduur en

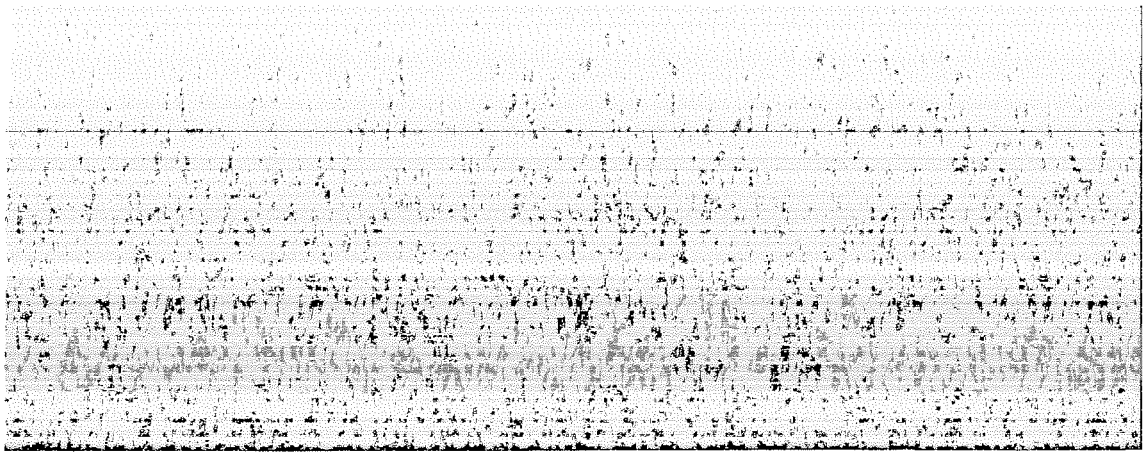


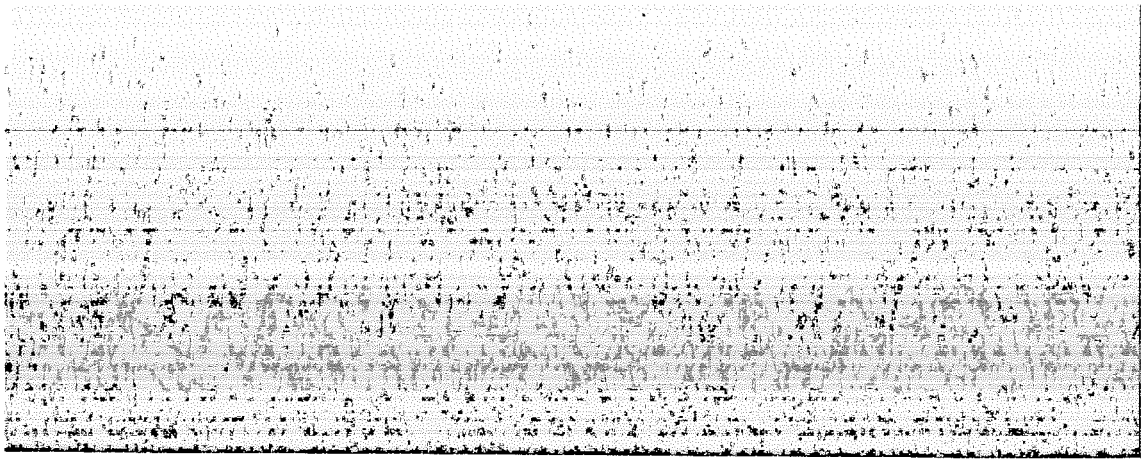
geboortegewicht. Bovendien werden de resultaten van dit onderzoek vergeleken met eerder gepubliceerde resultaten van zes soortgelijke onderzoeken.

In de afgelopen decennia zijn de overlevingskansen van de in dit onderzoek beschreven groepen risico-kinderen indrukwekkend verbeterd. Als gevolg hiervan is de aandacht van naonderzoeken verschoven van de kans op overleven, naar de kans op ongewenste latere gevolgen zoals ernstige handicaps. Het is van belang na te gaan of de toename van het aantal overlevende kinderen al of niet samengaat met een toename van het aantal kinderen met een ernstige handicap. Indien het aantal kinderen met een ernstige handicap zou zijn gestegen dan was de "major adverse outcome" gelijk gebleven.

De "major adverse outcome" werd berekend voor de vergelijkbare onderzoeken. Hieruit bleek dat in het midden van de jaren zeventig een daling van de mortaliteit samenging met een betrekkelijk hoge "major adverse outcome" ten gevolge van een toegenomen handicap percentage. In de jaren daarna verdween dit verschijnsel ten koste van een wat hoger sterfte percentage. In dit onderzoek echter daalde het sterfte percentage verder terwijl het handicap percentage laag bleef, hetgeen leidde tot het laagste "major adverse outcome" percentage dat tot nu toe beschreven is.

De voorlopige resultaten van het na-onderzoek op de leeftijd van 5 jaar laten vooralsnog zien, dat het lage handicap percentage dat op de leeftijd van 2 jaar werd gevonden realiteit blijkt. Resultaten van toekomstige onderzoeken op dit terrein moeten uitwijzen of de daling van de "major adverse oucome" ook zal doorzetten.





ACKNOWLEDGEMENTS

The Project On Preterm and Small for gestational age infants was initiated by the Division of Perinatology of the Dutch Paediatric Association. It was carried out as a nationwide collaborative study, on a voluntary basis, by the Dutch paediatricians (appendix H).

Several paediatricians cooperating in the survey, retired or changed jobs during the more than two years of follow-up. Their successors were in most cases willing to continue participation in the survey. Their readiness to cooperate in completing the follow-up data was of the utmost importance. Furthermore, the enthousiastic collaboration with family-doctors and doctors working in community child health centres and several institutions enabled us to minimize the loss to follow-up.

During the study the need surfaced for a counselling committee. Prof.dr. H.J. Huisjes (obstetrics), Dr. E.J.P. Lommen (general paediatrics), Prof.dr. A. Okken (neonatology), Prof.dr. P.J.J. Sauer (neonatology), succeeded later by Prof.dr. B.C.L. Touwen (developmental neurology), and Prof.dr. J.C. van Wieringen (social paediatrics) participated in such a committee. Their personal interest in the study was very elucidating and stimulating.

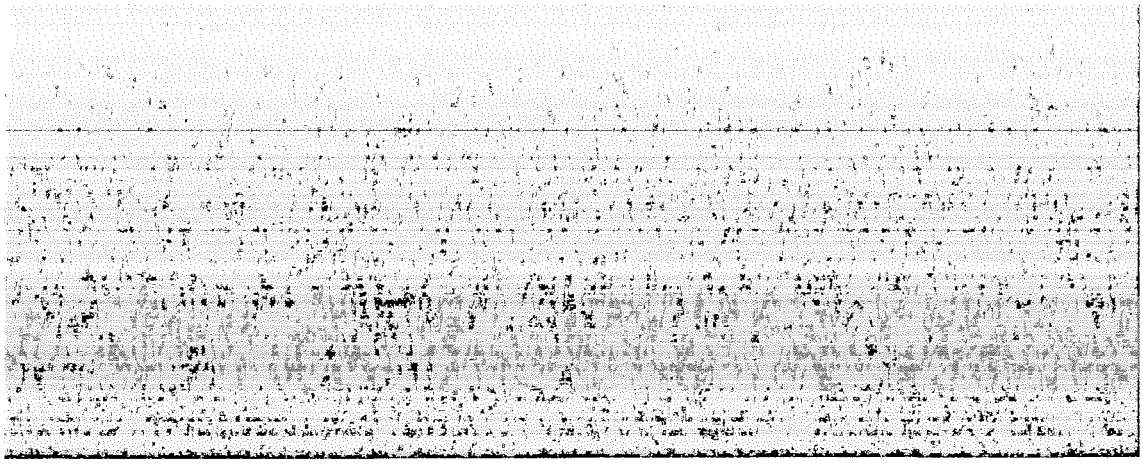
Robert Verwey (obstetrician), Margot van de Bor (neonatologist) and Lya den Ouden (neonatologist), took a keen interest in the progress of the study. It was very inspirational to work with them and I am grateful for their support.

During the phase of data collecting Janet Tonus-Dietz was in charge of the study centre secretariat. From 1985 Alwine Maat-Cohen and Ina Kloosterboer-Boerrigter were responsible for the administrative side of the study in general and of this thesis in particular.

Het Project Onderzoek Prematuritas en Small for gestational age werd gestart op initiatief van de Sectie Perinatologie van de Nederlandse Vereniging voor Kindergeneeskunde. Het werd, om des danks wille, uitgevoerd in een landelijk samenwerkingsverband van kinderartsen (appendix H).

Tijdens de ruim twee jaar van nacontrole legden meerdere kinderartsen, die vanaf het begin bij het project betrokken waren hun praktijk neer. Het was van het grootste belang voor het onderzoek, dat hun opvolgers meestal bereid waren het door deze deelnemers begonnen werk voort te zetten. Ook de samenwerking met consultatiebureau-, instellings- en huisartsen was essentieel voor het completeren van de gegevens.

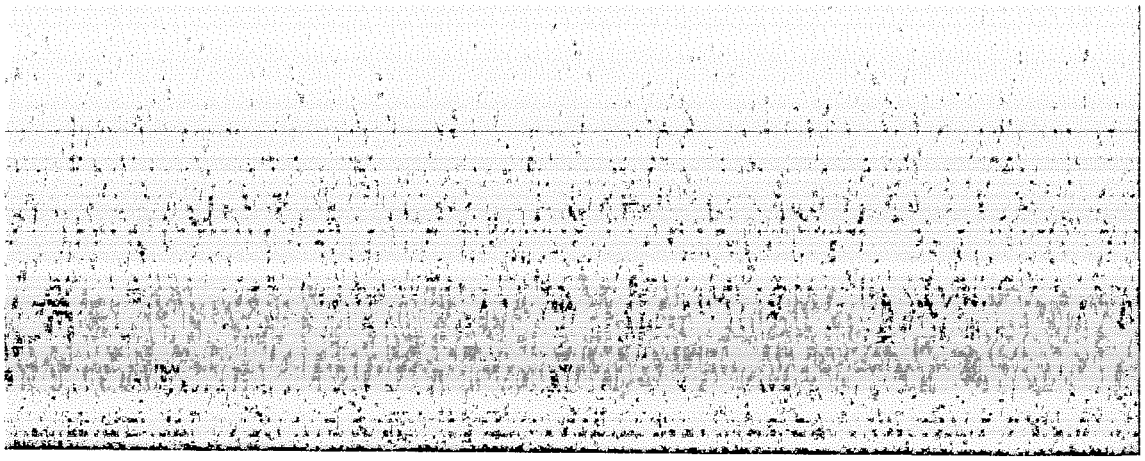
In de fase van bewerking van de gegevens werd een begeleidingscommissie gevormd met het doel de kwaliteit van het onderzoek te bevorderen en te bewaken. Prof.dr. H.J. Huisjes (obstetrie), Dr. E.J.P. Lommen (algemene kinder-



geneeskunde), Prof.dr. A. Okken (neonatologie), Prof.dr. P.J.J. Sauer (neonatologie), later opgevolgd door Prof.dr. B.C.L. Touwen (ontwikkelings neurologie), en Prof.dr. J.C. van Wieringen (sociale kindergeneeskunde) namen deze taak op zich. Hun inbreng werkte stimulerend en verhelderend.

Robert Verwey (vrouwenarts), Margot van de Bor (neonatoloog) en Lya den Ouden (neonatoloog), voelden zich zeer betrokken bij de voortzetting van het project. De samenwerking met hen werkte inspirerend en hun steun kwam vaak op het juiste moment.

Het project-secretariaat werd in de fase van gegevens verzameling beheerd door Janet Tonus-Dietz. Vanaf 1985 namen Alwine Maat-Cohen en Ina Kloosterboer-Boerrigter haar taak over; zij waren verantwoordelijk voor de secretariële werkzaamheden van het onderzoek in het algemeen en van dit proefschrift in het bijzonder.



CURRICULUM VITAE

(Doro)Thea M.C.B. van der Aa was born in Leiden on December 29th, 1953. In 1972, she finished high-school (gymnasium β) at the S Adelbert College in Wassenaar. She then entered the Leiden University to study medicine and qualified in 1979.

From 1980 till 1984 she followed her paediatric training at the Juliana Children Hospital, 's-Gravenhage (Dr. W. van Zeben† and Dr. H.H. Zoethout) and in the paediatric department of the University Hospital, Leiden (Prof. Dr. L.J. Dooren).

From December 1984 till July 1989 she joined the "Project On Preterm and Small for gestational age infants". Her main task was to coordinate the data collecting and processing of the two year follow-up period. For this project the Neonatal Centre, Paediatric Department, Leiden University Hospital, was financially supported by the Praeventiefonds, the Hague.

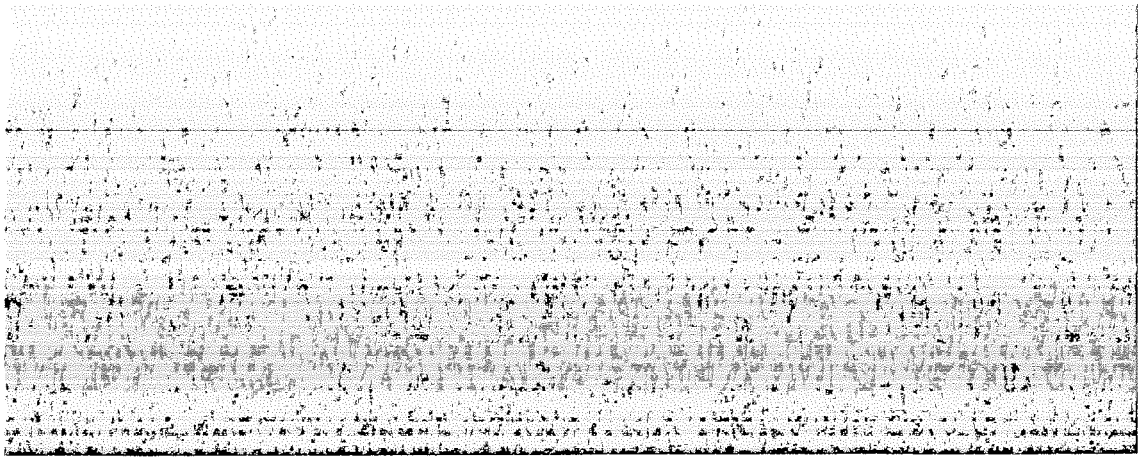
She is married to Gert Jan van Zeben, and has two children, a daughter Josefien and a son Pieter.

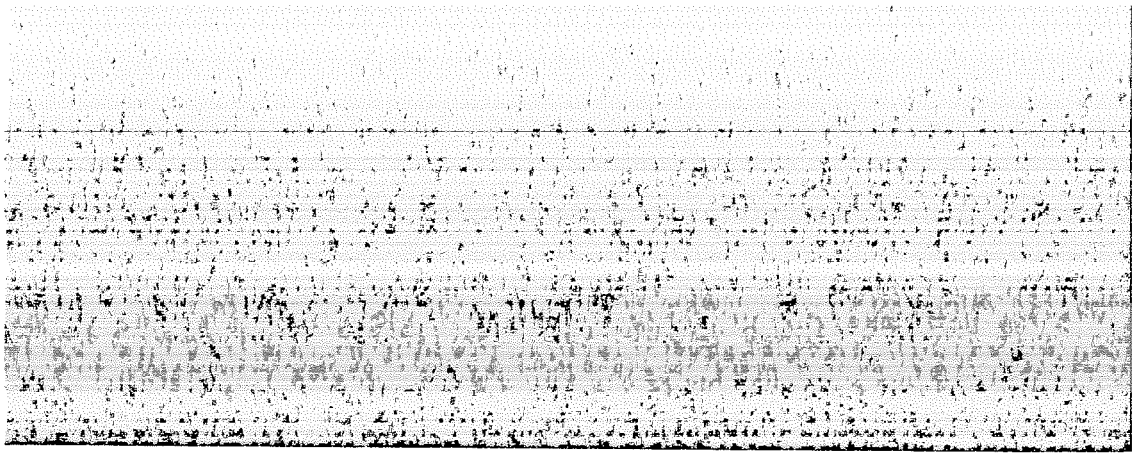
(Doro)Thea M.C.B. van der Aa werd op 29 december 1953 geboren te Leiden. In 1972 behaalde zij het diploma gymnasium β aan het S Adelbert College te Wassenaar. Aansluitend studeerde zij geneeskunde aan de Rijksuniversiteit Leiden alwaar in 1979 het artsexamen werd afgelegd.

Van 1980 tot 1984 werd zij opgeleid tot kinderarts in het Juliana Kinderziekenhuis te 's-Gravenhage (Dr. W. van Zeben† en Mevrouw Dr. H.H. Zoethout) en in de afdeling Kindergeneeskunde van het Academisch Ziekenhuis te Leiden (Prof. dr. L.J. Dooren).

Van december 1984 tot juli 1989 was zij werkzaam bij het "Project Onderzoek Prematuritas en Small for gestational age", waar zij zich met name heeft beziggehouden met de coördinatie en gegevensverwerking van het naonderzoek tot de leeftijd van twee jaar. Voor dit project ontvangt het Neonatologisch Centrum, afdeling Kindergeneeskunde, Academisch Ziekenhuis, Leiden, een subsidie van het Praeventiefonds.

Zij is getrouwd met Gert Jan van Zeben en heeft twee kinderen, een dochter Josefien en een zoon Pieter.





