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Parental education, parent-child relations and diagnosed mental

disorders in childhood: Prospective child cohort study

Bjørn E. Holstein, Sofie Weber Pant, Janni Ammitzbøll, Bjarne Laursen, Katrine Rich Madsen, Anne Mette Skovgaard, Trine Pagh Pedersen

Affiliation, all authors: University of Southern Denmark, National Institute of Public Health,

Copenhagen, Denmark

Corresponding author: Bjørn E. Holstein University of Southern Denmark National Institute of Public Health Studiestræde 6, DK 1455 Copenhagen, Denmark Telephone +45 23 42 43 18, e-mail bho@sdu.dk

Abstract

Background: Mental disorders in childhood is an important public health issue. We aimed to examine the prospective association between parental education at childbirth and diagnosed mental disorders in young children and explore whether this association was mediated or modified by parent-child relations in infancy.

Methods: Prospective cohort study of all newborn 2002-2010 from 16 municipalities in the capital region of Copenhagen, Denmark, with follow-up until their 8th birthday, N=40,762. Baseline data included information from national population registers and from health visitors' records at child ages 0 to 10 months. Outcome variable: any mental disorder diagnosed at hospital from age 11 months to 8 years.

Results: Low parental education was predictive of diagnosed child mental disorder, adjusted odds ratio (AOR) = 1.83 (95% CI 1.49-2.23). Problematic parent-child-relation at age 8-10 months was also predictive of mental disorder, AOR=2.06 (1.57-2.70) but did not mediate the association between parental education and mental disorder. AOR for mental disorders was 3.24 (2.03-5.16 for the combination vocational training and problematic parent-child-relation and 2.49 (1.42-4.38) for the combination primary school and problematic parent-child-relation.

Conclusion: Low parental education and problematic parent-child-relation were independent risk factors for diagnosed mental disorders in the age span 11 months to 8 years.

Key words: Child Health Database; Danish National Patient Register; child mental disorders; parentchild-relations; socioeconomic status

Introduction

Mental disorders among young people are major challenges to public health.¹ A pooled worldwide prevalence of 13.4% was shown in a meta-analysis from 2015 including 41 community studies of children and adolescents age 6-18 years.² A recent Danish nationwide cohort study explored the incidence of mental disorders diagnosed at hospitals and found that 7% of the general population were diagnosed before the age of eight years.³

Many studies have shown higher prevalence of mental health problems among children from families of lower compared to higher socioeconomic status (SES). A review by Reiss⁴ showed that in most of the included 55 studies, low SES was associated with higher rates of mental health problems, regardless of the applied indicator of SES (e.g. household income, parental education, occupational social class, neighborhood deprivation). This observation was supported by other reviews and studies published after Reiss's review.⁵⁻⁸ Most of the above-mentioned studies applied parents- or teacherreports on mental health problems. The few general population studies of diagnosed mental disorders in young children also suggest that social adversities such as low SES are associated with mental disorder.^{7, 9-10} Most of the above-mentioned studies concern older children, and there is a scarcity of studies including the full spectrum of mental disorders as health outcome in pre-school children.¹¹

Several studies explore whether aspects of the home environment can explain why children from lower SES groups have higher prevalence of mental health problems.¹²⁻¹⁴ A study from Norway¹² suggested that parenting practices may explain some of the association between family economy and externalizing and internalizing problems. Sarsour et al.¹³ suggested that parental responsivity and family companionship may mediate the association between SES and child executive function and Ursache et al.¹⁴ suggest that accumulated stress in low SES families is the causal factor.

Accumulating evidence points to the predictive role of the early parent-child-relationship regarding mental disorders later in childhood.^{9, 15-21} Low parental SES has been found associated with poorer parent-child-relations in infancy^{15, 22-23} and poor parent-child-relations in infancy is considered to mediate or modify the association between SES and child mental health problems,²¹ whereas social support has been suggested to buffer adverse effects of low SES.²⁴ The objectives of this paper were 1) to examine the association between parental SES and diagnosed mental disorders in young children and 2) to examine whether this association was mediated or modified by parent-child relationship in infancy.

