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# Psychiatric disorders and MND in non-handicapped preterm children

## Prevalence and stability from school age into adolescence

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**Abstract** In preterm children ( $N = 66$ ) without major physical and/or mental handicaps the prevalence of psychiatric disorders and minor neurological dysfunction (MND) was assessed at school age (8–10 years). In adolescence (15–17 years) 43 children were reassessed. The study sample was drawn from a cohort of non-handicapped preterm children ( $N = 218$ ) hospitalised in a Neonatal Intensive Care Unit because of serious neonatal complications. The findings in the preterm group were compared with two control groups ( $N = 20$  and  $N = 20$ ) matched for age and sex ratio. The association between psychiatric disorders on the one hand and group status (preterm versus control), MND, IQ and family adversity on the other was explored. At both ages the preterm children exhibited more psychiatric disorders and MND than controls. The very preterm and/or very low birth weight children contributed to the differential psychopathological findings between the preterm and

control groups. Besides preterm birth, the prevalence of psychiatric disorders was positively associated with MND and negatively associated with VIQ and family adversity. In the preterm group there was a shift from school age into adolescence into a predominance of anxious and depressive disorders. No significant changes with age were found with respect to the prevalence of MND and psychiatric disorders. Thus, very preterm and/or very low birth weight children are at increased risk of persistent psychiatric disorders, especially anxious and depressive disorders. In preterm children the development of psychopathology seems to be mediated by MND, decreased verbal abilities and family adversity.

**Key words** preterm – follow-up – psychiatric disorders – minor neurological dysfunction

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### Introduction

A substantial part of the (very) preterm/(very) low birth weight infants who survive without major handicaps do develop minor cognitive and neurological impairments and more often need special

education facilities [2, 16, 25, 27, 35]. Since neurological dysfunction and cognitive impairments are associated with behavioural problems and psychopathology [11, 12, 26], one might expect preterm children to be at an increased risk for the development of psychiatric disorders as well.

The research on the development of psychiatric disorders in non-handicapped preterm children conducted so far has a number of limitations and shows no consistent findings [7]. Follow-up studies mainly rely on checklists based on parents, teachers and/or youth-self reports to assess behavioural problems and/or psychopathology. However, screening instruments like the Child Behaviour Checklist [1] have limited diagnostic validity with respect to the prevalence and nature of psychiatric disorders [18]. Furthermore, in most studies a cross-sectional design was used or no longitudinal analyses of data on different time points were performed [6, 10, 15, 36].

The comparison of results of follow-up studies on non-handicapped preterm children is hampered by methodological differences, e.g. in selection criteria used, outcome measures and age at follow up. Some authors report an increased total number of behavioural problems [10, 15, 29] while others report an increased risk of a specific type of problems [6, 9, 27]. With respect to the nature of behavioural problems a predominance of internalising problems [10] as well as a predominance of externalising problems [6, 9] are reported, while in other studies an equal prevalence of externalising and internalising problems was found [15, 29, 37]. The change and persistence of behavioural problems in preterm children was explored in a few studies indicating that behavioural problems in these children persists into adolescence [27, 29].

Several factors are found to be associated with an increased risk for abnormal psychological development in low birth weight/preterm children, e.g. neonatal cerebral abnormalities [30, 37] and the prevalence of minor neurological dysfunction (MND) or so-called soft signs [5]. Findings on a possible differential outcome in preterm children related to sex are not consistent. There are reports on an equal risk in preterm boys and preterm girls [27] as well on gender differences with respect to certain types of behavioural problems [15]. Adverse environmental circumstances, e.g. low social-economic factors, are known to increase the risk of behavioural problems. Whether adverse environmental factors constitute an additional [27] or an extra risk [6] in preterm children is still unclear.