APPENDIX A

a-formulier

project onderzoek prematuritas en SGA in nederland (POPS)

praeventiefonds subsidie nr. 28-766

codeerinstructie:
als een (deel van een) gegeven onbekend is, coderen met 999.
indien niet van toepassing 888.

identificatie

formulier nummer POPS : _____

universitaire neonat. int. care unit : _____

registratienummer aldaar : _____

andere couveuse afdeling(en) : _____

registratienummer aldaar : _____

kaart nr. 1 101 [0 1]

01 **registratienummer POPS** 103 / 104 / 107 niet invullen

gegevens moeder

02 **geboortedatum** (dg / mnd / jr) 111

03 **meisjesnaam** (eerste 3 letters) 117

04 **postcode** (woonplaats) 120

05 **socio-economische groep:** **moeder:** beroep _____ **vader:** beroep _____ 126 niet invullen
opleiding _____ opleiding _____

wijze van **ziektekostenverzekering:** verplicht / vrijwillig / particulier

06 **bevolkingsgroep:**

beide ouders **kaukasisch** (blank)		nee 0	ja 1	127
een van beide of beide ouders	**mediterraan**	nee 0	ja 1	128
	negroïd	nee 0	ja 1	129
	aziatisch	nee 0	ja 1	130
	andere	nee 0	ja 1	131

07 **burgelijke staat moeder:** gehuwd 0 niet (meer) gehuwd, wel in gezinsverband levend met partner of ouders 1 niet (meer) gehuwd, alleen 2 anders 3 132

obstetrische gegevens

08 **datum laatste menstruatie** (dg / mnd / jr) 133

09 **aantal zwangerschappen vóór deze** 139

10 **aantal abortussen vóór deze** (0 t/m 15+6 weken = 0 t/m 111 dg) 140

11 **aantal partus immaturus en/of prematurus vóór deze** (16 t/m 36+6 weken = 112 t/m 258 dg) 141

12 **aantal levende kinderen** (8 = 8 of meer) 142

13 **ziekten vóór de zwangerschap:**	**hartaandoening**	nee 0	ja 1	143
	epilepsie	nee 0	ja 1	144
	diab. mellitus	nee 0	ja 1	145
	nierziekte	nee 0	ja 1	146
	hypertensie (diastolische bloeddruk ≥ 90 mm Hg)	nee 0	ja 1	147
14 **ziekten tijdens zwangerschap:**	**diab. mell. grav.**	nee 0 dieet 1	insuline 2	148
	actief bloedgroepantagonisme (Rh, Duffy, Kell, ABO), (positieve antistoftiter, plasmaferese, intrauteriene bloedtransfusies of vervroegde geboorte)	nee 0	ja 1	149
	hypertensie	nee 0 2 x ≥ 90 mm Hg diast. 1 pre- eclampsie 2 eclampsie 3		150
15 **intoxicaties tijdens de zwangerschap:**				
	roken	nee 0 ja 0-10 sig/dag 1 ja meer dan 10 sig/dag 2		151

formulier nummer POPS : _____

	alkoholverslaving	nee 0	ja 1	152
	soft drugs	nee 0	ja 1	153
	hard drugs	nee 0	ja 1	154
	methadon	nee 0	ja 1	155
16 ziekenhuisopname	tijdens en verbandhoudende met zwangerschap; herhaalde opnames bij elkaar tellen			
	nee 0	ja minder dan 1 week 1	ja 1 week of langer 2	156
17 CTG-afwijkingen	tijdens zwangerschap vóór partus (ja, indien Fischer-score < 5 of oordeel van obstetricus aanhouden, gebaseerd op b.v. type II-dips = late deceleraties, aantal 0-doorgangen, sinusoid patroon e.d.)	nee 0	ja 1 niet verricht 8	157
18 medicijngebruik	tijdens de zwangerschap (geen ijzer, vitamine, fluor vermelden)			
	diuretica	nee 0	ja 1	158
	antihypertensiva	nee 0	ja 1	159
	tranquillizers	nee 0	ja 1	160
	anti-epileptica	nee 0	ja 1	161
	antibiotica	nee 0	ja 1	162
	gestagenen	nee 0	ja 1	163
	asthma ther.	nee 0	ja 1	164
	andere	nee 0	ja 1	165
	namelijk _____			

kaart nr. 2 201 0 2

geboorte

19 geboortedatum	(dg / mnd / jr)	203
20 geboortetijdstip	(uur / min.)	209
21 zwangerschapsduur	(wk + dg) zoals opgegeven door obstetricus (op grond van amenorrhoe duur en/of echografie en/of zwangerschapstesten)	213 +
22 betrouwbaarheid termijn	zeker 0 dubieus 1 onbetrouwbaar 2	216
23 geslacht	vrouw 1 man 2 onduidelijk 3	217
24 ligging	van het kind bij de geboorte (ook invullen bij sectio caesarea)	
	achterhoofd 0 andere hoofd 1 stuit 2 dwars 3 overige 4	218
25 gebruik van weeënremmende middelen, langer dan 24 uur.		
β-mimetica (prepar, partusisten, Th 1165A, duvadilan)	nee 0 ja 1	219
prostaglandine synthetase remmers (b.v. Indomethacine)	nee 0 ja 1	220
andere	nee 0 ja 1	221
in combinatie met corticosteroiden	nee 0 ja 1	222
26 gebruik van weeën stimulerende middelen		
	nee 0 ja oxytocine 1 ja prostaglandine 2 andere 3	223
27 inleiding van de baring	d.m.v. amniotomie en/of weeënstimulerende middelen nee 0 ja 1	224
28 wijze van geboorte		
vaginaal **hoofdligging, spontaan**	ja 0 met expressie 1 nee 2	225
vacuumextractie	nee 0 ja 1	226
forcipale extractie	nee 0 ja 1	227
stuitgeboorte (Bracht)	nee 0 ja 1	228
stuitextractie	nee 0 ja 1	229
versie en extractie	nee 0 ja 1	230

formulier nummer POPS : _____

sectio caesarea nee 0
ja, bij staande vliezen zonder weeënactiviteit 1
ja, bij gebroken vliezen zonder weeënactiviteit 2
ja, bij staande vliezen met weeënactiviteit 3
ja, bij gebroken vliezen met weeënactiviteit 4 — 231 ☐

andere wijze van geboorte nee 0 ja 1 — 232 ☐

namelijk _____

28 CTG tijdens de partus (zie ook vraag 17) normaal 0 afwijkend 1 niet verricht 8 — 233 ☐

30 sedativa en / of analgetica tijdens de partus

pethidine nee 0 ja 1 — 234 ☐

valium nee 0 ja 1 — 235 ☐

andere nee 0 ja 1 — 236 ☐

31 anaesthesie tijdens de partus: epi / periduraal nee 0 ja 1 — 237 ☐

totaal nee 0 ja 1 — 238 ☐

locaal nee 0 ja 1 — 239 ☐

32 gebroken vliezen bij het begin van de partus

nee 0 minder dan 12 uur 1 12-24 uur 2 1-7 dg 3 langer dan 7 dg 4 — 240 ☐

33 elholte infectie met koorts en/of leucocytose van de moeder tijdens de partus nee 0 ja 1 — 241 ☐

34 vruchtwateraspect helder 0 meconiumhoudend 1 stinkend foetide 2 met bloed 3 — 242 ☐

kind

35 geboortegewicht (grammen) — 243 ☐☐☐☐

36 geboortelengte (cm) — 247 ☐☐☐

37 schedelomtrek (cm), (gemeten na minstens 24 uur en binnen 7 dagen) — 249 ☐☐☐

38 rijpingsscore (wk + dg) (bijv. volgens Dubowitz, Ballard, Finnstrøm, Mitchel-Farr of Parkin, a.v.p. onderstrepen welke methode gevolgd is) — 251 ☐☐ + ☐

39 apgar score

	0	1	2
hartfreq.	afw.	< 100	> 100
ademhaling	afw.	traag irreg	goed
tonus	slap	matig	goed
prikkelbaarh.	afw.	matig	goed
kleur	blauw-bleek	extrem. blauw	roze (acrocyan. mag)

na 1 minuut (niet verricht 88) — 254 ☐☐
na 3 minuten (niet verricht 88) — 256 ☐☐
na 5 minuten (niet verricht 88) — 258 ☐☐
na 10 minuten (niet verricht 88) — 260 ☐☐

40 pH arterieel navelstreng (2 decimalen) niet verricht 888 — 262 ☐,☐☐

pCO_2 arterieel navelstreng (kPa 1 decimaal; 1 kPa = 7,5 mm Hg) niet verricht 888 — 265 ☐☐,☐

41 pH veneus navelstreng (2 decimalen) niet verricht 888 — 268 ☐,☐☐

pCO_2 veneus navelstreng (kPa, 1 decimaal; 1 kPa = 7,5 mm Hg) niet verricht 888 — 271 ☐☐,☐

42 pH capillair binnen 30 min. na de geboorte (2 decimalen) niet verricht 888 — 274 ☐,☐☐

pCO_2 capillair binnen 30 min. na de geboorte (kPa, 1 decimaal; 1 kPa = 7,5 mm Hg) niet verricht 888 — 277 ☐☐,☐

43 meerling enkelvoud 0 tweeling 1e kind 1 tweeling 2e kind 2 drieling 1e kind 3 drieling volgende kind 4 vierling 1e kind 5 vierling volgende kind 6 vijf- of zesling 1e kind 7 vijf- of zesling volgende kind 8 — 280 ☐

kaart nr. 3 — 301 0 3

44 plaats van geboorte

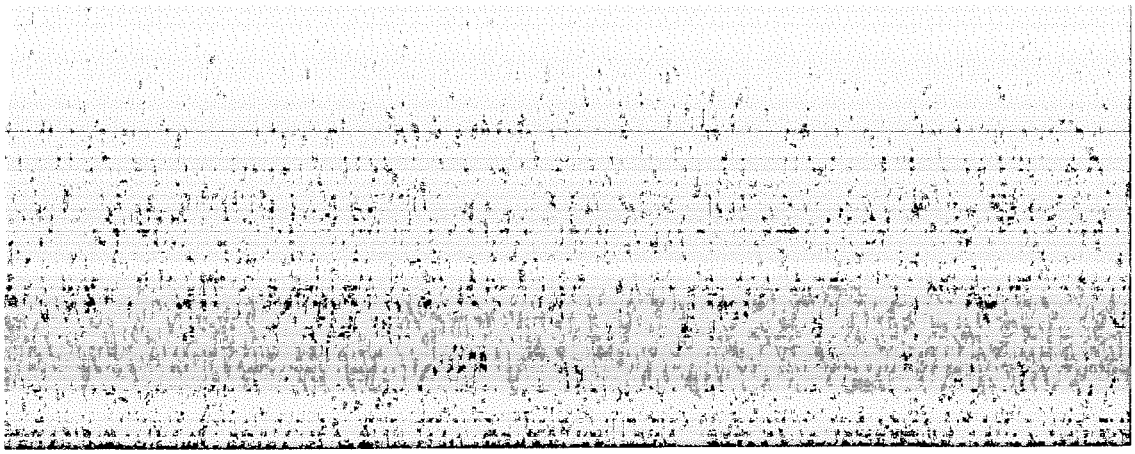
universitaire afd. verloskunde, met neonatologisch intensive-care-centrum 0 — 303 ☐

algemeen ziekenh. met neonatologische high-care en medium-care; enige intensive-care faciliteiten 1

algemeen ziekenh. met kinderarts, „opvang-couveuse" 2

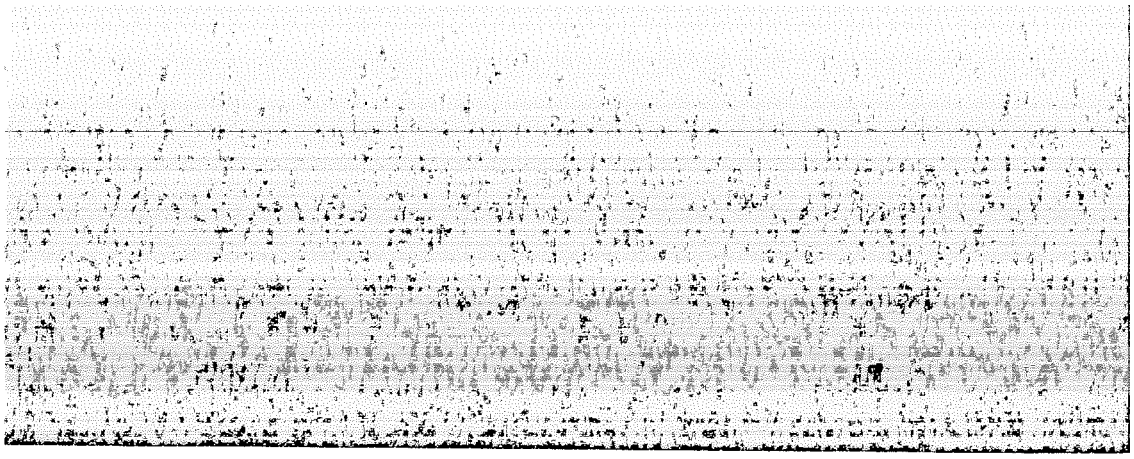
ziekenhuis of kraamkliniek zonder kinderarts 3

elders 4



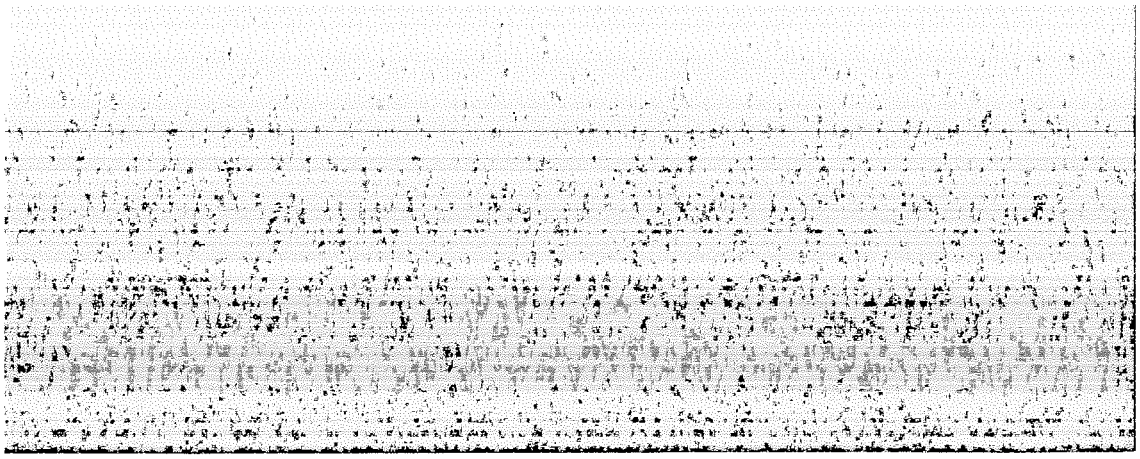
formulier nummer POPS : _____

45 transport	geen transport **0** intra-uterien, mevrouw niet in partu **1** intra-uterien, mevrouw wel in partu **2** zo snel mogelijk post partum, team uit centrum binnen 1 uur aanwezig **3** zo snel mogelijk post partum, tijdsverloop tot team uit centrum aanwezig > 1 uur **4** „secundair" transport na optreden pathologie **5** „secundair" transport na aanvankelijk dreigend overlijden **6**	304
46 wijze van transport	geen **0** intensive care-transport (babylance) door: Amsterdam VU **1** Amsterdam WG **2** Groningen **3** Leiden **4** Nijmegen **5** Rotterdam **6** Utrecht **7** ander transport **8** Maastricht 9	305
47 hypothermie	(op 1e levensdag < 35,5° C) nee **0** ja **1**	306
48 longafwijkingen	**I.R.D.S.** nee **0** klinisch (> 24 uur O_2-behoefte, kreunen e.d.) **1** röntgenologisch (> 24 uur granulair beeld, luchtbronchogram) **2**	307
	wet-lung nee **0** klinisch **1** röntgenologisch (interlobaire vochtlijn) **2**	308
	(cong.) pneumonie nee **0** ja **1**	309
	atelectase nee **0** ja **1**	310
	pneumothorax of pneu elders nee **0** ja **1**	311
	interstitieel emfyseem nee **0** ja **1**	312
	meconium aspiratie nee **0** ja **1**	313
	voedingsaspiratie nee **0** ja **1**	314
	bronchopulmonaire dysplasie nee **0** ja **1**	315
	Mikity Wilson nee **0** ja **1**	316
49 persisterende foetale circulatie	nee **0** ja **1** tolazoline **2**	317
50 open Ductus Botalli	(van haemodynamisch belang) nee **0** waarschijnlijk **1** ja (bewezen bij echo, hartcatheterisatie of operatie) **2**	318
therapie daarvoor	**conservatief** (vochtbeperking, diuretica) nee **0** ja **1**	319
	medicamenteus (Indomethacine) nee **0** ja **1**	320
	operatief nee **0** ja **1**	321
51 apnoe-aanvallen	(minstens 15 sec. of met bradycardie <100/min) nee **0** ja **1**	322
therapie:	**prikkelen** nee **0** ja **1**	323
	medicamenteus (coffeïne, theofylline etc.) nee **0** ja **1**	324
	CPAP nee **0** ja **1**	325
	IPPV nee **0** ja **1**	326
52 bradycardieën	(<100/min., **zonder** apnoe) nee **0** ja **1**	327
53 continuous positive airway pressure (CPAP) (aantal dagen, b.v. **004**)		328
54 intermittent positive airway pressure (IPPV) (aantal dagen, b.v. **008**)		331
55 congenitale infecties (positieve bloedkweek, sputumkweek e.d.; contaminatie huid e.d. **niet** als infectie opgeven)		
	cong. β-haem. strept. gr. B nee **0** ja **1** geen kweek verricht **8**	334
	hepatitis (hepatitis B virus) nee **0** ja **1** geen onderzoek verricht **8**	335
	herpes nee **0** ja **1** geen onderzoek verricht **8**	336
	cytomegalie nee **0** ja **1** geen onderzoek verricht **8**	337
	listeria nee **0** ja **1** geen onderzoek verricht **8**	338
	rubella nee **0** ja **1** geen onderzoek verricht **8**	339
	toxoplasmose nee **0** ja **1** geen onderzoek verricht **8**	340
	lues nee **0** ja **1** geen onderzoek verricht **8**	341



formulier nummer POPS : _____

56 **sepsis**	**klinisch beeld** sterk verdacht	nee 0	ja 1	342
	bloedbeeld typisch voor sepsis	nee 0	ja 1	343
	positieve bloedkweek	nee 0	ja 1	344
57 **sepsis verwekker**	**β-haemol. strept. gr. B**	nee 0	ja 1	345
	E-coli	nee 0	ja 1	346
	staphyl. aureus	nee 0	ja 1	347
	staphyl. epid. = albus	nee 0	ja 1	348
	andere	nee 0	ja 1	349
58 **meningitis**	**klinisch beeld** sterk verdacht	nee 0	ja 1	350
	positieve liquor kweek	nee 0	ja 1	351
59 **serum bilirubine**	hoogste waarde (capillair, in µmol/l)			352
60 **dag waarop deze waarde bereikt werd**				355
61 **fototherapie**	(aantal dagen)			357
62 **wisseltransfusies**	(aantal; uitgezonderd partiële wisseltransfusie wegens hyperviscositeit)			359
63 **indicatie voor wisseltransfusie**	**hyperbilirubinaemie**	nee 0	ja 1	360
	sepsis	nee 0	ja 1	361
	metabole stoornis	nee 0	ja 1	362
	intoxicatie	nee 0	ja 1	363
64 **totale parenterale voeding**	(mengsel van glucose, aminozuren en/of vet)	niet of < 24 uur 0 1 t/m 7 dg 1 8 t/m 28 dg 2 > 28 dg 3		364
65 **transpylorische voeding**	(oro-duodenaal, nasoduodenaal enz.)	niet of < 24 uur 0 1 t/m 7 dg 1 7 t/m 28 dg 2 > 28 dg 3		365
66 **necrotiserende enterocolitis**	nee 0 klinisch zeer verdacht 1 röntgenologisch duidelijk 2 operatief behandeld 3			366
67 **intracraniële bloeding**	(klinisch)	nee 0 verdacht 1	duidelijk 2	367
68 **diagnose intracraniële bloeding vastgesteld m.b.v.**				
	lumbaalpunctie	nee 0 verdacht 1	bewezen 2	368
	echografie	nee 0 verdacht 1	bewezen 2	369
	CT-scan	nee 0 verdacht 1	bewezen 2	370
	pulsatie-index Doppler	nee 0 verdacht 1	bewezen 2	371
	PA	nee 0	bewezen 2	372
69 **localisatie intracraniële bloeding**				
	subependymaal	nee 0	ja 1	373
	parenchymaal	nee 0	ja 1	374
	subarachnoïdaal	nee 0	ja 1	375
	intraventriculair	nee 0	ja 1	376
	cerebellair	nee 0	ja 1	377
	subduraal	nee 0	ja 1	378
70 **convulsies**	geen 0 op 1e levensdag 1 2e t/m 4e levensdag 2 5e dag of later 3			379
kaart nr. 4				401 0 4
71 **hydrocefalie**	**te snelle toename ventrikelgrootte**	nee 0	ja 1	403
	te snelle toename schedelomtrek	nee 0	ja 1	404
	frequente liquorpuncties	nee 0	ja 1	405
	ventrikulo-peritoneale of andere drainage	nee 0	ja 1	406



formulier nummer POPS : _____

72 afwijkingen centr. zenuwstelsel (tonus, motoriek, (neonatale) reflexen) normaal **0** dubieus **1** afwijkend **2** 407

73 afwijkingen perifere zenuwstelsel (Erbse parese, facialis parese, abducens parese e.d. nee **0** ja **1** 408