Methods

Setting: The municipality health surveillance in Denmark includes a series of home visits free of charge, which are delivered by health visitors to all families with newborn children.²⁵ Health visitors are registered nurses with a 1½ year further education comprising training in the assessment of health and development in children and evaluations of parent-child relations. Receiving these home visits is voluntary but the coverage rate is high as approximately 97% of all families accept this service provision. Most municipalities comply with the recommendations from the national health authority and offer at least five home visits during the child's first year: (a) a few days after delivery, (b) one to two weeks after delivery, (c) two to three months after delivery, (d) four to six months after delivery and (e) eight to ten months after delivery. Health visitors keep records from these home visits. Health visitors in a range of municipalities have organized a clinical database – the Child Health Database - where they store standardized data from their records from visits (b) to (e) to stimulate quality assurance and research. The health visitors apply a manual of definitions in order to secure comparability and stimulate validity of data in their records.²⁶ The records include the child's unique person identification number which ensure that data can be linked with national health and sociodemographic registers with complete data from the entire population.

Study design and study population: Prospective cohort study of children from birth to their 8th birthday. The *eligible study population* was all newborn from 1st January 2002 to 31st December 2010 from 16 municipalities in the capital region of Copenhagen, representing a mixture of metropolitan, urban and rural areas, who had their 8th birthday before 1st January 2019, and for whom data from health visitors' home visits were recorded in the Child Health Database, n=47,167.

Measures: The *independent variable* SES was measured by parents' education at childbirth, obtained from a complete population register. We categorized each child into five hierarchical levels by the parent in the household with the highest education at childbirth: Five or more years of completed university education (n=11,374), other higher education (n=10,414), completed high school (n=4,679), completed vocational education (n=10,509), and primary school (n=3,786). The parents belonged to the same educational level in 42.4% and to the adjacent level in 30.8% of the families. Mothers' had the highest educational level in 31.1% and fathers' in 26.5% of the families. We chose parental education as the most appropriate measure of SES. Contrary to income and occupational social class which fluctuate over time, education does not change much and cannot deteriorate. Educational attainment is the basic element of SES and influences other aspects of SES such as income, residential area, and occupational social class. According to Galobardes et al., education reflects material, intellectual, and other resources of the family of origin. Education captures 1) the long-term influences of early life circumstances on adult health, 2) the influence of adult resources on health, 3) the knowledge, skills and cognitive functioning which make people more receptive to health education messages and more able to communicate with and access appropriate health services.27

The *outcome variable* was any diagnosed mental disorder from the child's age 11 months to the 8th birthday, including all F-diagnoses (F00-F99) from the ICD-10 Classification of Mental and Behavioral

Disorders: Diagnostic Criteria for Research.²⁸ This includes general developmental disorders (F70-F79), specific developmental disorders (F 80-83), pervasive and other developmental disorders (F84-89), hyperkinetic disorders (F90), attention deficit disorder without hyperactivity (F98.8), mood disorders, emotional and stress-related disorders (F30-F34, F38-F45, F48, F 93), disorders of eating and sleep F50-F51, F 98.2), and disorders of behavioral (F91-F92) and of social functioning (F94.1-F94.2, F94.8). The data on mental disorders were obtained from the Danish National Patient Register which includes all hospital contacts with a 100% coverage.²⁹ Public health services including referrals and treatments at hospitals are free of charge in Denmark. Diagnostic assessments occur in pediatric and psychiatric in- and outpatient and emergency settings and is completed by medical doctors in accordance with the diagnostic criteria of ICD-10.³

The potential mediator or modifier variable, parent-child-relation, stems from the health visitor's record from home visit (e) at child age eight to ten months, i.e. measured after the exposure variable (parents' education at birth) and before the outcome variable (diagnosed mental disorders from 11th month to 8th birthday). The health visitors indicate a concern if the parent-child-relation is problematic or follow-up is needed, based on parents' information and direct observations of the parent-child interaction at home visits. The exact definition was any deviation from the following description: "The child is attended to; has appropriate clothing; the parents offer the child stimulating activities, are calm and confident in their behaviour resulting in a positive interaction; the parents can detect and meet the child's needs; the parents are aware of the child's weeping and can comfort the child; the parent-child-relation was available for a subset of data, children born in 2002, 2008, 2009 and 2010 (n=15,432), and analyses on the potential mediating or modifying effect of parent-child-relation are therefore carried out in this *restricted study population*. The proportion of children with concerns about the parent-child-relation these four years was about the same, 7.3%, 4.9%, 4.0% and 4.4%.