This paper addresses the following issues:

- The prevalence of psychiatric disorders and minor neurological dysfunction (MND) in preterm children without major handicaps compared to controls.
- The differential risk of psychiatric disorders within the preterm group related to birth weight and degree of prematurity.
- The nature of psychiatric disorders in preterm children

- The persistence and change of the prevalence of psychiatric disorders and MND and the nature of psychiatric disorders in the preterm group from school age into adolescence.
- The predictive properties of explanatory variables (family adversity, sex, cognitive abilities, MND, preterm birth) with respect to the prevalence of psychiatric disorders.

## Method

### ■ Subjects

In 1977 and 1978 323 preterm children (gestational age  $\leq 37$  weeks) were hospitalised in the Neonatal Intensive Care Unit (NICU) of the Wilhelmina Children's Hospital (WKZ) in Utrecht, one of the academic centres in the Netherlands with a supra regional function that provide neonatal care at the highest level. Of the preterm children 80 (27%) died. The preterm children who survived were followed up by paediatricians after discharge. We performed an extensive review of the paediatrician's records. On the basis of the data in the medical records, the children were classified as 'normal' or handicapped. Children expected to be able to attend normal schools were classified as normal. Children were classified as handicapped if they were so disabled by physical and/or mental handicaps that they were not expected to attend normal schools or already were attending facilities for disabled children. Of the surviving preterm children ( $N = 243$ ) 218 were classified as normal (67% of the total cohort) and 25 children (8% of the total cohort) had major handicaps, predominantly consisting of cerebral palsy ( $N = 14$ ), mental retardation ( $N = 14$ ) and/or congenital disorders ( $N = 6$ ). One child was classified as handicapped on basis of medical information received after the parents had been requested to participate in our study. The follow-up study of the non-handicapped children ( $N = 218$ ) consists of a questionnaire study using the Child Behaviour Checklist (CBCL) [1] parent form and clinical assessments. Initially we conducted CBCL assessments at the age of 5–7 years (T1), and 7–9 years (T2). From the T2 responders ( $N = 167$ , response rate 80%) a sample ( $N = 75$ , accounting for power and possible drop-outs) was drawn, stratified for sex and sum score on neonatal complications. The sum score was calculated of the scores on the presence and/or severity of neonatal complications, e.g., convulsions, hypoglycaemia, hyperbilirubinaemia. Post hoc 3 children were excluded; 2 children of immigrants because of language difficulties and 1 child suffering from Turner syndrome. Of the

**Table 1** Composition of the study sample according to gestational age and birth weight

	N (PCT)	Mean birth weight (range)	Mean gestational age (range)
Index A: <32 weeks/<1501 g	38 (58%)	1252 (700–1740)	30 (25–33)
Index B: 31–37 weeks and >1500 g	28 (42%)	2113 (1550–2870)	34 (32–37)
Total	66 (100%)	1617 (700–2870)	32 (25–37)

remaining sample 66 children (90%) participated in the first clinical assessment at the age of 8–10 years and  $N = 43$  (60%) were reassessed at the age of 15–17 years.

Post hoc analyses on birth weight, gestational age, mean sum score of neonatal complications ( $t$ -test) and sex ratio (chi-square) were performed to control whether the sample of 66 and the sample of 43 are representative for the original sample. In the sample of 66 mean gestational age and mean birth weight was lower than in the original sample ( $N = 218$ ): 31.7 versus 32.5 weeks ( $t = 2.02$ ,  $P = 0.045$ ) and 1617 versus 1771 grams ( $t = 2.0$ ,  $P = 0.047$ ) respectively. With respect to mean sum score on neonatal complications and sex ratio there were no significant differences between the sample of 66 and the original sample. Between the sample of 43 and the original sample no significant differences were found.

In order to analyse differential outcome related to differential perinatal risks the study sample was subdivided into two groups: very preterm (gestational age <32 weeks) children and/or very low birth weight (birth weight  $\leq 1500$  grams) children (Index A) and preterm children with gestational age 32–37 weeks and birth weight >1500 grams (Index B) (Table 1).