74 retrolentale fibroplasie nee **0** mogelijk **1** ja **2** geen fundoscopie verricht **8** 409
(mogelijk = verdacht, misschien in lichte mate; ja = bij fundoscopie duidelijk vastgestelde vaatproliferatie en/of ingroei, in beginfase of ernstiger)

75 medicamenteuze behandeling (uitgezonderd vitamines, ijzer e.d.)

antibiotica	nee **0** ja **1**	410
diuretica	nee **0** ja **1**	411
digoxine	nee **0** ja **1**	412
corticosteroiden	nee **0** ja **1**	413
anti-convulsiva (luminal wgs. hyperbilirubinaemie als „andere" coderen)	nee **0** ja **1**	414
andere	nee **0** ja **1**	415

76 aangeboren afwijkingen geen **0** wel met leven verenigbaar **1** niet met leven verenigbaar **2** 416

77 soort aangeboren afwijking (maximaal 6, zie lijst achterzijde) 417 419 421 423 425 427

78 overleden aan

aangeboren afwijking (zie vraag 76)	nee **0** ja **1** n.v.t. **8**	429
IRDS	nee **0** ja **1** n.v.t. **8**	430
intracraniële bloeding	nee **0** ja **1** n.v.t. **8**	431
congenitale infectie	nee **0** ja **1** n.v.t. **8**	432
sepsis	nee **0** ja **1** n.v.t. **8**	433
necrotiserende enterocolitis	nee **0** ja **1** n.v.t. **8**	434
andere, nl. _____	nee **0** ja **1** n.v.t. **8**	435

79 datum van overlijden (dg / mnd / jr) niet van toepassing **88 88 88** 436

80 tijdstip van overlijden (uren / min.) niet van toepassing **88 88** 442

81 wijze van overlijden spontaan **1** niet (verder) behandelbaar geacht **2** fout en/of accident **3** n.v.t. **8** 446

82 datum ontslag uit universitaire intensive care unit (dg / mnd / jr) (niet van toepassing **88 88 88**) 447

83 datum ontslag naar huis (of gezinsvervangend tehuis) (niet van toepassing **88 88 88**) 453
(beide data kunnen dus hetzelfde zijn)

84 toestand kind bij ontslag naar huis goed **0** dubieus **1** afwijkend **2** 459
(b.v. neurologische stoornis, longproblemen, voedingsproblemen enz.) n.v.t. **8**

85 gewicht bij ontslag naar huis (in grammen) niet van toepassing **88 88** 460

86 ontwikkeling kind bij ontslag naar huis, m.n. contact e.d. passend bij gecorr. leeftijd **0** 464
dubieus **1** achter **2** n.v.t. **8**

eigen coderingen inzender 465 470

nacontroles zullen verricht worden door

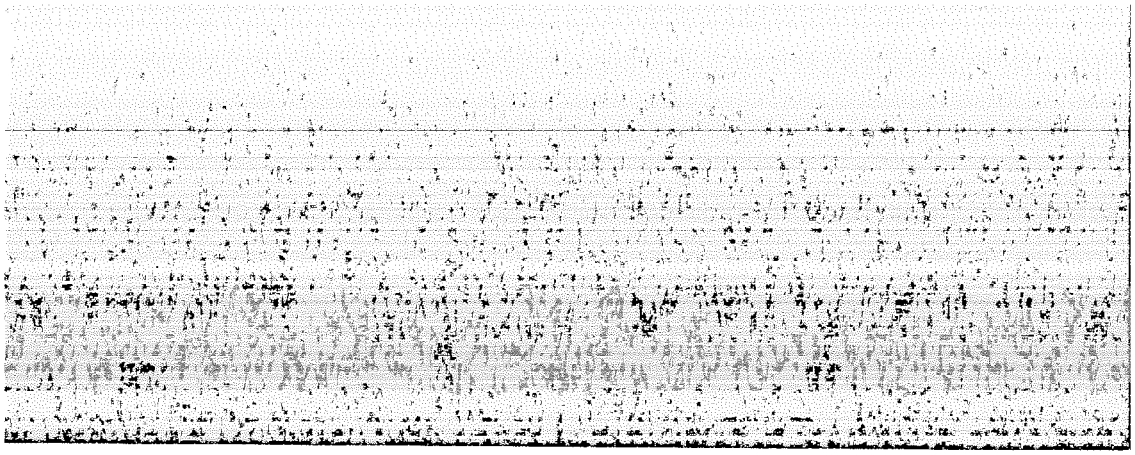
kinderarts _____

ziekenhuis _____
(deze krijgt b-c-d-e formulieren toegestuurd)

uitval op later tijdstip 475 niet invullen

2e centrum 476

2e andere afdeling 477



LIJST AANGEBOREN AFWIJKINGEN (zie vraag 77)

00 geen aangeboren afwijkingen

zenuwstelsel

01 anencefalie

02 microcefalie

03 spina bifida occulta

04 spina bifida aperta

05 hydrocefalie

06 meningomyelocele

07 encefalocele

09 andere cong. afw. centraal zenuwstelsel

zintuigen

10 microphthalmie

11 andere cong. afw. ogen

12 cong. afw. oren

hartvaatstelsel

20 vitium cordis

21 ontbreken van één navelarterie

29 andere cong. vaatanomalieën

ademhalingswegen

30 choanaal atresie

39 overige cong. afw. tractus respiratorius

spijsverteringsstelsel

40 gehemeltespleet

41 lipspleet

42 oesofago-tracheale fistel

43 oesofagus atresie

44 overige darmatresie incl. van de anus

45 hernia diafragmatica

49 andere cong. afw. tractus digestivus

urogenitaal systeem

50 hypospadie en epispadie

59 andere cong. afw. tractus urogenitalis

huid

60 naevus pigmentosus

61 haemangioma cavernosum

69 andere cong. huidafwijkingen

bewegingsstelsel

70 polydactylie

71 syndactylie

72 focomelie en amelie

73 congenitale heupluxatie

74 pes equinovarus

75 andere cong. afw. van de extremiteiten

76 cong. afw. van bot en skelet

79 andere cong. afw. van het bewegingsstelsel (inclusief spierstelsel)

overige congenitale afwijkingen

80 struma congenita

81 syndroom van Down

82 andere chromosoomafwijkingen

83 situs inversus

84 multipele congenitale afwijkingen

89 overige congenitale afwijkingen (niet nader omschreven)

90 inborn error of metabolism

91 syndroom van Potter

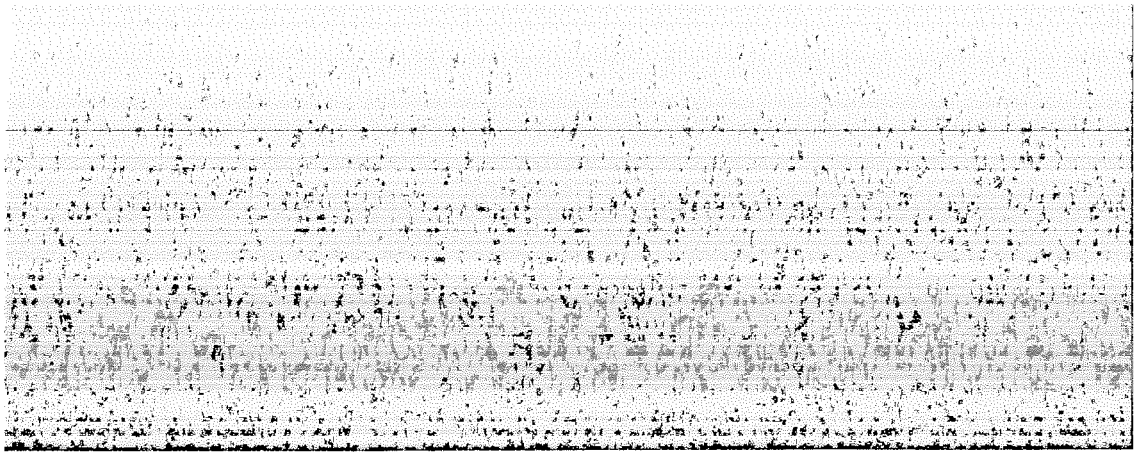
verzending van formulieren liefst m.b.v. voorgeadresseerde plaketiketten,of adresseren aan:

POPS, Academisch Ziekenhuis,

Gebouw 33,

Rijnsburgerweg 10

2333 AA LEIDEN



APPENDIX B

b-formulier

b_1

project onderzoek prematuritas en SGA in nederland (POPS)

praeventiefonds subsidie nr. 28-766

formulier nummer POPS : _____

poliklinische nacontrôle gecorrigeerde leeftijd **3 maanden**

geboortedatum : _____

datum ontslag naar huis : _____

streefdatum contrôle : _____

codeerinstructie:
als een (deel van een) gegeven onbekend is, coderen met 999.
indien niet van toepassing 888.

kaart nr. 5 501 0 5

01 registratienummer POPS 503

02 streefdatum contrôle (dg / mnd / jr) 511

03 contrôle datum (dg / mnd / jr) 517

04 niet voor nacontrôle beschikbaar wegens: 523
wel beschikbaar **0** overleden tussen ontslag en contrôle **1** (datum ___/___/___)
diagnose _____)
verhuisd **2** (nl. naar: _____
contrôle aldaar door: _____)
verdere medewerking door ouders geweigerd i.v.m. goede toestand kind **3**
verdere medewerking door ouders geweigerd i.v.m. slechte toestand kind **4**

05 lengte (cm) b.v. 63 cm : 063 524

06 gewicht (kg, 1 decimaal) b.v. 5780 g : 05,7 527 ,

07 schedelomtrek (cm) 530

psychomotoriek

(zie ook bijgevoegde handleiding onderzoekschema volgens Dr. H. J. van Wiechen)

1 maand:

08 ogen fixeren	ja **0**	nee **1**	532
09 reageert op toespreken (m)	ja **0**	nee **1**	533
10 beweegt armen evenveel	ja **0**	nee **1**	534
11 beweegt benen evenveel	ja **0**	nee **1**	535
12 heft kin even van onderlaag	ja **0**	nee **1**	536

2 maanden:

13 lacht terug (m)	ja **0**	nee **1**	537
14 volgt met ogen en hoofd	ja **0**	nee **1**	538

3 maanden:

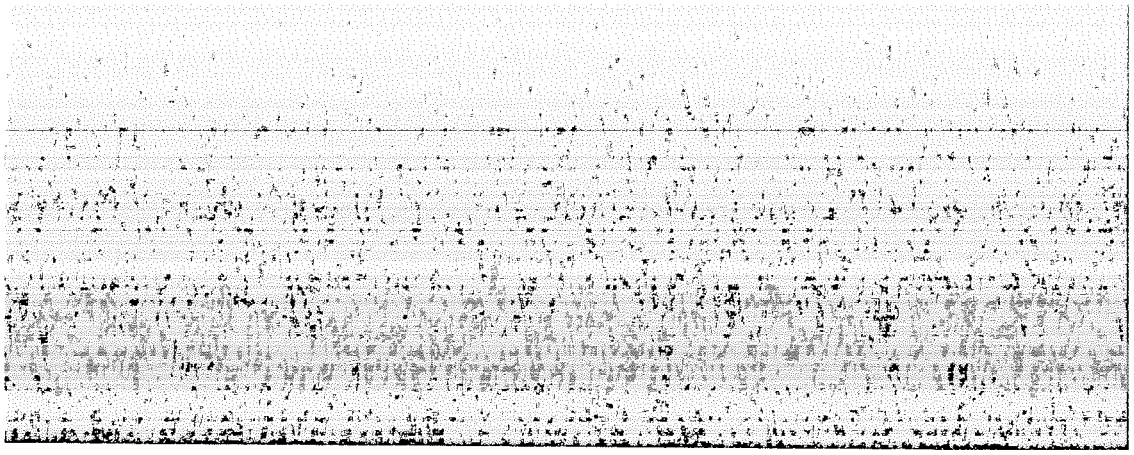
15 handen af en toe open	ja **0**	nee **1**	539
16 kijkt naar eigen handen (m)	ja **0**	nee **1**	540
17 maakt geluiden terug (m)	ja **0**	nee **1**	541
18 blijft hangen bij optillen onder de oksels	ja **0**	nee **1**	542
19 heft in buikligging hoofd tot 45°	ja **0**	nee **1**	543

6 maanden:

22 speelt met handen midden voor	ja **0**	nee **1**	546
23 pakt in rugligging voorwerp binnen bereik	ja **0**	nee **1**	547
24 neemt hoofd mee bij optrekken tot zit	ja **0**	nee **1**	548
25 draait hoofd naar geluid	ja **0**	nee **1**	549
26 bij vertikaal optillen, benen gebogen of trappelen	ja **0**	nee **1**	550
27 kijkt rond met 90° geheven hoofd	ja **0**	nee **1**	551

29 afwijkingen centraal zenuwstelsel (m.n. tonus, motoriek, reflexen)
nee **0** suspect **1** duidelijk afwijkend **2** 553

indien suspect, s.v.p. toelichten _____



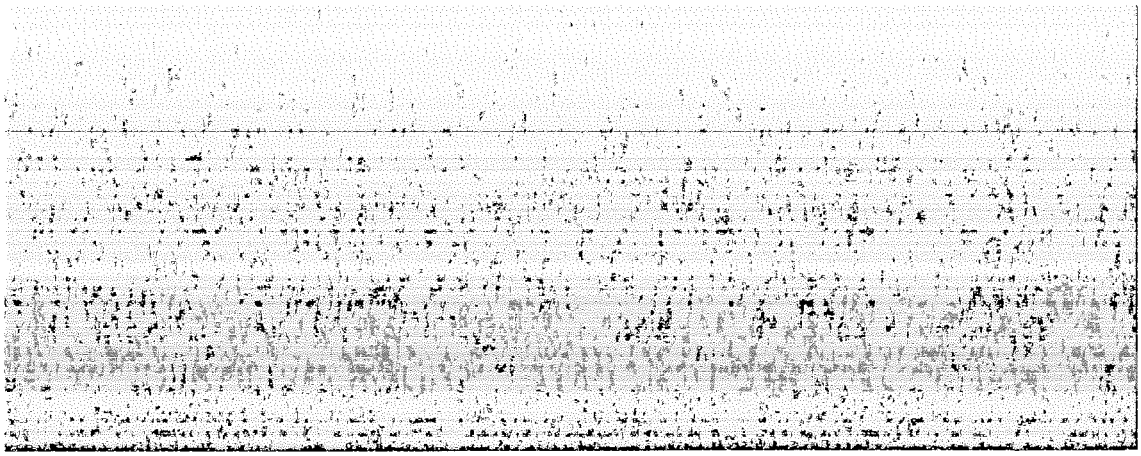
formulier nummer POPS : _____

30 afwijkingen perifeer zenuwstelsel	(Erbee parese, facialis parese, abducens parese a.d.)	nee 0	ja 1		554
31 convulsies	nee 0	ja zonder EEG-afwijkingen 1	ja met EEG-afwijkingen 2		555
32 fysiotherapie	nee 0	alleen periodiek adviezen aan ouders 1	geregelde behandeling door fysiotherapeut (N.D.T. = Bobath; Voyta, enz.) 2		556
33 afwijkingen tractus respiratorius	bronchopulmonale dysplasie	nee 0	ja 1		557
	Mikity Wilson	nee 0	ja 1		558
	andere chron. luchtwegafwijkingen	nee 0	ja 1		559
	recidiv. bovenste luchtweginfecties	nee 0	ja 1		560
	recidiv. (broncho) pneumonie	nee 0	ja 1		561
	andere infectieuze aandoeningen	nee 0	ja 1		562
34 afwijkingen tractus digestivus	voedingsproblemen (organisch)	nee 0	ja 1		563
	dyspepsie	nee 0	ja 1		564
	andere	nee 0	ja 1		565
35 hernia's	inguinalis	nee 0	ja 1	dubbelzijdig 2	566
	umbilicalis	nee 0	ja 1		567
	geopereerd	nee 0	ja 1		568
36 gehoorsafwijking	twijfel ouders en/of arts	nee 0	ja 1		569
	afwijkend audiologisch onderzoek	nee 0	ja 1		570
37 oogafwijkingen	**retrolentale fibroplasie** (licht = nog redelijke visus, ernstig = vrijwel blind aan één of beide ogen)	nee 0	licht 1	ernstig 2	571
	strabisme	nee 0	ja 1		572
	andere afwijking, nl. _____	nee 0	ja 1		573
38 ziekenhuisopname	tussen ontslag en deze controle	nee 0	ja 1		574
kaart nr. 6	indicatie _____				601 0 6

39 geconsult. overige specialisten	**oogarts**	nee 0	routine controle 1	op indicatie 2	603
	KNO-arts	nee 0	routine controle 1	op indicatie 2	604
	(kinder)neuroloog	nee 0	routine controle 1	op indicatie 2	605
	orthoped. chir.	nee 0	routine controle 1	op indicatie 2	606
	revalidatiearts	nee 0	routine controle 1	op indicatie 2	607
	kindercardioloog	nee 0	routine controle 1	op indicatie 2	608
	andere nl. _____	nee 0	routine controle 1	op indicatie 2	609

(als "routine-controle" aangeven wanneer ± alle nagecontroleerde kinderen door de betreffende specialist worden gezien, b.v. consult oogarts als routine wanneer u alle ex-prematuren poliklinisch laat nazien op retrolentale fibroplasie.
als „op indicatie" aangeven, wanneer het consult plaatsvindt omdat er waarschijnlijk afwijkingen op dat terrein zijn, b.v. wanneer u het kind verwijst omdat de moeder denkt dat het kind niet goed ziet).