Normal birth weight children without gestational and perinatal complications were selected for the control group. The control children were obtained via schools. For the first assessment control children were selected from a municipal elementary school ( $N = 20$ ). The control group was matched for age and sex distribution with the preterm group. For the second assessment it was not possible to trace these control children having no access to the personal data, e.g. addresses. Therefore another control group was obtained via secondary education schools. In the Netherlands there is wide variety in secondary education facilities and consequently in secondary educational levels. Therefore the second control group ( $N = 20$ ) was matched for age and sex distribution as well as for distribution of educational level. At the first clinical examinations, mean age was 9 years and 3 months (range 8–10 years) in both the preterm and the control group. At the second assessment in the preterm group mean age was 16 years and 3 months (range 15–17 years) and in controls 16 years and 2 months (range 15–17 years).

## ■ Assessment

For logistic reasons it was not possible to assess blindly for control or preterm status. However, the persons who made the assessments of the preterm children were blind for neonatal status (birth weight, gestational age, and perinatal complications) and at the second assessment also for the results of the first assessment.

Intelligence was tested by means of the WISC-R. Total IQ (TIQ), verbal IQ (VIQ) and performance IQ (PIQ) were calculated.

The neurological examination was conducted by the method according to Touwen [32]. This examination focuses on minor neurological dysfunction (MND). The results of the neurological examination were summarised in 6 clusters: posture and muscle tone; reflexes; co-ordination and balance; fine manipulative abilities; choreiform dyskinesia; mirror movements. The performances on the clusters were dichotomised into deviant (score 1) and normal (score 0). Subsequently a sum score was calculated (see Touwen, 32 and Hadders-Algra et al., 17 for scoring criteria). The sum score was subdivided into three categories: no MND; MND-1 (1 or 2 deviant clusters) and MND-2 (more than 2 deviant clusters) [17].

The psychiatric assessment consisted of a semi-structured child interview, viz. a slightly modified version of the Child Assessment Schedule (CAS) [20, 21], and the slightly modified Graham and Rutter parent interview [13]. On the basis of these interviews the raters (P.S. and H.v.E.) made a consent judgement on the presence, severity and nature of psychiatric disorders. The severity of psychiatric disorders was scored on the basis of the degree to which the psychiatric symptoms interfered with the child's development and impeded joining in every day life. Psychiatric disorders were scored on a three point scale: 0, no disorder; 1, mild disorders that require no treatment and 2, moderate-severe disorders that require treatment. The psychiatric disorders were classified according to DSM-IV (DSM-III classifications of the first assessment were converted into DSM-IV classifications) [3]. Subsequently the classifications were categorised into 4 broad categories: DSM-IV category Anxiety Disorders, DSM-IV category Mood Disorders, DSM-IV category Attention-Deficit and

Disruptive Behaviour disorders and other disorders (e.g., nocturnal enuresis, tic disorder, language disorder, etc.).

A sum score on the Family Adversity Index (FAI) [28] was calculated from items of the parent interview. The FAI contains items on the caretakers (one parent, stepparent), mental health problems in the caretakers, physical problems in the caretakers, unemployment, family stress (financial etc.), quality of relation of the caretakers, death of relatives and low socio-economic status. The socio-economic status (SES) was scored according to the highest education of the parents, using the method described in the educational index developed by the "Instituut voor Toegepaste Sociologie" (Institute for Applied Sociology) in Nijmegen [34].

### ■ Data analyses

Statistical analyses were performed using SPSS version 9.0 and the FORTRAN MIXOR program [19]. Significant differences were set at  $P < 0.05$ .

*t*-Tests were used to analyse differences between the preterm children and control groups with respect to mean IQ scores, mean FAI and mean SES. Accounting for the skewed distribution of MND in controls, the Mann-Whitney test was used to analyse differences in the mean number of deviant neurological clusters.

Differences between responders and non-responders at the second assessment were analysed by means of *t*-tests (birth weight, gestational age, SES, FAI) and by means of cross tabulations (distribution of psychiatric disorders and MND).