40 psychosociale problemen	**veel huilen**	nee 0		ja 1	610
	slaapstoornis	nee 0		ja 1	611
	onrust	nee 0		ja 1	612
	voedingsmoeilijkheden	nee 0		ja 1	613
	dreigende mishandeling	nee 0		ja 1	614
	mishandeling	nee 0		ja 1	615
	andere, nl _____	nee 0		ja 1	616
41 lengte moeder	(cm)				617
42 lengte vader	(cm)				620
eigen coderingen inzender					623
					628



c-formulier

c1

project onderzoek prematuritas en SGA in nederland (POPS)

praeventiefonds subsidie nr. 28-766

formulier nummer POPS : _____

poliklinische nacontrôle gecorrigeerde leeftijd **6 maanden**

geboortedatum : _____

streefdatum contrôle : _____

codeerinstructie:
als een (deel van een) gegeven onbekend is, coderen met 999.
indien niet van toepassing 888.

kaart nr. 7 701 0 7

01 registratienummer POPS 703

02 streefdatum contrôle (dg / mnd / jr)* 711

03 contrôle datum (dg / mnd / jr) 717

04 niet voor nacontrôle beschikbaar wegens: 723

wel beschikbaar **0** overleden tussen ontslag en contrôle **1** (datum ____/____/____,

diagnose _____)

verhuisd **2** (nl. naar: _____

contrôle aldaar door: _____)

verdere medewerking door ouders geweigerd i.v.m. goede toestand kind **3**

verdere medewerking door ouders geweigerd i.v.m. slechte toestand kind **4**

05 lengte (cm) b.v. 63 cm : 063 724

06 gewicht (kg, 1 decimaal) b.v. 7780 g : 07,7 727 ,

07 schedelomtrek (cm) 730

psychomotoriek

(zie ook bijgevoegde handleiding onderzoekschema volgens Dr. H. J. van Wiechen)

3 maanden:

08 handen af en toe open ja 0 nee 1 732

09 kijkt naar eigen handen (m) ja 0 nee 1 733

10 maakt geluiden terug (m) ja 0 nee 1 734

11 blijft hangen bij optillen onder de oksels ja 0 nee 1 735

12 heft in buikligging hoofd tot 45° ja 0 nee 1 736

6 maanden:

15 speelt met handen midden voor ja 0 nee 1 739

16 pakt in rugligging voorwerp binnen bereik ja 0 nee 1 740

17 neemt hoofd mee bij optrekken tot zit ja 0 nee 1 741

18 draait hoofd naar geluid ja 0 nee 1 742

19 bij vertikaal optillen, benen gebogen of trappelen ja 0 nee 1 743

20 kijkt rond met 90° geheven hoofd ja 0 nee 1 744

9 maanden:

22 pakt voorwerp over ja 0 nee 1 746

23 houdt voorwerp vast, pakt nog een voorwerp in andere hand ja 0 nee 1 747

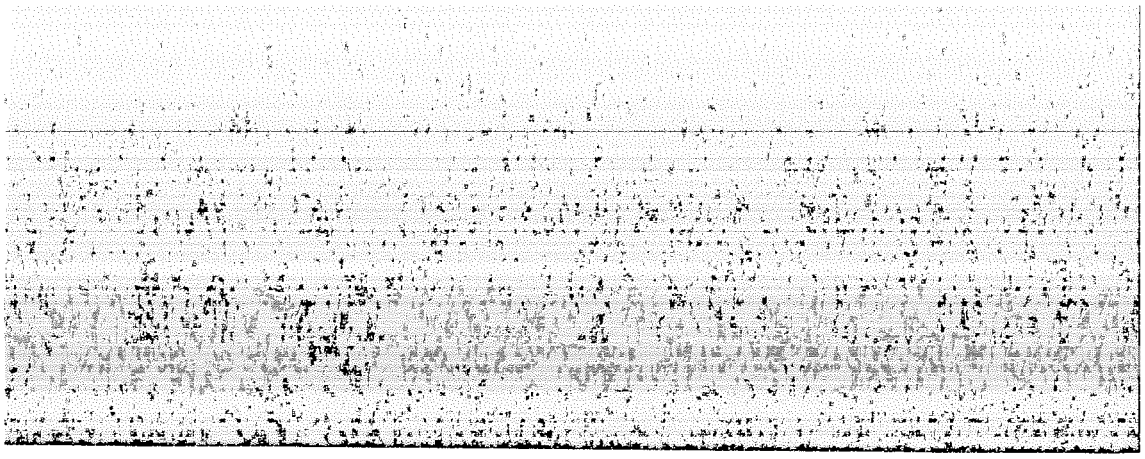
24 speelt met beide voeten (m) ja 0 nee 1 748

25 rolt zich om van rug naar buik en omgekeerd (m) ja 0 nee 1 749

26 kan hoofd goed ophouden in zit ja 0 nee 1 750

27 zit op billen, ook met gestrekte benen ja 0 nee 1 751

28 zegt dada - baba of gaga (m) ja 0 nee 1 752



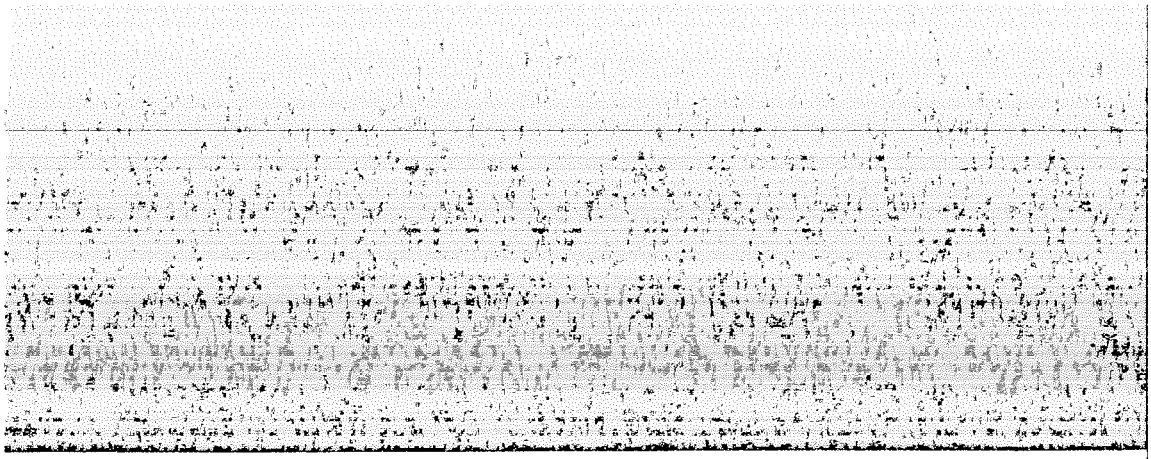
formulier nummer POPS : _____

29 afwijkingen centraal zenuwstelsel (m.n. tonus, motoriek, reflexen)	nee 0	suspect 1	duidelijk afwijkend 2		753
	indien suspect, a.v.p. toelichten _____				
30 afwijkingen perifeer zenuwstelsel (Erbse parese, facialis parese, abducens parese e.d.)	nee 0	ja 1			754
31 convulsies	nee 0	ja zonder EEG-afwijkingen 1	ja met EEG-afwijkingen 2		755
32 fysiotherapie	nee 0	alleen periodiek adviezen aan ouders 1			756
	geregelde behandeling door fysiotherapeut (N.D.T. = Bobath; Voyta, enz.) 2				
33 afwijkingen tractus respiratorius	bronchopulmonale dysplasie	nee 0	ja 1		757
	Mikity Wilson	nee 0	ja 1		758
	andere chron. luchtwegafwijkingen	nee 0	ja 1		759
	recidiv. bovenste luchtweginfecties	nee 0	ja 1		760
	recidiv. (broncho) pneumonie	nee 0	ja 1		761
	andere infectieuze aandoeningen	nee 0	ja 1		762
34 afwijkingen tractus digestivus	voedingsproblemen (organisch)	nee 0	ja 1		763
	dyspepsie	nee 0	ja 1		764
	andere	nee 0	ja 1		765
35 hernia's	inguinalis	nee 0	ja 1	dubbelzijdig 2	766
	umbilicalis	nee 0	ja 1		767
	geopereerd	nee 0	ja 1		768
36 gehoorsafwijking	twijfel ouders en/of arts	nee 0	ja 1		769
	afwijkend audiologisch onderzoek	nee 0	ja 1		770
37 oogafwijkingen	**retrolentale fibroplasie**	nee 0	licht 1	ernstig 2	771
	(licht = nog redelijke visus, ernstig = vrijwel blind aan één of beide ogen)				
	strabisme	nee 0	ja 1		772
	andere afwijking, nl. _____	nee 0	ja 1		773
38 ziekenhuisopname	tussen vorige POPS-contrôle en deze	nee 0	ja 1		774
	indicatie _____				
kaart nr. 8					801 0 8

39 geconsult. overige specialisten	**oogarts**	nee 0	routine contrôle 1	op indicatie 2	803
	KNO-arts	nee 0	routine contrôle 1	op indicatie 2	804
	(kinder)neuroloog	nee 0	routine contrôle 1	op indicatie 2	805
	orthoped. chir.	nee 0	routine contrôle 1	op indicatie 2	806
	revalidatiearts	nee 0	routine contrôle 1	op indicatie 2	807
	kindercardioloog	nee 0	routine contrôle 1	op indicatie 2	808
	andere nl. _____	nee 0	routine contrôle 1	op indicatie 2	809

(als "routine-contrôle" aangeven wanneer ± alle nagecontroleerde kinderen door de betreffende specialist worden gezien, b.v. consult oogarts als routine wanneer u alle ex-prematuren poliklinisch laat nazien op retrolentale fibroplasie.
als „op indicatie" aangeven, wanneer het consult plaatsvindt omdat er waarschijnlijk afwijkingen op dat terrein zijn, b.v. wanneer u het kind verwijst omdat de moeder denkt dat het kind niet goed ziet).

40 psychosociale problemen	**veel huilen**	nee 0	ja 1	810
	slaapstoornis	nee 0	ja 1	811
	onrust	nee 0	ja 1	812
	voedingsmoeilijkheden	nee 0	ja 1	813
	dreigende mishandeling	nee 0	ja 1	814
	mishandeling	nee 0	ja 1	815
	andere, nl _____	nee 0	ja 1	816
eigen coderingen inzender				823
				828



d-formulier

d_1

project onderzoek prematuritas en SGA in nederland (POPS)

praeventiefonds subsidie nr. 28-766

formulier nummer POPS : _____

poliklinische nacontrôle gecorrigeerde leeftijd **12 maanden**

geboortedatum : _____

streefdatum controle : _____

codeerinstructie:
als een (deel van een) gegeven onbekend is, coderen met 999.
indien niet van toepassing 888.

kaart nr. 9 901 [0 | 9]

01 registratienummer POPS 903 [| | | | | |]

02 streefdatum contrôle (dg / mnd / jr) 911 [| | | | | |]

03 contrôle datum (dg / mnd / jr) 917 [| | | | | |]

04 niet voor nacontrôle beschikbaar wegens: 923 [ ]

wel beschikbaar **0** overleden tussen ontslag en contrôle **1** (datum ____/____/____,

diagnose _____)

verhuisd **2** (nl. naar: _____

contrôle aldaar door: _____)

verdere medewerking door ouders geweigerd i.v.m. goede toestand kind **3**

verdere medewerking door ouders geweigerd i.v.m. slechte toestand kind **4**

05 lengte (cm) b.v. 73 cm : 073 924 [| |]

06 gewicht (kg, 1 decimaal) b.v. 9780 g : 09,7 927 [| | , |]

07 schedelomtrek (cm) 930 [| |]

psychomotoriek

(zie ook bijgevoegde handleiding onderzoekschema volgens Dr. H. J. van Wiechen)

9 maanden:

08 pakt voorwerp over ja **0** nee **1** 932 [ ]

09 houdt voorwerp vast, pakt nog een voorwerp in andere hand ja **0** nee **1** 933 [ ]

10 speelt met beide voeten (m) ja **0** nee **1** 934 [ ]

11 rolt zich om van rug naar buik en omgekeerd (m) ja **0** nee **1** 935 [ ]

12 kan hoofd goed ophouden in zit ja **0** nee **1** 936 [ ]

13 zit op billen, ook met gestrekte benen ja **0** nee **1** 937 [ ]

14 zegt dada - baba of gaga (m) ja **0** nee **1** 938 [ ]

12 maanden:

15 blijft los zitten ja **0** nee **1** 939 [ ]

16 pakt propje met duim en wijsvinger ja **0** nee **1** 940 [ ]

17 kruipt vooruit, buik op grond (m) ja **0** nee **1** 941 [ ]

18 trekt zich op tot staan (m) ja **0** nee **1** 942 [ ]

19 zwaait "dag, dag" (m) ja **0** nee **1** 943 [ ]

20 brabbelt bij zijn spel (m) ja **0** nee **1** 944 [ ]

15 maanden:

22 doet blokje in/uit doos ja **0** nee **1** 946 [ ]

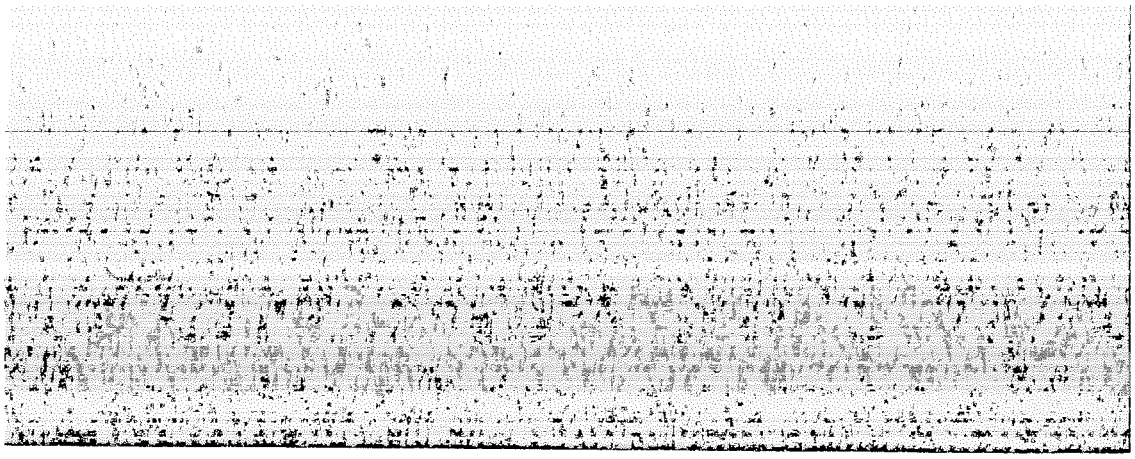
23 speelt "geven en nemen" (m) ja **0** nee **1** 947 [ ]

24 kruipt, buik vrij van de grond (m) ja **0** nee **1** 948 [ ]

25 loopt langs (m) ja **0** nee **1** 949 [ ]

26 begrijpt enkele dagelijks gebruikte woorden (m) ja **0** nee **1** 950 [ ]

27 gebruikt 2 woorden met begrip (m) ja **0** nee **1** 951 [ ]

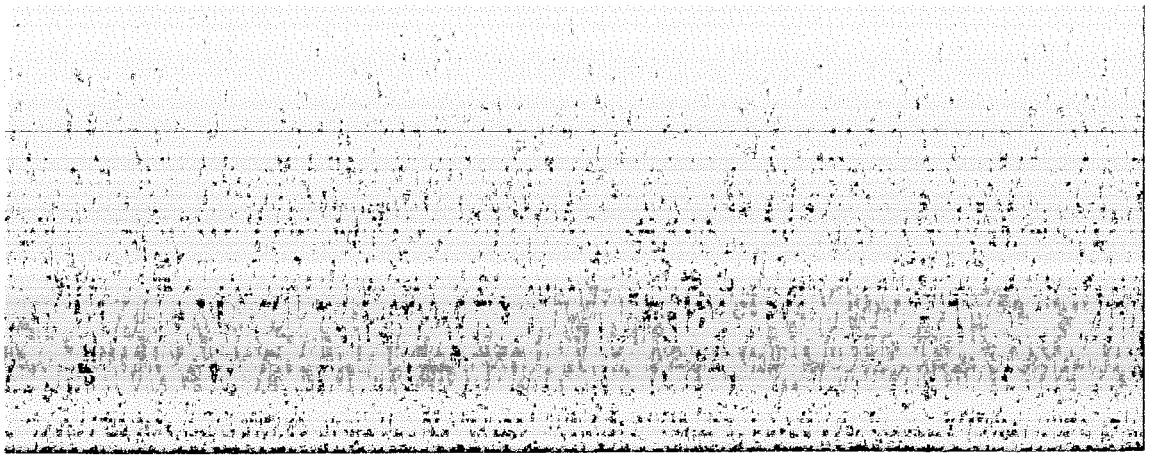


formulier nummer POPS : _____

29 afwijkingen centraal zenuwstelsel (m.n. tonus, motoriek, reflexen)	nee 0	suspect 1	duidelijk afwijkend 2		953
	indien suspect, a.v.p. toelichten _____				
30 afwijkingen perifeer zenuwstelsel (Erbse parese, facialis parese, abducens parese e.d.)			nee 0	ja 1	954
31 convulsies	nee 0	ja zonder EEG-afwijkingen 1	ja met EEG-afwijkingen 2		955
32 fysiotherapie	nee 0	alleen periodiek adviezen aan ouders 1			956
	geregelde behandeling door fysiotherapeut (N.D.T. = Bobath; Voyta, enz.) 2				
33 afwijkingen tractus respiratorius	bronchopulmonale dysplasie		nee 0	ja 1	957
	Mikity Wilson		nee 0	ja 1	958
	andere chron. luchtwegafwijkingen		nee 0	ja 1	959
	recidiv. bovenste luchtweginfecties		nee 0	ja 1	960
	recidiv. (broncho) pneumonie		nee 0	ja 1	961
	andere infectieuze aandoeningen		nee 0	ja 1	962
34 afwijkingen tractus digestivus	voedingsproblemen (organisch)		nee 0	ja 1	963
	dyspepsie		nee 0	ja 1	964
	andere		nee 0	ja 1	965
35 hernia's	inguinalis	nee 0	ja 1	dubbelzijdig 2	966
	umbilicalis		nee 0	ja 1	967
	geopereerd		nee 0	ja 1	968
36 gehoorsafwijking	twijfel ouders en/of arts		nee 0	ja 1	969
	afwijkend audiologisch onderzoek		nee 0	ja 1	970
37 oogafwijkingen	**retrolentale fibroplasie**		nee 0	licht 1 ernstig 2	971
	(licht = nog redelijke visus, ernstig = vrijwel blind aan één of beide ogen)				
	strabisme		nee 0	ja 1	972
	andere afwijking, nl. _____		nee 0	ja 1	973
38 ziekenhuisopname	tussen vorige POPS-contrôle en deze		nee 0	ja 1	974
	indicatie _____				
kaart nr. 10					1001 1 0
39 geconsult. overige specialisten	**oogarts**	nee 0	routine contrôle 1	op indicatie 2	1003
	KNO-arts	nee 0	routine contrôle 1	op indicatie 2	1004
	(kinder)neuroloog	nee 0	routine contrôle 1	op indicatie 2	1005
	orthoped. chir.	nee 0	routine contrôle 1	op indicatie 2	1006
	revalidatiearts	nee 0	routine contrôle 1	op indicatie 2	1007
	kindercardioloog	nee 0	routine contrôle 1	op indicatie 2	1008
	andere nl. _____	nee 0	routine contrôle 1	op indicatie 2	1009

(als "routine-contrôle" aangeven wanneer ± alle nagecontroleerde kinderen door de betreffende specialist worden gezien, b.v. consult oogarts als routine wanneer u alle ex-prematuren poliklinisch laat nazien op retrolentale fibroplasie.
als „op indicatie" aangeven, wanneer het consult plaatsvindt omdat er waarschijnlijk afwijkingen op dat terrein zijn, b.v. wanneer u het kind verwijst omdat de moeder denkt dat het kind niet goed ziet).