Cross tabulations of ordinal variables calculating Somers'd were conducted to predict column categories from row categories. Exact significance was calculated in order to correct for asymptotic cell filling.

Odds ratios for psychiatric disorders requiring treatment were calculated dichotomising the psychiatric judgement scores into no or mild disorders (score 0) and disorders requiring treatment (score 1).

Sex differences and the interaction effects between group status (preterm versus control) and sex were analysed by means of cross tabulations calculating Somers'd (distribution of psychiatric disorders and MND) and univariate analyses of variance (mean psychiatric judgement score and mean MND score) respectively.

We refrained from performing logistic regression techniques to analyse the association (main effects and interaction effects) between group status (preterm groups versus controls), MND, FAI, PIQ, VIQ and the frequency distribution of psychiatric disorders because of insufficient cell filling. Also, due to

insufficient cell filling we did not perform analyses on the association between psychiatric morbidity and the different neurological clusters.

Instead we analysed the association between the mean psychiatric judgement score (dependent variable) and group status, MND, FAI, PIQ, VIQ (explanatory variables) in the following ways.

Firstly, univariate analyses of variance were applied to investigate the interactions between group status (index A, index B, control groups) on the one hand and MND, FAI, PIQ and VIQ on the other. In these analyses the scores on FAI at the first and second assessment were dichotomised into low and high scores with the mean FAI-score of the total sample (preterm sample of 66 plus control group1 and preterm sample of 43 plus control group 2) as a cut-off point. VIQ and PIQ were dichotomised into scores  $<100$  and  $\geq 100$ . Secondly, linear regression was performed to analyse the predictive power of the explanatory variables.

The MIXOR computer program was used to analyse the persistence and change in the preterm group with respect to psychiatric judgement scores and MND scores. Furthermore, possible interactions between group membership (Index A versus Index B) and time were analysed with this program. MIXOR provides marginal likelihood estimates for mixed effects ordinal regression models, utilising a Fisher-scoring solution. These models can be used for analysis of dichotomous and ordinal outcomes from a longitudinal design. The idea of nesting or clustering and the presence of fixed effects in addition to random effects is common to the mixed effects regression models. For longitudinal data the repeated measures are clustered within individuals while the subject effects represent the random effects. Further these models allow for the presence of missing data and make no assumption regarding either cluster sample size or independence of observations.

## Results

### ■ Responders versus non-responders

With regard to mean birth weight, mean gestational age and mean SES, there were no differences between the preterm children responding at both assessments and those responding only at the first assessment. Also there were no differences between responders and non-responders with regard to the findings at the first assessment, viz. mean score on FAI, the proportion of psychiatric disorders and the proportion of MND.

**Table 2** Mean total IQ (TIQ), performat IQ (PIQ) and verbal IQ (VIQ) in preterm (Index A and Index B) and control children

	8–10 years			15–17 years		
	Control 1 N = 20	Index A N = 38	Index B N = 28	Control 2 N = 20	Index A N = 24	Index B N = 19
TIQ	108.3	100.8	106.3	109.8	97.3*	108.1
PIQ	112.0	104.6	110.0	110.3	100.1	112.2
VIQ	103.9.	97.0	102.4	111.2	95.5*	102.9

\* $P < 0.05$ , T-test, control versus Index A

### ■ Preterm versus controls: SES, FAI and IQ

No differences between the preterm and control groups were found at either assessment with regard to mean SES and mean score on the FAI.

At the first assessment there were no significant differential IQ scores between the preterm children and control group (Table 2). At the second assessment mean TIQ in the Index A preterm group was significantly lower than in the control group, originating from differences in VIQ.

### ■ Preterm versus controls: prevalence of psychiatric disorders and MND

At the age of 8–10 years as well as at the age of 15–17 years the proportion of psychiatric disturbances was significantly higher in the Index A preterm group than in the control groups (Table 3). No differential prevalence of psychiatric disorders was found between controls and the Index B preterm group. Comparing the VLBW/very preterm group with controls with respect to the proportion of disorders requiring treatment versus no/mild disorders the

odds ratios were 5.5 (95% Confidence Interval 1.4–21.4) at the age of 8–10 years and 3.8 (95% CI interval 0.9–15.4) at the age of 15–17 years.

Both in the preterm children and the control groups no sex differences were found with respect to the prevalence of psychiatric disorders.

At both ages the preterm children exhibited more MND than controls (Table 3). This was the case in both preterm groups. There were no interaction effects between group status and sex on the prevalence of MND. At school age boys exhibited MND more often than girls (Somers'd  $-0.304$ ,  $P = 0.001$ ). In adolescence no sex differences were found in this respect.

### ■ Association of psychiatric disorders with group status, MND, FAI and IQ

Univariate analyses of variance of the mean score on the psychiatric judgement scale revealed no interaction effects of group status (index A, index B, control) on the one hand and the factors FAI (low/high), VIQ ( $<100/\geq 100$ ) and PIQ ( $<100/\geq 100$ ) on the other.

Linear regression analyses showed that at the age of 8–10 years psychiatric problems are best predicted by group status and VIQ. At the age of 15–17 years MND, VIQ and FAI accounted for 30% of variance in the prevalence of psychiatric disorders (Table 4).

### ■ Persistence and change of MND in the preterm children

Of the preterm children examined neurologically at both assessments ( $N = 42$ ) 47% had non-varying scores with respect to the MND categories (no MND,

**Table 3** Prevalence of psychiatric disorders (PD) and Minor Neurological Dysfunction (MND) in preterm (Index A and Index B) and control children

	8–10 years			15–17 years		
	Control 1 N = 20	Index A N = 38	Index B N = 28	Control 2 N = 20	Index A N = 24	Index B N = 19
PD						
None	8 (40%)	7 (18.4%)	8 (28.6%)	16 (80%)	9 (37.5%)	9 (47.4%)
Mild	10 (50%)	11 (28.9%)	12 (42.9%)	2 (10%)	6 (25%)	6 (31.6%)
Requiring treatment	2 (10%)	20 (52.6%)	8 (28.6%)	2 (10%)	9 (37.5%)	4 (21.1%)
Somers'd <sup>a</sup>		0.450**	NS		0.438**	NS
MND <sup>b</sup>						
None	12 (63.2%)	6 (16.7%)	8 (29.6%)	14 (70%)	8 (33.3%)	7 (36.8%)
MND-1	6 (31.6%)	16 (44.4%)	9 (33.3%)	5 (25%)	8 (33.3%)	7 (36.8%)
MND-2	1 (5.3%)	14 (38.9%)	10 (37.0%)	1 (5%)	8 (33.3%)	5 (26.3%)
Somers'd <sup>a</sup>		0.564***	0.435**		0.433**	0.379*
Mean number of deviant clusters	0.6	2.3	1.8	0.6	1.6	1.5
Mann–Whitney-test (U) <sup>a</sup>		141.5***	144.5**		143.5*	115.5*

<sup>a</sup>Index A versus control; index B versus control; exact significance: \*  $P < 0.05$ ; \*\*  $P < 0.01$ ; \*\*\*  $P < 0.001$

<sup>b</sup>Missing data at 8–10 years in Index A ( $N = 2$ ), Index B ( $N = 1$ ) and control ( $N = 1$ )

**Table 4** Stepwise regressions of psychiatric disorders in preterm and control children

Model	Variables entered	Beta	Sig.	R	R square	Variables removed
8–10 years (N = 82)						
1	VIQ	-0.482	0.000	0.482	0.232	FAI
2	VIQ	-0.428	0.000			PIQ
	Group	-0.255	0.010	0.542	0.294	MND
15–17 years (N = 63)						
1	MND	0.489	0.000	0.489	0.239	Group
2	MND	0.507	0.000			PIQ
	FAI	0.244	0.028	0.546	0.275	
3	MND	0.426	0.000			
	FAI	0.247	0.023			
	VIQ	-0.234	0.042	0.588	0.313	