40 psychosociale problemen	**veel huilen**		nee 0	ja 1	1010
	slaapstoornis		nee 0	ja 1	1011
	onrust		nee 0	ja 1	1012
	voedingsmoeilijkheden		nee 0	ja 1	1013
	dreigende mishandeling		nee 0	ja 1	1014
	mishandeling		nee 0	ja 1	1015
	andere, nl _____		nee 0	ja 1	1016
eigen coderingen inzender					1023
					1028



APPENDIX E

e-formulier

e1

project onderzoek prematuritas en SGA in nederland (POPS)

praeventiefonds subsidie nr. 28-766

formulier nummer POPS : _____

poliklinische nacontrôle gecorrigeerde leeftijd **24 maanden**

geboortedatum : _____

streefdatum contrôle : _____

codeerinstructie:
als een (deel van een) gegeven onbekend is, coderen met 999.
indien niet van toepassing 888.

kaart nr. 11 1101 1 1

01 **registratienummer POPS** 1103

02 **streefdatum contrôle** (dg / mnd / jr) 1111

03 **contrôle datum** (dg / mnd / jr) 1117

04 **niet voor nacontrôle beschikbaar wegens:** 1123
wel beschikbaar 0 overleden tussen ontslag en contrôle 1 (datum ____/____/____
diagnose _____)
verhuisd 2 (nl. naar: _____
contrôle aldaar door: _____)
verdere medewerking door ouders geweigerd i.v.m. goede toestand kind 3
verdere medewerking door ouders geweigerd i.v.m. slechte toestand kind 4

05 **lengte** (cm) b.v. 88 cm : 088 1124

06 **gewicht** (kg, 1 decimaal) b.v. 13,1 kg : 13 1 1127 ,

07 **schedelomtrek** (cm) 1130

psychomotoriek

(zie ook bijgevoegde handleiding onderzoekschema volgens Dr. H. J. van Wiechen)

18 maanden:

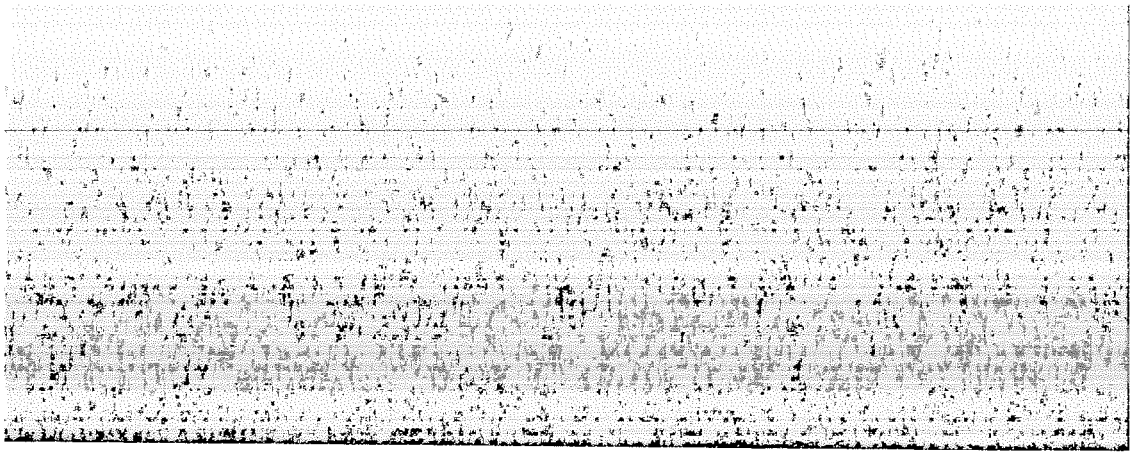
08 **stapelt 2 blokjes**	ja 0	nee 1	1132
09 **gaat op onderzoek uit** (m)	ja 0	nee 1	1133
10 **zegt 3 "woorden"** (m)	ja 0	nee 1	1134
11 **wijzen/pakken van 2 genoemde voorwerpen**	ja 0	nee 1	1135
12 **loopt los**	ja 0	nee 1	1136
13 **gooit bal zonder om te vallen**	ja 0	nee 1	1137

24 maanden:

15 **stapelt 3 blokjes**	ja 0	nee 1	1139
16 **doet anderen na** (m)	ja 0	nee 1	1140
17 **drinkt zelf uit beker** (m)	ja 0	nee 1	1141
18 **zegt "zinnen" van 2 woorden** (m)	ja 0	nee 1	1142
19 **doet op verzoek bal in doos**	ja 0	nee 1	1143
20 **raapt vanuit hurkzit iets op**	ja 0	nee 1	1144
21 **loopt goed los**	ja 0	nee 1	1145

30 maanden:

22 **stapelt 6 blokjes**	ja 0	nee 1	1146
23 **plaatst ronde vorm in stoof**	ja 0	nee 1	1147
24 **trekt kledingstuk uit** (m)	ja 0	nee 1	1148
25 **eet zelf met lepel** (m)	ja 0	nee 1	1149
26 **noemt zichzelf bij eigen naam of "ik"** (m)	ja 0	nee 1	1150
27 **wijst 5 voorwerpen aan in boek**	ja 0	nee 1	1151
28 **schopt bal weg**	ja 0	nee 1	1152

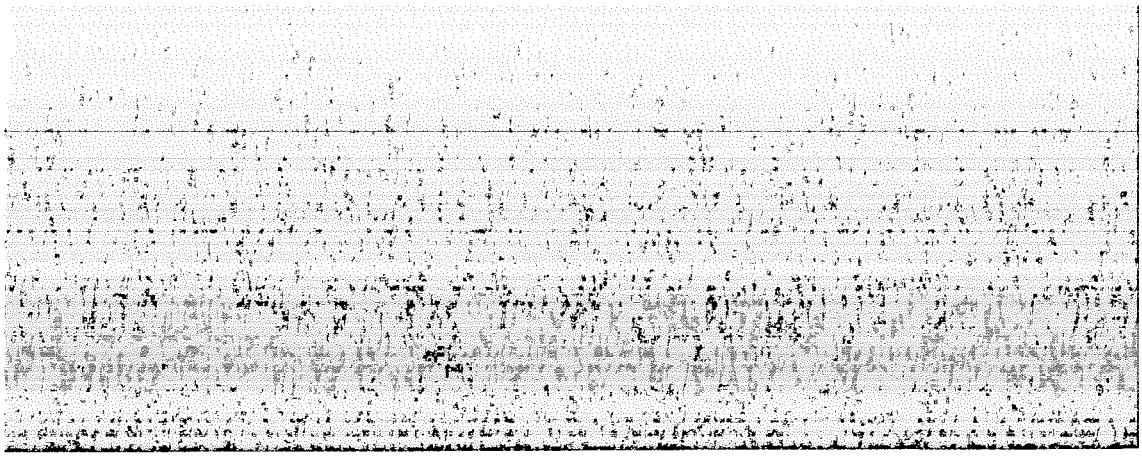


formulier nummer POPS : _____

29 afwijkingen centraal zenuwstelsel (m.n. tonus, motoriek, reflexen)	nee 0	suspect 1	duidelijk afwijkend 2		1153
	indien suspect, a.v.p. toelichten _____				
30 afwijkingen perifeer zenuwstelsel (Erbse parese, facialis parese, abducens parese e.d.)	nee 0	ja 1			1154
31 convulsies	nee 0	ja zonder EEG-afwijkingen 1	ja met EEG-afwijkingen 2		1155
32 fysiotherapie	nee 0	alleen periodiek adviezen aan ouders 1			1156
	geregelde behandeling door fysiotherapeut (N.D.T. = Bobath; Voyta, enz.) 2				
33 afwijkingen tractus respiratorius	bronchopulmonale dysplasie	nee 0	ja 1		1157
	Mikity Wilson	nee 0	ja 1		1158
	andere chron. luchtwegafwijkingen	nee 0	ja 1		1159
	recidiv. bovenste luchtweginfecties	nee 0	ja 1		1160
	recidiv. (broncho) pneumonie	nee 0	ja 1		1161
	andere infectieuze aandoeningen	nee 0	ja 1		1162
34 afwijkingen tractus digestivus	voedingsproblemen (organisch)	nee 0	ja 1		1163
	dyspepsie	nee 0	ja 1		1164
	andere	nee 0	ja 1		1165
35 hernia's	inguinalis	nee 0	ja 1	dubbelzijdig 2	1166
	umbilicalis	nee 0	ja 1		1167
	geopereerd	nee 0	ja 1		1168
36 gehoorsafwijking	twijfel ouders en/of arts	nee 0	ja 1		1169
	afwijkend audiologisch onderzoek	nee 0	ja 1		1170
37 oogafwijkingen	**retrolentale fibroplasie**	nee 0	licht 1	ernstig 2	1171
	(licht = nog redelijke visus, ernstig = vrijwel blind aan één of beide ogen)				
	strabisme	nee 0	ja 1		1172
	andere afwijking, nl. _____	nee 0	ja 1		1173
38 ziekenhuisopname	tussen vorige POPS-contrôle en deze	nee 0	ja 1		1174
	indicatie _____				
kaart nr. 12					1201 1 2
39 geconsult. overige specialisten	**oogarts**	nee 0	routine contrôle 1	op indicatie 2	1203
	KNO-arts	nee 0	routine contrôle 1	op indicatie 2	1204
	(kinder)neuroloog	nee 0	routine contrôle 1	op indicatie 2	1205
	orthoped. chir.	nee 0	routine contrôle 1	op indicatie 2	1206
	revalidatiearts	nee 0	routine contrôle 1	op indicatie 2	1207
	kindercardioloog	nee 0	routine contrôle 1	op indicatie 2	1208
	andere nl. _____	nee 0	routine contrôle 1	op indicatie 2	1209

(als "routine-contrôle" aangeven wanneer ± alle nagecontroleerde kinderen door de betreffende specialist worden gezien, b.v. consult oogarts als routine wanneer u alle ex-prematuren poliklinisch laat nazien op retrolentale fibroplasie.
als „op indicatie" aangeven, wanneer het consult plaatsvindt omdat er waarschijnlijk afwijkingen op dat terrein zijn, b.v. wanneer u het kind verwijst omdat de moeder denkt dat het kind niet goed ziet).

40 psychosociale problemen	**veel huilen**	nee 0	ja 1		1210
	slaapstoornis	nee 0	ja 1		1211
	onrust	nee 0	ja 1		1212
	voedingsmoeilijkheden	nee 0	ja 1		1213
	dreigende mishandeling	nee 0	ja 1		1214
	mishandeling	nee 0	ja 1		1215
	andere, nl _____	nee 0	ja 1		1216
eigen coderingen inzender					1223
					1228



e3

formulier nummer POPS : _____

41 socio-economische groep: **moeder:** beroep _____ **vader:** beroep _____ 1233 ☐ niet invullen
opleiding _____ opleiding _____
wijze van **ziektekostenverzekering:** verplicht/vrijwillig/particulier

42 geboortedatum moeder (dg / mnd / jr) 1234 ☐☐☐☐☐☐

43 lengte moeder (cm) 1240 ☐☐☐

44 lengte vader (cm) 1243 ☐☐☐

45 verdere bijzonderheden, die u tot nu toe niet hebt kunnen coderen, bijvoorbeeld:

later vastgestelde congenitale afwijking (cor vitum, cong.heupdysplasie e.d.)

nee **0** ja **1** onbekend **9** 1246 ☐

indien deze vraag met ja beantwoord is, gaarne toelichten

_____

ziekte of aandoening, die (waarschijnlijk) geen verband houdt met de vroegere pre- of dysmaturiteit

nee **0** ja **1** onbekend **9** 1247 ☐

indien deze vraag met ja beantwoord is, gaarne toelichten

_____

indien vraag 29 (CZS-afwijkingen) met suspect (1) of duidelijk afwijkend (2) beantwoord is, s.v.p. nader definiëren:

46 conclusie na 2 jaar nacontrole: normaal **0** lichte handicap **1** ernstige handicap **2** 1248 ☐

toelichting:

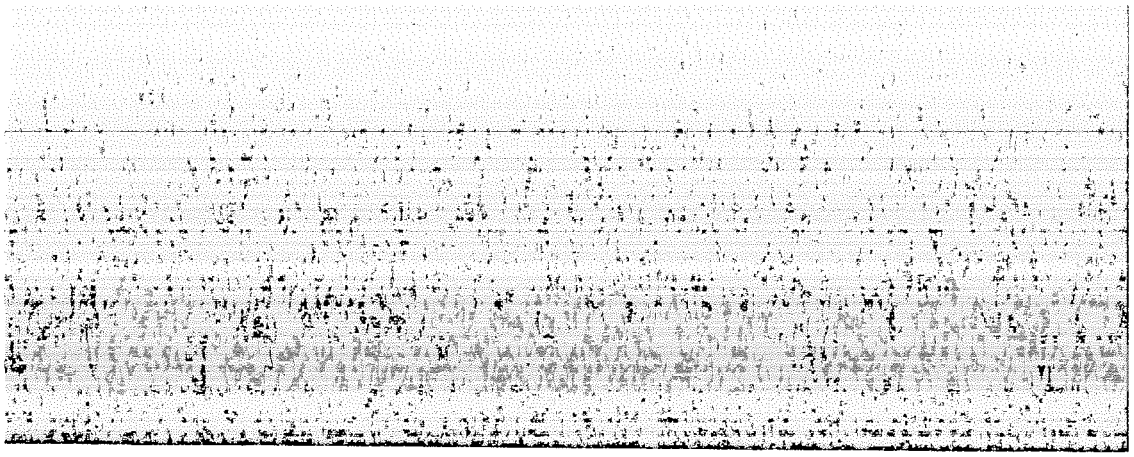
lichte handicap: afwijking, ondanks welke het kind (waarschijnlijk) een gewone school zal kunnen bezoeken, en normaal in de maatschappij zal kunnen functioneren.

(bv. visus- of gehoorstoornis die met hulpmiddelen redelijk te corrigeren is, lichte afwijking CZS, lichte mentale retardatie d.w.z. DQ 80-90 of 3-4 maanden ontwikkelingsachterstand)

ernstige handicap: afwijking, waardoor het kind (waarschijnlijk) geen gewone school zal kunnen bezoeken, en die ernstig zal ingrijpen in het normale leven.

(bv. ernstige visus- of gehoorstoornis, ernstige afwijking CZS, ernstige retardatie d.w.z. DQ <80 of 5 of meer maanden ontwikkelingsachterstand)

47 registratienummer POPS _____



APPENDIX F

f-formulier

f_1

project onderzoek prematuritas en SGA in nederland (POPS)

praeventiefonds subsidie nr. 28-766

formulier nummer POPS : _____

geboortedatum : _____

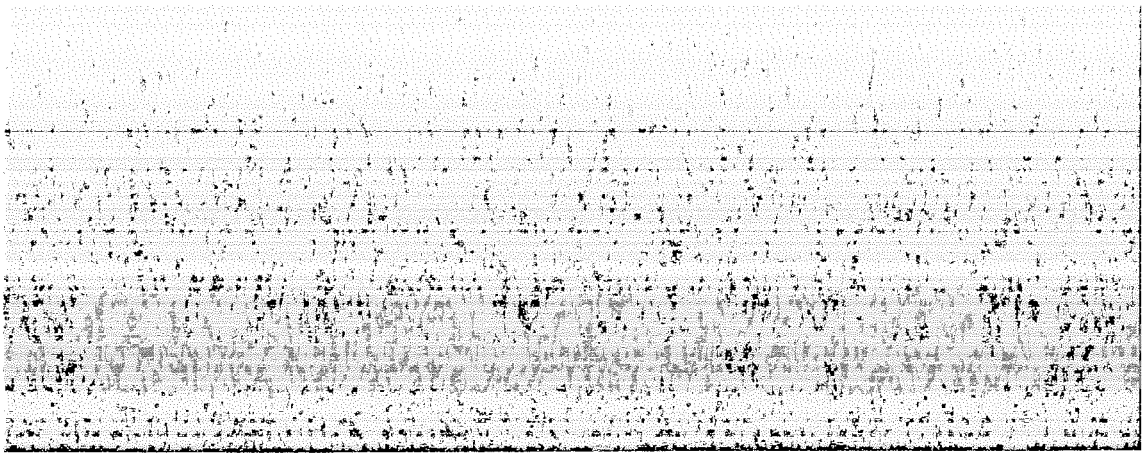
datum van overlijden : _____

codeerinstructie:
als een (deel van een) gegeven onbekend is, coderen met 999.
indien niet van toepassing 888.

kaart nr. 13

01	**registratienummer POPS**			1301 1 3 / 1303 / 1304 / 1307
02	**is obductie verricht?**	ja 0	nee 1	1311
09	**heeft de obductie nieuwe diagnose(n) opgeleverd?**	nee 0	ja 1	1312

zo ja, welke? _____



PSYCHO - MOTORISCHE ONTWIKKELING 0 - 15 MND.

naam: reg.nr.

geb.datum:

zwangerschapsduur weken		Leeftijd in weken of maanden																								opmerkingen
		R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	
4 wkn 1 mnd	1. Ogen fixeren																									
	2. Reageert op toespreken (M)																									
	3. Beweegt armen evenveel																									
	4. Beweegt benen evenveel																									
	5. Heft kin even van onderlaag																									
8 wkn 2 mnd	6. Lacht terug (M)																									
	7. Volgt met ogen én hoofd																									
13 wkn 3 mnd	8. Handen af en toe open																									
	9. Kijkt naar eigen handen (M)																									
	10. Maakt geluiden terug (M)																									
	11. Blijft hangen bij optillen onder de oksels																									
	12. Heft in buikligging hoofd tot 45°																									
26 wkn 6 mnd	13. Speelt met handen middenvoor																									
	14. Pakt in rugligging voorwerp binnen bereik																									
	15. Neemt hoofd mee bij optrekken tot zit																									
	16. Draait hoofd naar geluid																									
	17. Bij vertikaal optillen, benen gebogen of trappelen																									
	18. Kijkt rond met 90° geheven hoofd																									
39 wkn 9 mnd	19. Pakt voorwerp over																									
	20. Houdt voorwerp vast, pakt nog een voorwerp in andere hand																									
	21. Speelt met beide voeten (M)																									
	22. Rolt zich om van rug naar buik en omgekeerd (M)																									
	23. Kan hoofd goed ophouden in zit																									
	24. Zit op billen, ook met gestrekte benen																									
	25. Zegt dada - baba of gaga (M)																									
52 wkn 12 mnd	26. Blijft los zitten																									
	27. Pakt propje met duim en wijsvinger																									
	28. Kruipt vooruit, buik op grond (M)																									
	29. Trekt zich op tot staan (M)																									
	30. Zwaait "dag,dag" (M)																									
	31. Brabbelt bij zijn spel (M)																									
65 wkn 15 mnd	32. Doet blokje in/uit doos																									
	33. Speelt "geven en nemen" (M)																									
	34. Kruipt, buik vrij van de grond (M)																									
	35. Loopt langs (M)																									
	36. Begrijpt enkele dagelijks gebruikte woorden (M)																									
	37. Gebruikt twee woorden met begrip (M)																									

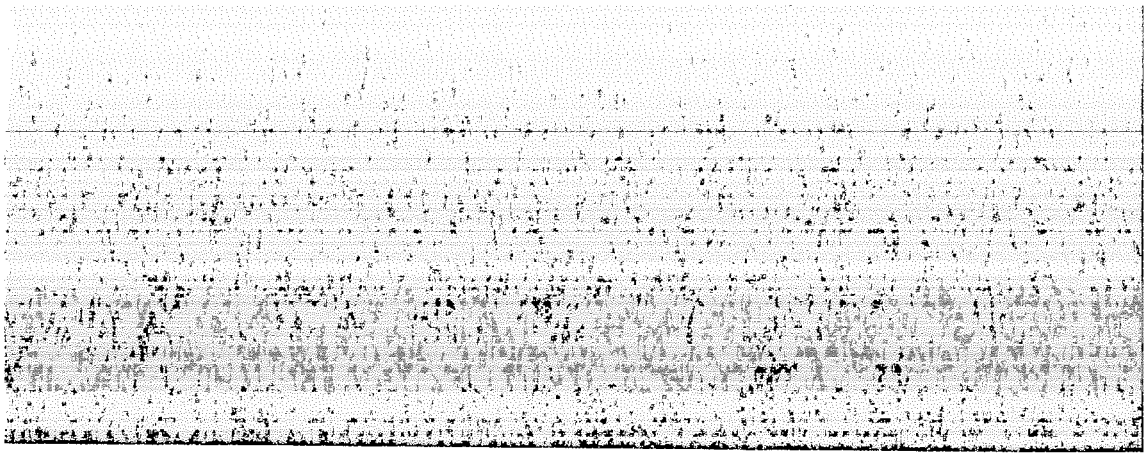
samenvatting:

Onderzoekschema volgens Dr.H.J.van Wiechen.

(gewijzigde uitgave 1981)

Op de aanbevolen onderzoekleeftijden toonde tenminste 90% van een groep Nederlandse kinderen de betreffende ontwikkelingskenmerken ("leeftijdsspreiding ontwikkelingskenmerken zuigelingen periode" N.I.P.G./T.N.O. 1979)

Andere geraadpleegde bronnen, Touwen 1973, Cools & Hermanns 1976.



PSYCHO - MOTORISCHE ONTWIKKELING 18 - 54 MND.

naam: | reg.nr.