Group: index A, index B, control

MND-1, MND-2). The change in MND category scores was not significant, nor there were significant differential changes between the index A and index B preterm children in this respect. Of the preterm children with MND-1 or MND-2 at school age 70% still had MND (MND-1 or MND-2) in adolescence. Of the preterm children with no MND at both ages (N = 5) 1 child exhibit a mild psychiatric disorder and the remaining 4 had no psychiatric disorder. Persistence of MND proved to be significantly related with the presence of psychiatric disorders in adolescence (Table 5).

In the index A group the mean number of deviant neurological clusters significantly decreased from school age into adolescence (paired sample *t*-test, *t* = 2.6, *P* = 0.02). The index B group showed no significant change in this respect.

**Table 5** Persistent MND and prevalence of psychiatric disorder in preterm children

			Psychiatric disorder T2			Total
			None	Mild	Requiring treatment	
MND	MND T1 > 0 & MND T2 = 0	N	6	4	0	10
		%	60.0%	40.0%	0%	100%
	MND T1 > 0 & MND T2 > 0	N	7	5	11	23
		%	30.4%	21.7%	47.8%	100%
Total		N	13	9	11	33
		%	39.4%	27.3%	33.3%	100%

Somers'd 0.487, *P* < 0.05 (exact significance)  
T1 8–10 years; T2 15–17 years**Table 6** Persistence and change of psychiatric problems in preterm children (N = 43)

8–10 years	15–17 years			
	None	Mild	Requiring treatment	Non-varying response
None (N = 10)	9 (90%)	0	1 (10%)	9
Mild (N = 18)	6 (33.3%)	6 (33.3%)	6 (33.3%)	6
Requiring treatment (N = 15)	3 (20%)	6 (40%)	6 (40%)	6
Total (N = 43)	18	12	13	21 (49%)

### Persistence and change of the prevalence and nature of psychiatric disorders in the preterm children

The course over time of psychiatric problems in the preterm group is diverse, varying from improvement, stable condition to deterioration (Table 6). With respect to psychiatric judgement scores the percentage of preterm children (N = 43) with non-varying scores was 49% (Table 5). Absence of psychiatric morbidity at school age appears to be stable into adolescence in the vast majority of the preterm children. In the preterm children with psychiatric disorders requiring treatment there was an equal transition to psychiatric disorders requiring treatment, mild disorders and absence of psychiatric disorders into adolescence. Of the children with psychiatric disorders (mild or requiring treatment) 70% still have psychiatric symptomatology (mild or serious) that fulfill the criteria of a DSM-IV classification. The changes in psychiatric judgement scores were not significant, nor there was a significant interaction between group and time in this respect.

The distribution of principal diagnoses at age 8–10 years and 15–17-years is listed in Table 7.

At school age the distribution of principal diagnoses in the preterm children with psychiatric disorders (mild or requiring treatment) (N = 33) was 1 (3%) depressive disorders, 9 (27%) anxious disorders, 11 (33%) disruptive disorders and 12 (37%) other disorders. In adolescence the distribution of principal diagnoses (N = 25) was 7 (28%) depressive disorders, 10 (40%) anxiety disorders, 3 (12%) disruptive disorders and 5 (20%) other disorders. The shift in

**Table 7** Distribution of categorical principle psychiatric diagnosis (mild and requiring treatment) in preterm children