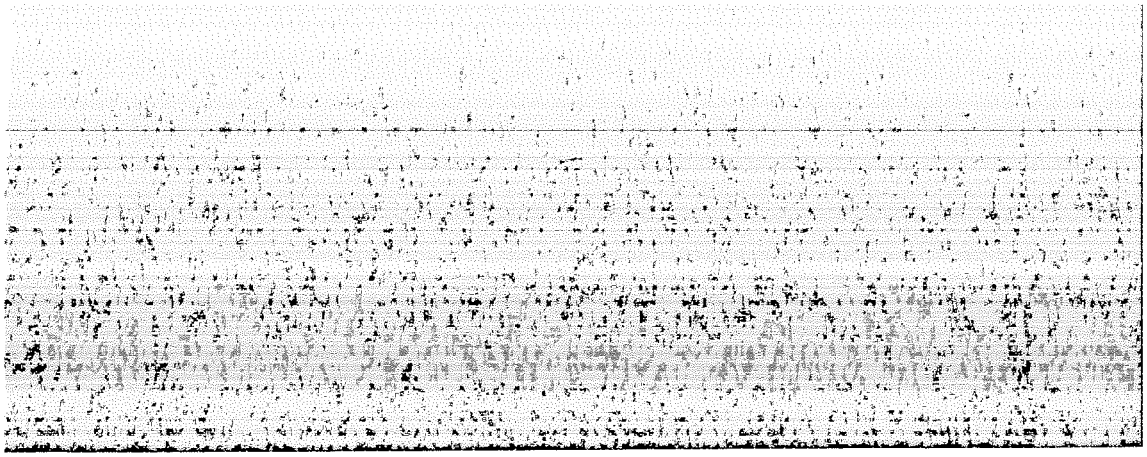
geb.datum:

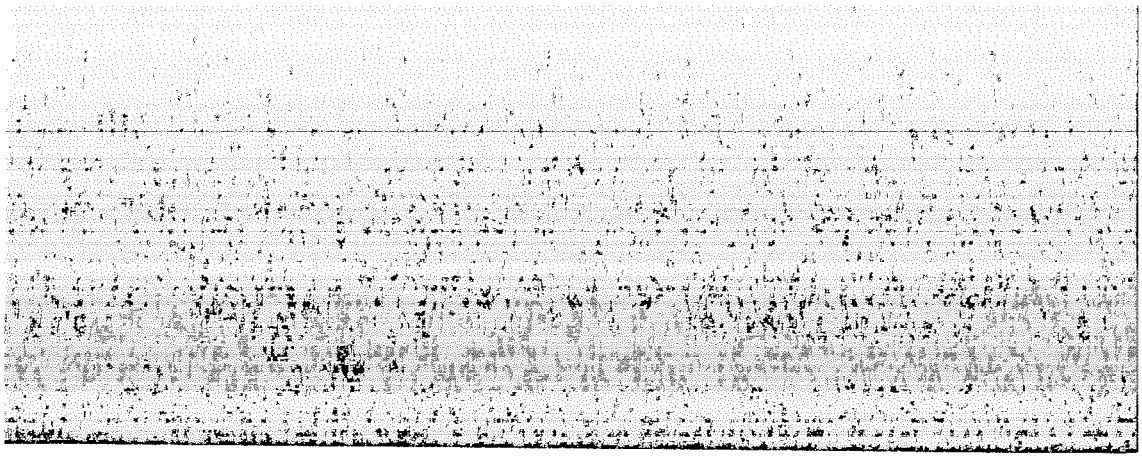
		Leeftijd in jaren en maanden																				opmerkingen
		R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	
18 mnd	38. Stapelt 2 blokjes																					
	39. Gaat op onderzoek uit (M)																					
	40. Zegt 3 'woorden' (M)																					
	41. Wijzen/pakken van 2 genoemde voorwerpen																					
	42. Loopt los																					
	43. Gooit bal zonder om te vallen																					
2 jr	44. Stapelt 3 blokjes																					
	45. Doet anderen na (M)																					
	46. Drinkt zelf uit beker (M)																					
	47. Zegt 'zinnen' van 2 woorden (M)																					
	48. Doet op verzoek bal in doos																					
	49. Raapt vanuit hurkzit iets op																					
	50. Loopt goed los																					
2 jr 6 mnd	51. Stapelt 6 blokjes																					
	52. Plaatst ronde vorm in stoof																					
	53. Trekt kledingstuk uit (M)																					
	54. Eet zelf met lepel (M)																					
	55. Noemt zichzelf bij eigen naam of "ik" (M)																					
	56. Wijst 5 voorwerpen aan in boek																					
	57. Schopt bal weg																					
3 jr	58. Bouwt trein met schoorsteen na																					
	59. Tekent vertikale lijn na																					
	60. Plaatst 3 vormen in stoof																					
	61. Zegt 'zinnen' van 3 of meer woorden (M)																					
	62. Wijst 4 lichaamsdelen aan																					
	63. Fietst op driewieler (M)																					
3 jr 9 mnd	64. Bouwt brug na																					
	65. Houdt potlood met vingers vast																					
	66. Plaatst 4 vormen in stoof																					
	67. Trekt eigen kledingstuk aan (M)																					
	68. Praat tijdens het spel (M)																					
	69. Vraagt waarom (M)																					
	70. Springt met beide voeten tegelijk																					
4 jr 6 mnd	71. Tekent kruis na																					
	72. Wast, droogt handen (M)																					
	73. Is goed verstaanbaar voor anderen																					
	74. Vertelt wat thuis of elders gebeurd is (M)																					
	75. Legt op verzoek blokje op/onder/voor/achter/naast stoel																					
	76. Kan minstens 5 tellen op één voet staan																					

samenvatting:

Onderzoekschema volgens Dr. H.J. van Wiechen (gewijzigde uitgave 1981).

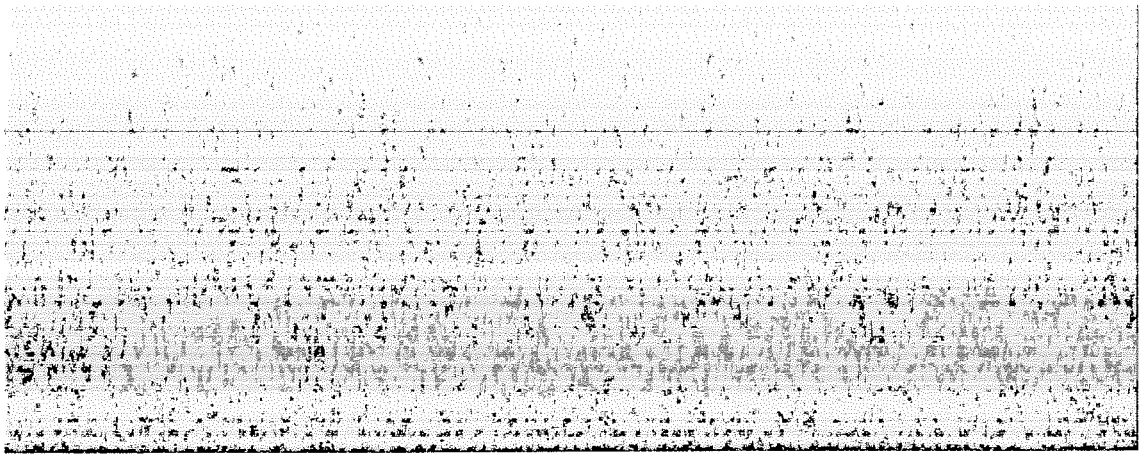
De meeste ontwikkelingskenmerken worden op de aanbevolen onderzoeksmomenten getoond door tenminste 90% van een groep Nederlandse kinderen (Schlesinger-Was, 1981).
Andere geraadpleegde bronnen: Cools en Hermanns, 1977; Schaerlaekens, 1977.



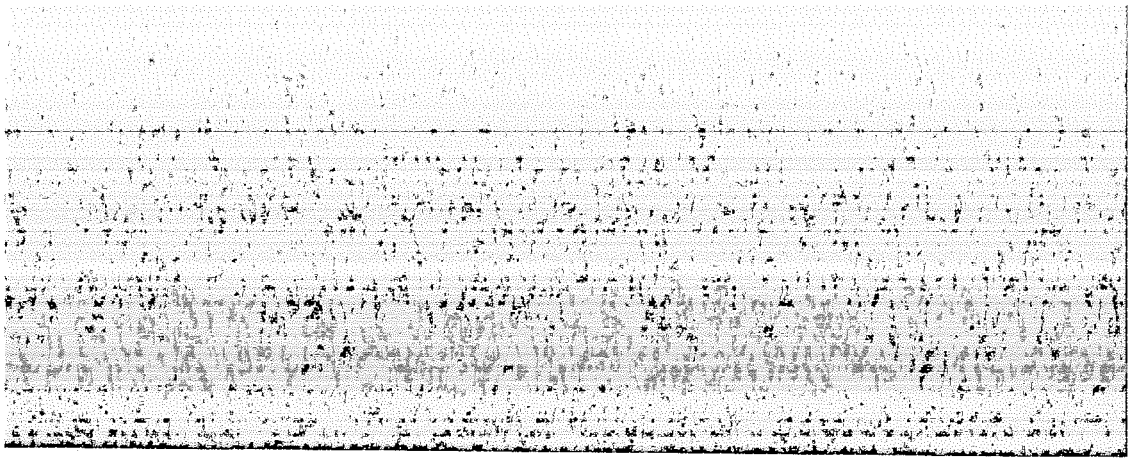


DEELNEMERSLIJST KINDERARTSEN POPS 1983 (anno 1983)
(Project onderzoek Prematuritas en Small for Gestational age)

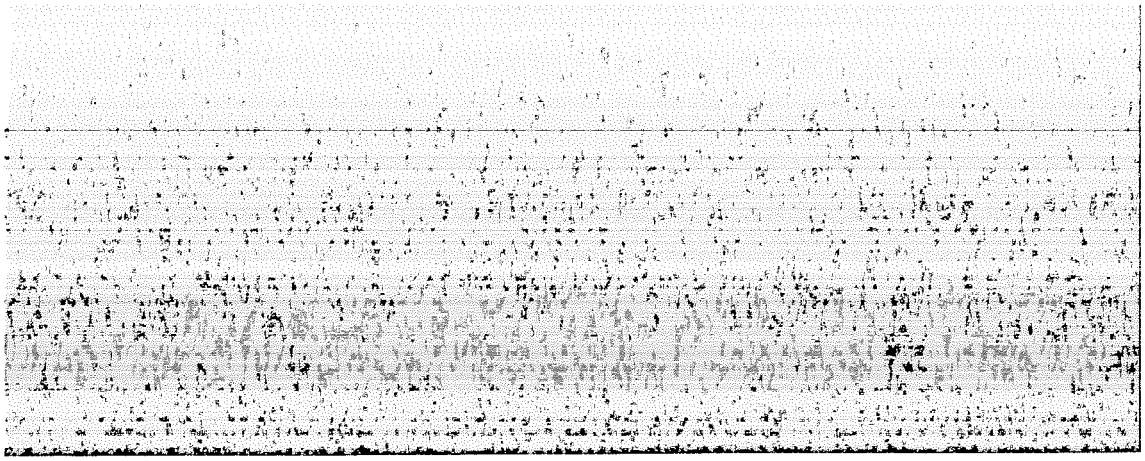
1.	AMSTERDAM	Academisch Ziekenhuis der Vrije Universiteit	Prof.Dr.C.Versluys Mw.J.Derksen-Samson Mw.D.H.van der Vorm
2.	AMSTERDAM	Academisch Medisch Centrum	Mw.Dr.J.G.Koppe M.J.K.de Kleine Mw.J.H.Kok Dr.R.de Leeuw Mw.A.Marinkovic-Ilsen Mw.H.Smolders-de Haas
3.	GRONINGEN	Academisch Ziekenhuis	Dr.A.Okken S.Bambang Oetomo
4.	LEIDEN	Academisch Ziekenhuis	Prof.Dr.J.H.Ruys Mw.M.van de Bor Mw.A.den Ouden Mw.D.van Zoeren-Grobben
9.	MAASTRICHT	Ziekenhuis St.Annadal	Prof.Dr.L.H.J.Ramaekers Dr.C.E.Blanco W.J.Maertzdorf Dr.F.J.Walther
5.	NIJMEGEN	St.Radboud Ziekenhuis	Dr.J.M.Boon Dr.L.A.A.Kollée C.H.Schröder T.S.Thé
6.	ROTTERDAM	Sophia Kinderziekenhuis	Prof.Dr.J.W.Mettau W.Baerts Dr.W.P.F.Fetter Dr.P.J.J.Sauer
7.	UTRECHT	Wilhelmina Kinderziekenhuis	R.Ch.Senders B.P.Cats Mw.I.van Ertbruggen L.J.Gerards Mw.T.G.Krediet
005.	ALKMAAR	Medisch Centrum Alkmaar	J.F.van der Blij
006.	ALMELO	Stichting Streekziekenhuis Almelo	R.P.Beekman N.Hofstee F.J.A.M.Holtus
007.	ALPHEN A /D RIJN	Ziekenhuis Rijnoord	D.K.Nanlohy
008.	AMERSFOORT	Stichting Prot.-Chr. Ziekenhuis "De Lichtenberg"	Mw.H.J.Dijkhuis A.van Rhijn Dr.H.G.Scholten
010.	AMSTERDAM	Andreas Ziekenhuis	Dr.J.W.C.de Groot Mw.M.J.van Houten
011.	AMSTERDAM	Sint Lucas Ziekenhuis	Mw.M.K.Sanders
013.	APELDOORN	Juliana Ziekenhuis	R.F.Oosterkamp Dr.H.G.Sie
012.	APELDOORN	Lukas Ziekenhuis	A.J.W.Leenders
014.	ARNHEM	Gemeenteziekenhuis	R.J.de Boer W.Brussel Mw.B.M.Lankester-Knape J.Verhage J.H.Wilton
015.	ARNHEM	St.Elisabeth's Gasthuis	R.J.de Boer W.Brussel Mw.B.M.Lankester-Knape J.Verhage J.H.Wilton



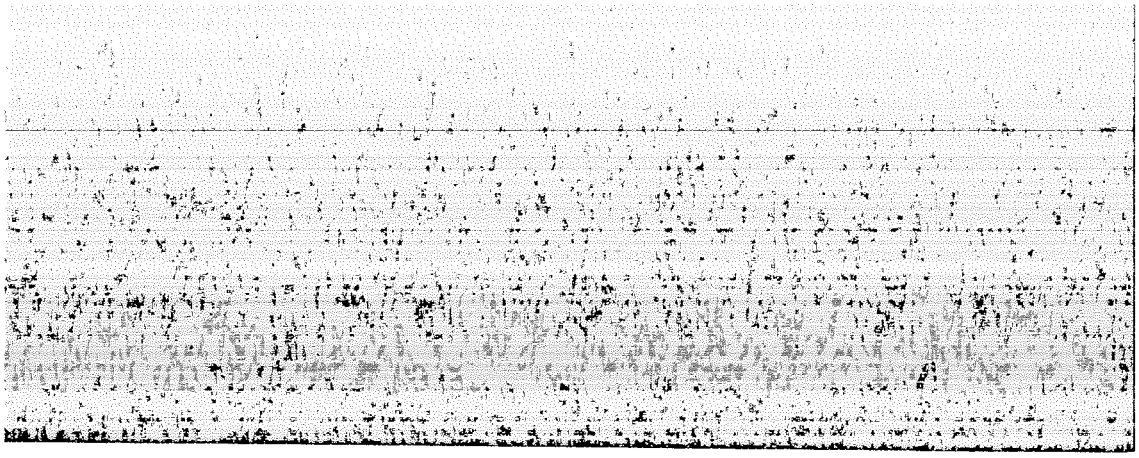
073.	ARNHEM	Hervormd Diaconessenhuis	Mw.R.H.M.Dijkman-Neerinckx K.T.Kwik
016.	ASSEN	Wilhelmina Ziekenhuis	G.F.Nelck Mw.M.L.Vos-Bender H.Wierenga
017.	BERGEN OP ZOOM	Stichting Ziekenhuis "Lievensberg"	H.W.van Kerkwijk L.G.M.Wilberts
099.	BLARICUM	Streekziekenhuis Gooi-Noord: Diakonessenhuis, Naarden; Majella Ziekenhuis, Bussum Ziekenhuis St.Jan-Hoog-Laren	Mw.G.Engel C.E.van Marle E.F.J.Notermans
074.	BOXTEL	St.Liduina Stichting	B.E.M.van den Boezem G.J.van de Vlist
020.	BREDA	St.Ignatius Ziekenhuis	Th.J.I.M.van Heijst H.J.Werre
046.	BRUNSSUM	St.Gregorius Ziekenhuis	M.Soewarso
036.	COEVORDEN	Stichting Streekziekenhuis Coevorden / Hardenberg	C.Blok Mw.I.Dominicus
021.	DELFT	Reinier de Graaf Stichting / St.Hippolytus Ziekenhuis	Mw.A.L.T.Overbeek-van Gils P.J.C.v.d.Straaten L.Vlasveld
022.	DEN HELDER	Stichting Gemini Ziekenhuis	Dr.N.Beganovic J.A.M.v.d.Ham A.M.P.Koolen
023.	DEVENTER	Stichting St.Jozef Ziekenhuis / St.Geertruiden Ziekenhuis	Mw.A.H.Cromme-Dijkhuis Dr.H.Holl Dr.J.J.van der Vlugt
024.	DOETINCHEM	St.Jozef Ziekenhuis	J.Blijleven R.H.H.Wilms
075.	DOKKUM	Prot.-Chr. Ziekenhuis "De Sionsberg"	P.A.van de Bijl K.Went
025.	DORDRECHT	Gemeente Ziekenhuis	R.Schornagel C.E.Vos
027.	DORDRECHT	Diaconessenhuis "Refaja"	N.Ceelie Mw.C.M.E.Smit
026.	DORDRECHT	R.K.Ziekenhuis	J.Hagendoorn Mw.I.C.van Kesteren
028.	EINDHOVEN	Stichting "Catharina Ziekenhuis	L.T.F. Jansen A.G.W.M.Tielens Dr.J.J.J.Waelkens
097.	EINDHOVEN	Diaconessenhuis	B.I.Agoston J.Toorman
029.	EINDHOVEN	Stichting St.Josephziekenhuis	Mw.D.Lambooy-van Laar Dr.E.J.P.Lommen Dr.C.de Monchy
030.	EMMELOORD	Dr.J.H.Jansenziekenhuis	Mw.G.Nijessen
091.	ENSCHEDE	Ziekenhuis van de Vereniging "Ziekenzorg"	J.H.W.Boeve H.de Nijs Bik
077.	GELEEN	Medisch Centrum Geleen	F.A.Rive
031.	GOES	Stichting Oosterschelde Ziekenhuizen: "De Bevelanden", Goes; Zweedse Rode Kruis Ziekenhuis, Zierikzee	Dr.P.W.de Haas H.Verwey
100.	GORINCHEM	Het Streekziekenhuis Prinses Beatrix	P.Zwart Dr.W.A.R.Huybers
032.	GOUDA	Bleuland Ziekenhuis	E.J.C.Schipper C.V.Tjon Pian Gi
033.	GOUDA	St.Jozef Ziekenhuis	Mw.A.F.F.Manusama Mw.F.Thijssen-Bos



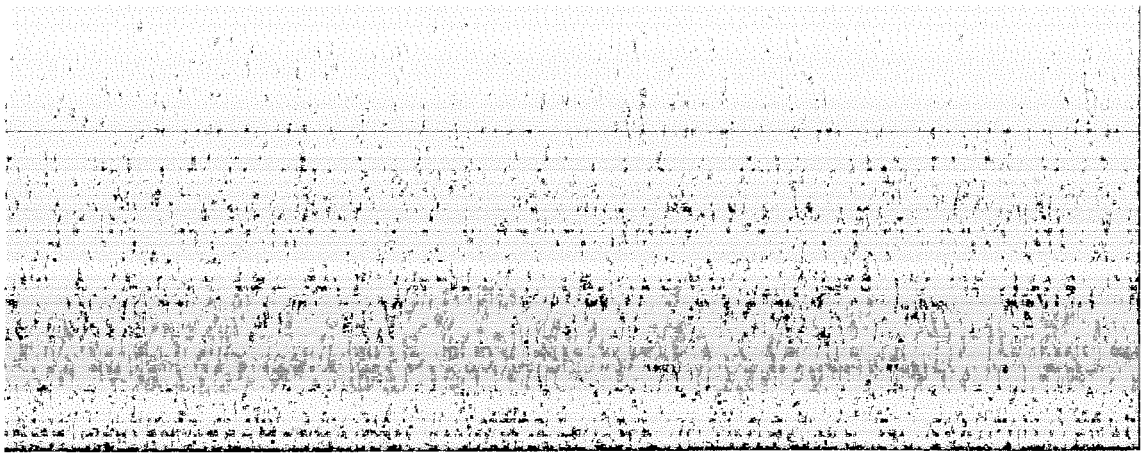
002.	's-GRAVENHAGE	Juliana Kinderziekenhuis	G.F.Drejer F.H.M.Jansen G.M.de Jong J.M.Kouwenberg Mw.M.M.Wagenvoort
094.	GRONINGEN	R.K.Ziekenverpleging onder de titel van "Onze Lieve Vrouwe Behoudenis der Kranken"	H.D.Hamming N.Sorgedrager H.A.Woltil
101.	HARLINGEN	Streekziekenhuis "Oranjeoord"	M.Moens
037.	HEEMSKERK	Sint Jozef Ziekenhuis	P.Harmsen J.W.L.M.Meertens
038.	HEEMSTEDE	Diaconessenhuis	Mw.E.C.van Meeuwen Mw.H.H.Kiezebrink-Lindenhovius
039.	HEERENVEEN	De Tjongerschans	C.J.P.Weyer Tj.Wiersma
040.	HEERLEN	"De Wever" Ziekenhuis	C.H.N.Brackel Mw.Dr.M.L.M.Houben P.M.V.M.Theunisse J.M.J.Sijstermans
041.	HELMOND	St.Lambertus Ziekenhuis /St. Willibrordus Ziekenhuis, Deurne	R.P.Droog J.P.de Jager Dr.P.J.H.Wijers
078.	's-HERTOGENBOSCH	Carolus Ziekenhuis	R.J.G.S.Heydendael G.J.van de Vlist
042.	's-HERTOGENBOSCH	Groot Ziekengasthuis	J.Hoekstra F.A.E.Nabben A.H.F.van Olphen
098.	's-HERTOGENBOSCH	Protestants Ziekenhuis "Willem Alexander"	B.E.M.van den Boezem Dr.W.van Lookeren Campagne
079.	HILVERSUM	Diaconessenhuis	Mw.W.A.Kingma
081.	HOOGEVEEN	Ziekenhuis "Bethesda"	J.H.M.Bollen J.F.Janssen
043.	HOORN	Algemeen Streekziekenhuis "West-Friesland"	Dr.B.Baldewsing P.C.Overberg
044.	HOORN	St.Jans Gasthuis	J.G.Drewes L.J.van Oudheusden
045.	KAMPEN	Ziekenhuizen N.W.Overijssel / Stadsziekenhuis	Mw.M.van Ruth
046.	KERKRADE	St.Jozef Ziekenhuis St. Elisabethkliniek,Heerlen	A.J.da Costa
047.	LEEUWARDEN	Medisch Centrum Leeuwarden	P.A.v.d.Bijl Mw.H.L.E.Kamann K.Went
003.	LEIDEN	Diaconessenhuis	Mw.A.Talma Mw.G.M.A.Swart
001.	LEIDERDORP	St.Elisabeth-Ziekenhuis	Dr.S.E.Bos Mw.A.R.Smit
004.	LEIDSCHENDAM	Sint Antoniushove	Th.A.Nijenhuis Mw.M.H.Ens-Dokkum
102.	LELYSTAD	Zuiderzeeziekenhuis	H.J.J.Jacobs Mw.A.S.G.Kossakowski
049.	MEPPEL	Hervormd Diaconessenhuis	Dr.I.M.Baldew A.C.M.van Kessel
082.	MIDDELBURG	Het Gasthuis	H.Doorn
050.	NIJMEGEN	Canisius-Wilhelmina Ziekenhuis	F.J.L.M. Hoevenaars Dr.P.M.V.van Wieringen Mw.C.L.M.van der Zee



051.	OSS	St.Anna Ziekenhuis	H.L.P.Smeets
052.	PURMEREND	St.Liduina Ziekenhuis	J.L.Ket
			J.B.Wibawa
105.	ROOSENDAAL	Ziekenhuis "St.Franciscus"	Dr.F.A.M.Meersschaert
			A.R.M.Mourmans
083.	ROTTERDAM	Sint Clara Ziekenhuis	B.C.van Pelt
			R.Rodrigues Pereira
057.	ROTTERDAM	Stichting Van Dam-Bethesda Ziekenhuis	J.H.G.Zwijnenberg
054.	ROTTERDAM	Ziekenhuis "Eudokia"	P.A.LeMaire
			H.Oving
084.	ROTTERDAM	Ikazia Ziekenhuis	W.J.den Ouden
055.	ROTTERDAM	St.Franciscus Gasthuis	Mw.J.C.M.B.Versteeg
			Mw.C.J.A.van de List-Nuver
			Mw.J.C.M.Stigter
056.	ROTTERDAM	Zuiderziekenhuis	Mw.A.M.Oudesluys-Murphy
058.	SCHIEDAM	Schieland Ziekenhuis	Mw.A.E.C.Crone-Venneman
			B.A.Leliveld
059.	SITTARD	Ziekenhuis "De Goddelijke Voorzienigheid"	J.J.M.Peters
			E.J.M.Raven
			Dr.S.P.M.van der Zee
060.	SNEEK	St.Antonius Ziekenhuis	R.van Eijk
			R.J.Bakker
103.	STADSKANAAL	Prot.Chr. Ziekenhuis "Refaja"	Mw.Y.C.Bastiaans
			A.M.Voorhoeve
085.	TILBURG	St.Elisabeth-Ziekenhuis	R.A.Holl
			Dr.W.H.Puyn
			J.A.Rammeloo
061.	TILBURG	Maria-Ziekenhuis	J.R.Marcar
			H.M.J.Klinkers
			A.S.Tibosch
093.	UTRECHT	Ziekenhuis Overvecht	Dr.T.W.J.Schulpen
096.	VEENENDAAL	"Juliana Ziekenhuis"	B.S.Voorbrood
062.	VEGHEL	Stichting St.Joseph Ziekenhuis	Mw.W.v.d.Broek-Hotke
063.	VELP	Het Ziekenhuis	R.J.de Boer
			W.Brussel
			Mw.B.M.Lankester-Knape
			J.Verhage
			J.H.Wilton
064.	VENLO	Stichting Ziekenhuis Venlo-Tegelen	Mw.A.W.M.Gierlings
066.	VLISSINGEN	Stichting Bethesda-St. Joseph-ziekenhuis	Mw.E.G.Jansen
086.	WAGENINGEN	Stichting Pieter Pauw	H.Th.Spit
104.	WARNSVELD	Het Nieuwe Spittaal	L.H.A.Hinkofer
			F.E.L.M.Sutorius
087.	WINSCHOTEN	St.Lucas-ziekenhuis	R.A.Elias
			H.C.van Weert
088.	WINTERSWIJK	Stichting Ziekenhuisvoorzieningen Oost-Achterhoek	W.G. Bliek
092.	WOERDEN	Hofpoort Ziekenhuis	Mw.G.W.D.Bloem
			Mw.M.C.van Doornik
			P.A.W.A.Renardel de Lavalette
067.	IJMUIDEN-OOST	Zeeweg Ziekenhuis	A.G.Ketel
			Mw.N.A.L.Biervliet-Dahlberg
089.	IJSSELSTEIN	Interconfessioneel Streekziekenhuis "Isselwaerde"	P.A.W.A.Renardel de Lavalette
068.	ZEVENAAR	Streekziekenhuis Zevenaar	A.J.Manders
			F.B.M.Verheij

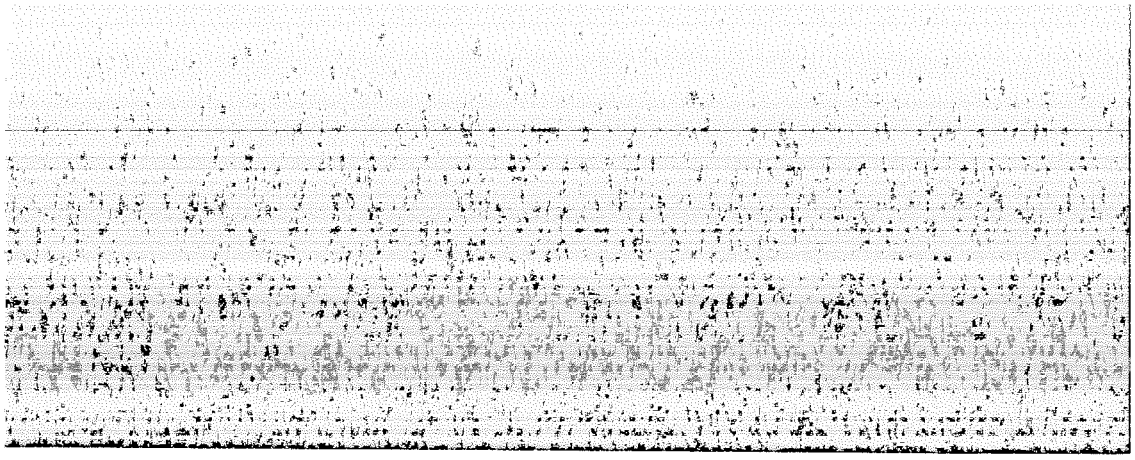


069.	ZWOLLE	Stichting Sophia Ziekenhuis	Mw.Dr.J.J.M.van Collenburg J.F.van Gils Dr.J.G.v.Lookeren Campagne
070.	ZWOLLE	Ziekenhuis "De Weezenlanden"	Mw.Dr.J.J.M.van Collenburg F.van der Logt Mw.Dr.K.G.N.Tjo

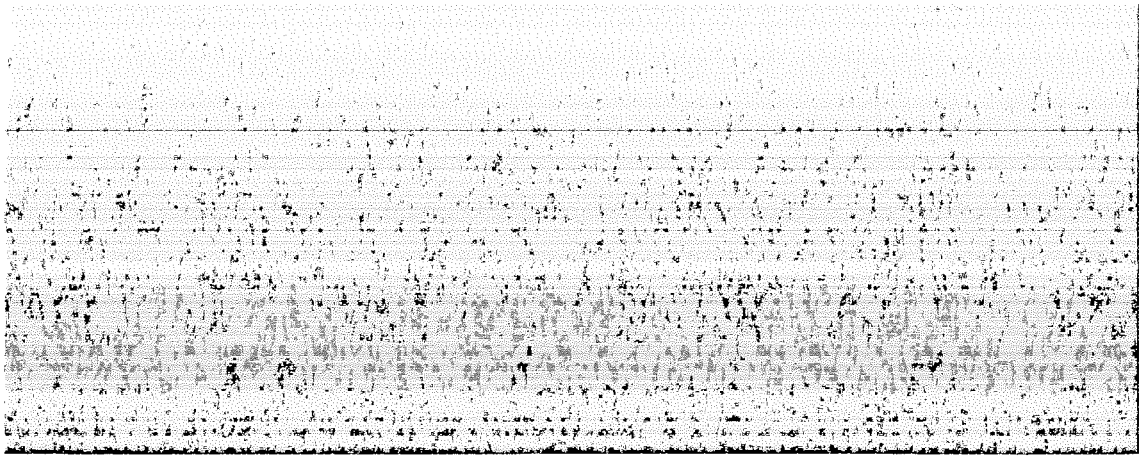


DEELNEMERSLIJST KINDERARTSEN POPS 1983 (anno 1986)
(Project onderzoek Prematuritas en Small for Gestational age)

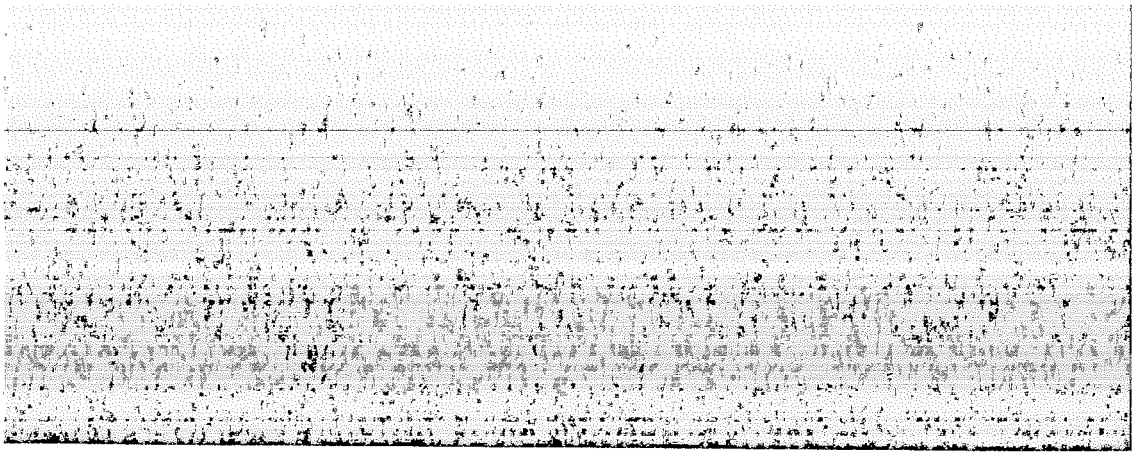
1.	AMSTERDAM	Academisch Ziekenhuis der Vrije Universiteit	Mw.J.F.Samson
2.	AMSTERDAM	Academisch Medisch Centrum	Mw.Dr.J.G.Koppe M.J.K.de Kleine Mw.Dr.J.H.Kok Dr.R.de Leeuw Mw.Dr.A.Marinkovic-Ilsen Mw.H.Smolders-de Haas
3.	GRONINGEN	Academisch Ziekenhuis	Prof.Dr.A.Okken S.Bambang Oetomo
4.	LEIDEN	Academisch Ziekenhuis	Prof.Dr.J.H.Ruys H.M.Berger F.van Bel Mw.M.van de Bor Mw.A.L.den Ouden Mw.D.van Zoeren-Grobben
9.	MAASTRICHT	Academisch Ziekenhuis	Dr.F.J.Walther W.J.Maertzdorf P.Degraeuwe
5.	NIJMEGEN	St.Radboud Ziekenhuis	Dr.L.A.A.Kollée Dr.J.M.Boon K.D.Liem W.Geven
6.	ROTTERDAM	Sophia Kinderziekenhuis	W.Baerts Dr.W.P.F.Fetter
7.	UTRECHT	Wilhelmina Kinderziekenhuis	R.Ch.Senders B.P.Cats Mw.I.van Ertbruggen L.J.Gerards Mw.T.G.Krediet
005.	ALKMAAR	Medisch Centrum Alkmaar	J.F.van der Blij
006.	ALMELO	Stichting Streekziekenhuis Almelo	R.P.Beekman N.Hofstee F.J.A.M.Holtus
007.	ALPHEN a /d RIJN	Ziekenhuis Rijnoord	D.K.Nanlohy R. Brunsting
008.	AMERSFOORT	Stichting Prot.-Chr. Ziekenhuis "De Lichtenberg"	Mw.H.J.Dijkhuis A.van Rhijn Dr.H.G.Scholten
010.	AMSTERDAM	Andreas Ziekenhuis	Mw.M.J.van Houten A.T.Buikema
011.	AMSTERDAM	Sint Lucas Ziekenhuis	Mw.M.K.Sanders
013.	APELDOORN	Juliana Ziekenhuis	R.F.Oosterkamp Dr.H.G.Sie
012.	APELDOORN	Lukas Ziekenhuis	A.J.W.Leenders M.Hofkamp T.A.de Heer-Groen
014.	ARNHEM	Stichting Ziekenhuis De Malberg Lokatie: Malberg GZ	R.J.de Boer W.Brussel J.C.Mulder J.Verhage J.H.Wilton
015.	ARNHEM	Stichting Ziekenhuis De Malberg Lokatie: Malberg EG	R.J. de Boer W. Brussel J.C. Mulder J. Verhage J.H. Wilton



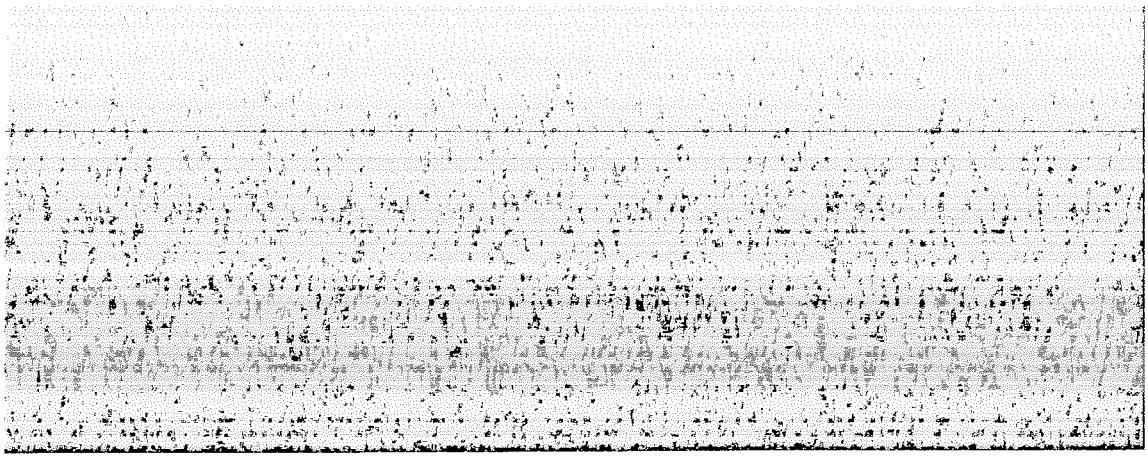
073.	ARNHEM	Hervormd Diaconessenhuis	Mw.R.H.M.Dijkman-Neerincx
			K.T.Kwik
016.	ASSEN	Wilhelmina Ziekenhuis	G.F.Nelck
			Mw.M.L.Vos-Bender
			H.Wierenga
017.	BERGEN OP ZOOM	Stichting Ziekenhuis	H.W.van Kerkwijk
		"Lievensberg"	L.G.M.Wilberts
099.	BLARICUM	Streekziekenhuis Gooi-Noord:	Mw.G.Engel
		Diakonessenhuis, Naarden;	C.E.van Marle
		Majella Ziekenhuis, Bussum	E.F.J.Notermans
		Ziekenhuis St.Jan-Hoog-Laren	
074.	BOXTEL	St.Carolus-Liduina Ziekenhuis	R.J.G.S.Heydendaal
		en Verpleeghuis	W.J.van der Toom
			A.R.Schuitema-Dijkstra
020.	BREDA	St.Ignatius Ziekenhuis	Th.J.I.M.van Heijst
			H.J.Werre
046.	BRUNSSUM	St.Gregorius Ziekenhuis	M.Soewarso
036.	COEVORDEN	St. Streekziekenhuis	C.Blok
		Coevorden /Hardenberg	Mw.I.Dominicus
021.	DELFT	Reinier de Graaf	Mw.A.L.T.Overbeek-van Gils
		Ziekenhuis	P.J.C.van der Straaten
			L.Vlasveld
022.	DEN HELDER	Stichting Gemini	J.A.M.van den Ham
		Ziekenhuis	A.M.P.Koolen
			F.R.Langerijs
023.	DEVENTER	Stichting St.Jozef	Mw.A.H.Cromme-Dijkhuis
		Ziekenhuis /St. Geertruiden	Dr.H.Holl
		Ziekenhuis	Dr.J.J.van der Vlugt
024.	DOETINCHEM	St.Jozef Ziekenhuis	M.P.J.M.Cuppen
			R.H.H.Wilms
075.	DOKKUM	Prot. Chr. Ziekenhuis	P.A.van der Bijl
		"De Sionsberg"	K.Went
			J.W.Doddema
025.	DORDRECHT	Gemeente Ziekenhuis	R.Schornagel
			C.E.Vos
027.	DORDRECHT	Diaconessenhuis	N.Ceelie
		"Refaja"	Mw.C.M.E.Smit
026.	DORDRECHT	R.K.Ziekenhuis	A.N. Bosschaart
			Mw.I.C.van Kesteren
028.	EINDHOVEN	Catharina Ziekenhuis	A.G.W.M.Tielens
			Dr.J.L.M.Strengers
			Dr.J.J.J.Waelkens
097.	EINDHOVEN	Diaconessenhuis	B.I.Agoston
			J.Toorman
029.	EINDHOVEN	Stichting St.Josephziekenhuis	Mw.D.Lambooy-van Laar
			Dr.E.J.P.Lommen
			Dr.N.Beganovic
030.	EMMELOORD	Dr.J.H.Jansenziekenhuis	Mw.G.Nijessen
			Mw.C.M.Bontemps-Hommen
			A.J.Stege
091.	ENSCHEDE	Ziekenhuis van de	J.H.W.Boeve
		Vereniging "Ziekenzorg"	H.de Nijs Bik
077.	GELEEN	Medisch Centrum Geleen	F.A.Rive
031.	GOES	Ziekenhuis Bergzicht	Dr.P.W.de Haas
			H. Verwey
100.	GORINCHEM	Beatrixziekenhuis	P.Zwart
			Dr.W.A.R.Huybers
032.	GOUDA	Bleuland Ziekenhuis	E.J.C.Schipper
			C.V.Tjon Pian Gi