			15–17 years					
			None	Depressive	Anxious	Disruptive	Other	Total
8–10 years	None	<i>N</i>	9	1	0	0	0	10
		%	90%	10%	0%	0%	0%	100%
		% of Total	20.9%	2.3%	0%	0%	0%	23.3%
	Depressive	<i>N</i>	0	1	0	0	0	1
		%	0%	100%	0%	0%	0%	100%
		% of Total	0%	2.3%	0%	0%	0%	2.3%
	Anxious	<i>N</i>	2	2	3	1	1	9
		%	22.2%	22.2%	33.3%	11.1%	11.1%	100%
		% of Total	4.7%	4.7%	7.0%	2.3%	2.3%	20.9%
	Disruptive	<i>N</i>	3	1	4	2	1	11
		%	27.3%	9.1%	36.4%	18.2%	9%	100%
		% of Total	7.0%	2.3%	9.3%	4.7%	2.3%	25.6%
	Other	<i>N</i>	4	2	3	0	3	12
		%	33.3%	16.7%	25%	0%	25%	100%
		% of Total	9.3%	4.7%	7.0%	0%	7%	27.9%
Total	<i>N</i>	18	7	10	3	5	43	
	% of Total	41.9%	16.3%	23.3%	7%	11.6%	100%	

principal diagnoses from school age into adolescence was significant (MIXOR:  $P = 0.002$ ).

The distribution of principal diagnoses in those children with a psychiatric disorder requiring treatment at school age ( $N = 15$ ) was 0% depressive disorder, 33.3% anxiety disorders, 33.3% disruptive disorders and 33.3% other disorders. In adolescence 30.8% of the preterm children exhibiting psychiatric disorders requiring treatment suffered from depressive disorders, 53.8% from anxiety disorders, 7.7% from disruptive disorders and 7.7% from other disorders.

No differential findings between the preterm groups were found with respect to the nature of psychiatric disorders.

## Discussion

Our study has some limitations. The attrition rate at the second assessment was relatively high (40%) in the preterm group. No differential findings between the preterm responders and non-responders at the second assessment were found with respect to the variables investigated in this study. However, variables not explored in this study, e.g. family circumstances and psychiatric status of the non-responders at the time of the second assessment, might bias the assumption of the comparability of the responders and non-responders. Preterm children and controls were not assessed blindly, which might have biased the judgment of the assessor. The treatment practice of preterm children in some aspects has changed substantially since the period when our sample was born (late seventies). The incidence of serious mental and physical disabilities in preterm children has been

practically stable during the last few decades. However, changes in treatment practice might lead to differential outcome findings in non-handicapped preterm children born at different periods. Our sample might be at relatively lower risk for psychiatric disorders because of a smaller proportion of extremely preterm children. These children have a high risk for diverse neonatal complications e.g. neonatal brain haemorrhages and respiratory distress. On the other hand, our sample might be at increased risk of not profiting from advantageous treatment policies developed in later decades.

Another limitation of our study is that we did not investigate the relation between outcome data and (neonatal) brain abnormalities visualised by cerebral imaging techniques. In the period our sample was born cerebral imaging was not routine practice in NICU and the more sophisticated imaging techniques developed in the last decade were not available. In our study possible cerebral dysfunction was investigated in an indirect way by means of the prevalence of minor neurological dysfunction or so-called neurological soft signs.

We were not able to follow up the initial control group. It was therefore not possible to analyse differential longitudinal changes between the preterm group and controls. Finally, due to a relatively high drop out at the second assessment and subsequently relatively small study sample there was a limited choice of longitudinal statistical techniques.

Bearing these limitations in mind, our findings on the issues we addressed in this study can be summarised as follows.

The preterm children although free from major handicaps exhibit more psychiatric disorders compared to normal birth weight controls. The risk of

psychiatric morbidity appear to be related to birth weight and degree of prematurity: compared to controls there is a 4 (in adolescence) to 5 (at school age) fold risk in VLBW/very preterm children in contrast to the Non-VLBW/Non-very preterm children having no elevated risk in this respect. Furthermore, the percentage of VLBW/very preterm children with psychiatric disorders requiring treatment is about three to four times as high as that found in the general population [8, 33].

Our finding of a higher prevalence of psychiatric disorders in non-handicapped preterm children is in line with findings in studies using questionnaires and defining outcome in terms of clinically relevant behavioural problems [10, 15, 29, 36]. On the other hand, in our questionnaire study with the CBCL on the same cohort of preterm children from which the current sample was drawn, the only thing that parents report is a higher prevalence of social problems [27]. The differential findings in the current study and the questionnaire study can be explained in several ways. As discussed in the introduction section screening instruments like the CBCL have limited diagnostic properties. For instance, behavioural checklist filled in by parents and teachers might to be less sensitive for certain type of disorders, viz. internalising disorders [18]. Differential findings might also be explained by differential reporting of informants. There are indications that the parents of preterm children, when compared to other informants (e.g., teachers), tend to underreport the problems in their children, especially when these children grow older [6, 29].

Both the very preterm/VLBW children and the Non-VLBW/ Non-very preterm displayed an excess of MND. Although the mean number of minor neurological dysfunctions decreased with age, there were no significant changes in the prevalence of MND. The majority of the preterm children (70%) had persistent minor abnormalities on at least 1 of the neurological domains. This finding is in contrast to the sharp decline in MND after puberty as reported in other studies [24].

At school age the distribution of psychiatric diagnoses in our preterm group is comparable to that in the general population with an approximately equal distribution of internalising and externalising disorders [8, 33]. However, in adolescence there was a shift into predominately internalising disorders, viz. anxiety and depressive disorders. This finding might be explained by the high persistence of MND. There are indications that, although the underlying mechanism still is unknown, the prevalence of MND of in adolescence increases the risk of internalising disorders [5, 26]. Another putatively explanation for the predominance of internalising problems are alternations in brain functioning, e.g. the hypothalamic-pituitary-

adrenal axis, resulting from physical and emotional stress due to premature birth and subsequently intensive care treatment [4, 23]. In contrast to several other studies we did not find preterm children to be especially susceptible for the development of the Attention Deficit Hyperactivity Disorder (ADHD). Differences in diagnostic instruments (checklists versus clinical psychiatric examination) might account for these differential findings. Furthermore, attention problems are a non-specific symptom and are prevalent in children and adolescents with diverse psychiatric disorders [31], e.g. depressive disorder.

Psychopathology in preterm children may follow various developmental trajectories. Behavioural problems present at early age may disappear at later age, reflecting the plasticity of the central nervous system and/or a temporary retardation in social-emotional and cognitive development. It is also possible that in preterm children early psychiatric morbidity remains stable, reflecting more permanent deficits in brain functioning. In our sample there are no significant changes over time in the prevalence of psychiatric disorders. The absence of psychiatric disorders at school age appears to be a good predictor for the absence of psychiatric disorders in adolescence (90% of the cases). The persistence rate of serious psychiatric disorders (40%) in the preterm group is comparable with that found in the general population [8, 22]. Of the preterm children with psychiatric disorders (mild or serious) at school age the majority (70%) still have psychiatric symptoms into adolescence that fulfil the criteria for a DSM-IV classification. It is well known that various factors influence the risk and course of psychiatric morbidity, viz. sex, prenatal and perinatal complications, cerebral dysfunctions, cognitive abilities and environmental circumstances. In this study the prevalence and severity of psychiatric disorder proved to be best predicted by neonatal status, MND, VIQ and family adversity. We suggest that the high persistence of MND found in our sample reflects more permanent deficits in brain development and subsequently is associated with a high persistence of psychiatric symptomatology in preterm children.

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## Conclusion

Very preterm and/or very low birth weight children are at increased risk of psychiatric disorders, especially anxious and depressive disorders. In preterm children the development of psychopathology seems to be mediated by minor neurological dysfunctions (MND), decreased verbal abilities and family adversity.



We suggest that the differential psychiatric outcome within our preterm group relates to a differential incidence of neonatal adversities and a subsequent differential risk for abnormal brain development and organisation. The association of

MND with anxiety and depressive disorders is still unexplained. Further research on preterm children investigating the relation between the development of psychopathology and parameters of brain dysfunction is needed.

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