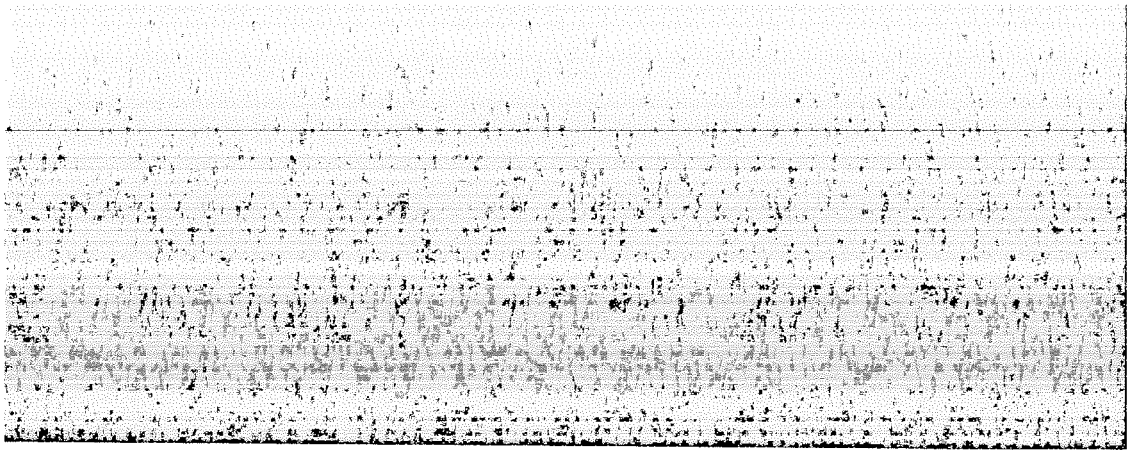
033.	GOUDA	St.Jozef Ziekenhuis	Mw.A.F.F.Manusama
			Mw.F.Bos
002.	's-GRAVENHAGE	Juliana	G.F.Drejer
		Kinderziekenhuis	F.H.M.Jansen
			G.M.de Jong
			J.M.Kouwenberg
			Mw.M.M.Wagenvoort
094.	GRONINGEN	R.K.Ziekenverpleging	H.D.Hamming
		onder de titel van "Onze Lieve	N.Sorgedrager
		Vrouwe Behoudenis der Kranten"	H.A.Woltil
101.	HARLINGEN	Streekziekenhuis "Oranjeoord"	M.Moens
037.	HEEMSKERK	Sint Jozef Ziekenhuis	P.Harmsen
			J.W.L.H.Meertens
038.	HEEMSTEDE	Diaconessenhuis	Mw.E.C.van Meeuwen
			Mw.H.H.Kiezebrink-Lindenhovius
039.	HEERENVEEN	De Tjongerschans	C.J.P.Weyer
			Tj.Wiersma
040.	HEERLEN	"De Wever" Ziekenhuis	C.H.N.Brackel
			J.M.J.Sijstermans
			P.M.V.M.Theunissen
041.	HELMOND	Streekziekenhuis	R.P.Droog
		Helmond /Deurne	J.P.de Jager
			Dr.P.J.H.Wijers
078.	's-HERTOGENBOSCH	Carolus Ziekenhuis	R.J.G.S.Heydendael
			W.J.van der Toom
042.	's-HERTOGENBOSCH	Groot Ziekengasthuis	J.H.Hoekstra
			F.A.E.Nabben
			A.H.F.van Olphen
098.	's-HERTOGENBOSCH	Protestants Ziekenhuis	B.E.M.van den Boezem
		"Willem Alexander"	Dr.W.van Lookeren Campagne
079.	HILVERSUM	Diaconessenhuis	F.M.Banens
			Mw.W.A.Kingma
			H.L.G.van Tinteren
081.	HOOGEVEEN	Ziekenhuis Bethesda	J.H.M.Bollen
			J.F.Janssen
043.	HOORN	Westfries Gasthuis	J.G.Drewes
		Lokatie: Streek	L.J. van Oudheusden
			P.C.Overberg
			Dr.B.Baldewsing
044.	HOORN	Westfries Gasthuis	J.G. Drewes
		Lokatie: St. Jan	L.J. van Oudheusden
			P.C. Overberg
045.	KAMPEN	Ziekenhuizen N.W.Overijssel, Stads-	Mw.M.van Ruth
		ziekenhuis "De Engelenbergstichting"	
046.	KERKRADE	St.Jozef Ziekenhuis	A.J.da Costa
		St. Elisabethkliniek, Heerlen	
047.	LEEUWARDEN	Medisch Centrum Leeuwarden	P.A.van der Bijl
			J.W.Doddema
			Mw.H.L.E.Kamann
			K.Went
			Mw.I.I.C.Wijmenga
003.	LEIDEN	Diaconessenhuis	Mw.A.Talma
			Mw.G.M.A.Swart
001.	LEIDERDORP	St.Elisabeth Ziekenhuis	Dr.S.E.Bos
			Mw.A.R.Smit
			Mw.P.E.C.Mourad-Baars
			J.J.Gosen



004.	LEIDSCHENDAM	Sint Antoniushove	Th.A.Nijenhuis
			Mw.M.H.Ens-Dokkum
102.	LELYSTAD	Zuiderzeeziekenhuis	F.de Jager
			Mw.A.S.G.Kossakowski
			J.W.Pilon
049.	MEPPEL	Hervormd	Dr.I.M.Baldew
		Diaconessenhuis	A.C.M.van Kessel
082.	MIDDELBURG	Gasthuis	H.Doorn
			E.G.Jansen
050.	NIJMEGEN	Canisius-Wilhelmina	F.J.L.M. Hoevenaars
		Ziekenhuis	Dr.P.M.V.van Wieringen
			Mw.C.L.M.van der Zee
051.	OSS	St.Anna Ziekenhuis	H.L.P.Smeets
			J.A.M.Widdershoven
			P.Gerrits
052.	PURMEREND	Streekziekenhuis	J.L.Ket
		Waterland	J.B.Wibawa
105.	ROOSENDAAL	Ziekenhuis	Dr.F.A.M.Meersschaert
		St. Franciscus	A.R.M.Mourmans
083.	ROTTERDAM	Sint Clara Ziekenhuis	B.C.van Pelt
			R.Rodrigues Pereira
057.	ROTTERDAM	Van Dam-Bethesda Ziekenhuis	J.H.G.Zwijnenberg
054.	ROTTERDAM	Ziekenhuis Eudokia	P.A.LeMaire
			H.A.A.Damen
084.	ROTTERDAM	Ikazia Ziekenhuis	Mw.N.D.Boon
			W.J.den Ouden
055.	ROTTERDAM	St.Franciscus Gasthuis	Mw.J.C.M.B.Versteeg
			Mw.C.J.A.van de List-Nuver
			Mw.J.C.M.Stigter
056.	ROTTERDAM	Zuiderziekenhuis	Mw.A.M.Oudesluys-Murphy
058.	SCHIEDAM	Schielandziekenhuis	Mw.A.E.C.Crone-Venneman
			B.A.Leliveld
059.	SITTARD	Ziekenhuis	J.J.M.Peters
		"De Goddelijke	E.J.M.Raven
		Voorzienigheid"	Dr.S.P.M.van der Zee
060.	SNEEK	St.Antonius Ziekenhuis	R.van Eyk
			R.J.Bakker
103.	STADSKANAAL	Prot. Chr.Ziekenhuis	Mw.Y.C.Bastiaans
		"Refaja"	D.Lenstra
085.	TILBURG	St.Elisabeth-Ziekenhuis	R.A.Holl
			Dr.W.H.Puyn
			J.A.Rammeloo
061.	TILBURG	Maria-Ziekenhuis	J.R.Marcar
			H.M.J.Klinkers
			A.S.Tibosch
093.	UTRECHT	Ziekenhuis Overvecht	Dr.T.W.J.Schulpen
			A.W.M.Rupert
096.	VEENENDAAL	Juliana Ziekenhuis	B.S.Voorbrood
062.	VEGHEL	Stichting St.Joseph	Mw.W.van de Broek-Hotke
		Ziekenhuis	J.W.C.M.Heynens
063.	VELP	Het Ziekenhuis	R.J.de Boer
			J.H.Wilton
064.	VENLO	Sint Maartens Gasthuis	J.M. Donk
			Mw.A.W.M.Gierlings
			Dr.T.S.The
066.	VLISSINGEN	Stichting Streekziekenhuis	H.Doorn
		Walcheren	Mw.E.G.Jansen
086.	WAGENINGEN	Stichting Pieter Pauw	H.Th.Spit

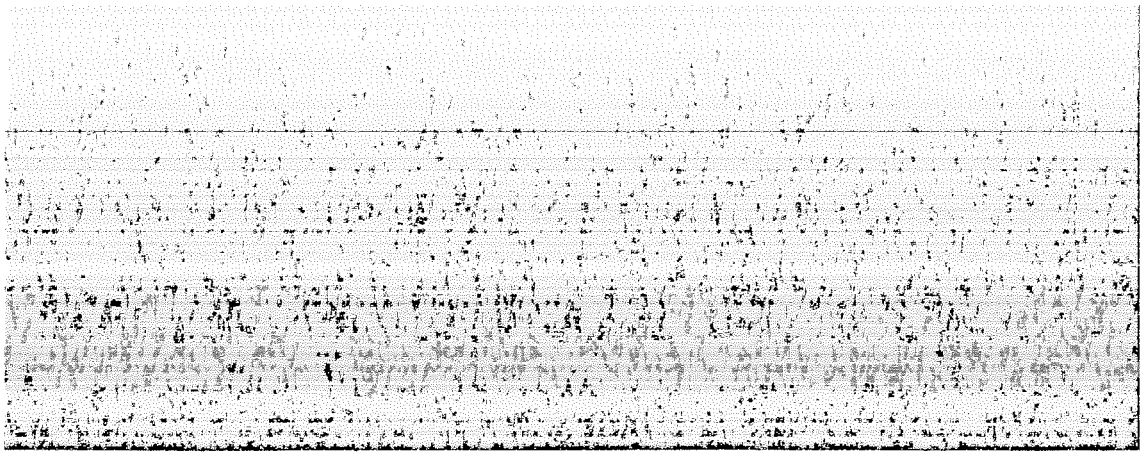


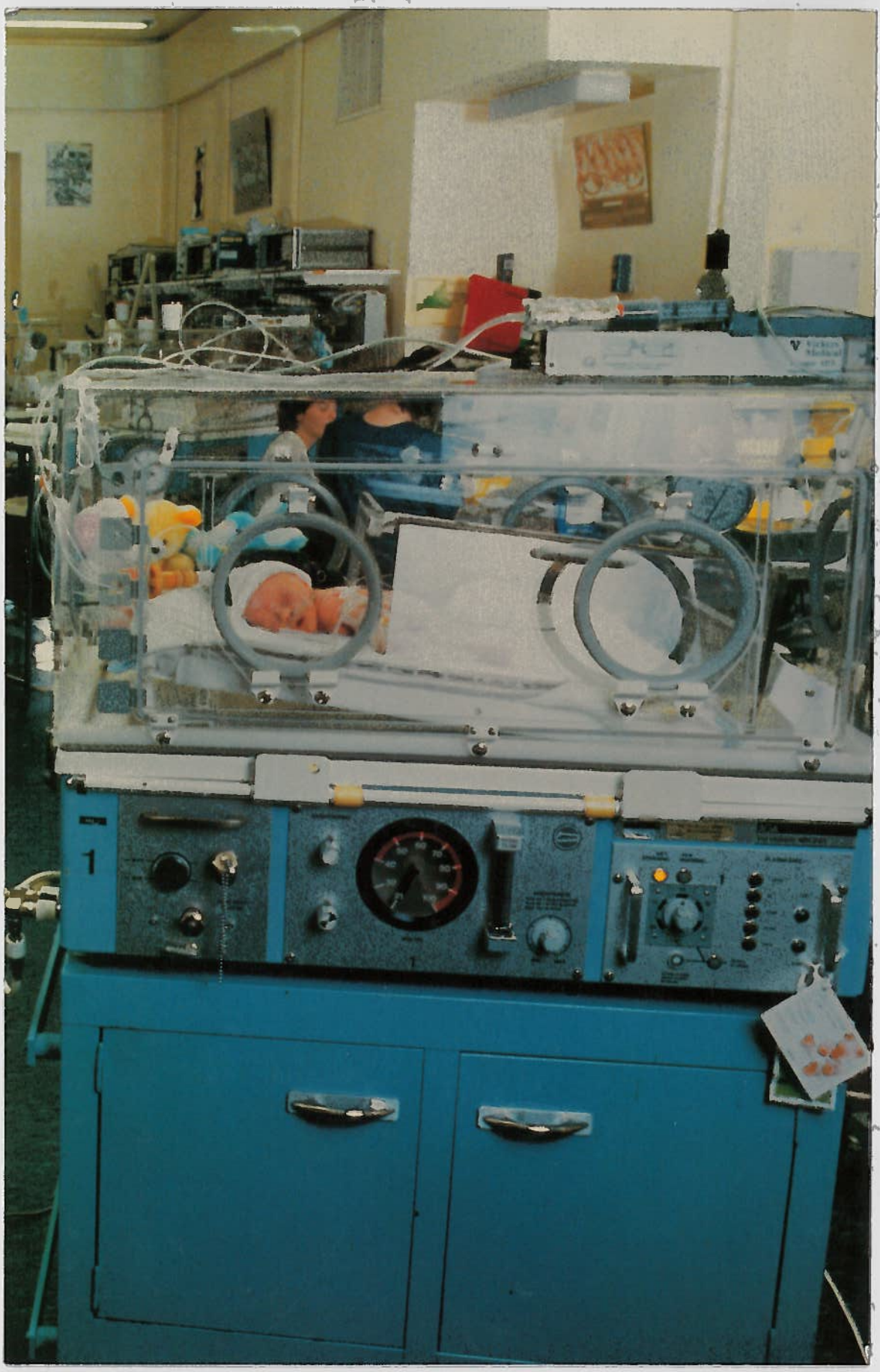
104.	WARNSVELD	Het Nieuwe Spittaal	L.H.A.Hinkofer F.E.L.M.Sutorius
087.	WINSCHOTEN	St.Lucas Ziekenhuis	R.A.Elias H.C.van Weert
088.	WINTERSWIJK	Streekziekenhuis Koningin Beatrix	A.J.M.van Kuppevelt F.G.J.Küpers
092.	WOERDEN	Hofpoort Ziekenhuis	Mw.G.W.D.Bloem Mw.M.C.van Doornik P.A.W.A.Renardel de Lavalette
067.	IJMUIDEN-OOST	Zeeweg Ziekenhuis	Mw.N.A.L.Dahlberg J.A.M.Gerver
089.	NIEUWEGEIN	Stichting St. Antonius Ziekenhuis	P.A.W.A.Renardel de Lavalette
068.	ZEVENAAR	Streekziekenhuis Zevenaar	A.J.Manders F.B.M.Verheij
069.	ZWOLLE	Stichting Sophia Ziekenhuis	Mw.Dr.J.J.M.van Collenburg J.F.van Gils Dr.J.G.v.Lookeren Campagne
070.	ZWOLLE	Ziekenhuis "De Weezenlanden"	Mw.Dr.J.J.M.van Collenburg E.van de Logt Mw.Dr.K.G.Tjoa



AANVULLING DEELNEMERSLIJST KINDERARTSEN POPS per 31 maart 1986

	AMERSFOORT	Sint Elisabeth Ziekenhuis	Dr.P.H.G.Hogeman
			Dr.P.Kraus
110.	AMSTELVEEN	Stichting Ziekenhuis Amstelveen	Dr.A.L.M.Israels
			Dr.E.Mulder
	AMSTERDAM	Burgerziekenhuis	A.J.Koers
			K.L.Tjia
90.	BREDA	Ziekenhuis De Baronie	P.W. Hendriks
			H.J.J.Jacobs
			Mw.M.J.de Koningh
	DIRKSLAND	Stichting Het Van Weel Bethesda Ziekenhuis	J.van Loo
106.	EDE	Ziekenhuis Gelderse Vallei, Ede	A.M.Hemmes
	ENSCHEDE	de Stadsmaten	H.del Canho
			J.K.van der Woude
	GRONINGEN	Diakonessenhuis	Dr.N.J.Jansonius
			Dr.H.A.Polman
			H.A.van Dijk
107.	HAARLEM	Elisabeth Gasthuis	Mw.A.Hammond
			C.van Steijnen
108.	HARDERWIJK	Ziekenhuis Sint Jansdal	J. Hagendoorn
			W.Peelen
109.	HENGELO	Streekziekenhuis Midden Twente	N.Kors
			A.van der Wagen
	OOSTERHOUT	Sint Joseph Ziekenhuis	A.A.M.de Steenhuysen Piters
	RAAMSDONKVEER	Sint Theresia Ziekenhuis	H.J.Snelten
	ROERMOND	St. Laurentius Ziekenhuis	W.F.J.van der Kolk
			L.W.A.M.Schulhof
	UTRECHT	Ziekenhuis Oudenrijn	Dr.B.Janssen
			M.Schraagen
	VLAARDINGEN	Holy-Ziekenhuis	J.W.Oltmans
	WAALWIJK	Sint Nicolaas Ziekenhuis	K.van Drumpt
	WEERT	St. Jans-Gasthuis	H.Mulder
			P.D.M.M.Verschure
	ZAANDAM	Juliana Ziekenhuis	J.Vonk

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