The analyses included the following *control variables*: From the *National Birth Register*: Gestational age (born 37^{th} week or later vs. born before week 37), birth weight (<2500 g, 2500-3999 g, >3999 g), and mother's age at childbirth (<25 vs. \geq 25). From sociodemographic population registers: family composition (child lives with both parents, yes vs. no), parents' employment (i.e. whether the parents have a job, categorized as 2, 1 or 0 parents in job or education), and parents' origin (categorized as 2, 1 or 0 parents of Danish origin). From the Child Health Database: Concern about mother's mental health in the first six months after delivery defined as "signs of depressive mood, anxiety, sleep problems, neglect of overt problems, or referred to psychiatric care" (concern at 0 vs. at least one home visit).

Statistical procedures to examine the association between parental SES and diagnosed mental disorders in young children: We excluded children with missing data on parental education, diagnosed mental disorder from 11th month of life to the 8th birthday, and/or any of the control variables, resulting in an *applied study population* of 40,762 children. The first step was contingency tables for inspection of data and use of chi²-test for heterogeneity. The second step was multivariate logistic regression analysis of the association between parental education and diagnosed mental disorder, adjusted for the above-mentioned control variables.

Statistical procedures to examine whether this association was mediated or modified by the parentchild relationship in infancy was based on the above-mentioned *restricted study population* of 15,432 children. We used Baron & Kenny's method for mediation³⁰ and conducted multivariate logistic regression analyses to examine: 1) whether parental education was associated with parent-childrelation, 2) whether parent-child-relation was associated with a mental disorder diagnosed from the 11th month to the child's 8th birthday, and 3) whether inclusion of parent-child relation in the statistical model resulted in a diminishing odds ratio of the association between parental education

and child mental disorder. To examine effect modification, we calculated adjusted OR (95% CI) for child mental disorder by combinations of parental education and concern about parent-child-relation with the most favorable group (highest education and no concerns) as reference group.

Data protection and ethical issues: The study was approved by the Danish Data Protection Agency (registration number 10.366, University of Southern Denmark) and complied with national regulations of data protection and consent. Data from the health visitors' records are stored at the National Institute of Public Health in accordance with the Danish Data Protection Legislation and data are exclusively used for research and statistical analyses. Linkage with register data was administered by Statistics Denmark and the involved researchers did not have access to personal identification. According to the Danish legislation, informed consent is not required for register-based studies.

Results

Study population: Table 1 presents the eligible, the applied and the restricted study population by the applied variables. The distribution of the three study populations by the exposure variable, the outcome variable and the control variables are very much alike. To assess the risk of selection bias, we tested the difference between the non-included 25,330 and the restricted study population of 15,432. There was a small but statistically significant higher proportion of children with two parents in job or education in the restricted study population, p<0.0001. Otherwise there were no significant differences.

Mental disorders: Within the applied study population, a total of 1,616 children (4.0%) were diagnosed with a mental disorder between age 11 month and eight years. A total of 1,082 (2.7%) were diagnosed with a neuro-developmental disorder including mental retardation (n=436), autism-spectrum disorders (n=510) and disorders of hyperactivity and inattention, ADHD (N=554). Disorders

of not primarily developmental origin, e.g. disorders of behaviour emotions, eating, sleep, and other disorders were diagnosed in 806 children (2.0%).

Association between parental education and a child mental disorder: Table 2 shows the crosstabulation of parental education and all other variables. The proportion of mental disorders was significantly higher among children of parents with primary school than children of parents having at least five years of university education (p<0.01). The proportion with concern about the parent-childrelation at eight to ten months and the proportion of children with adverse medical and social characteristics (born before 37th week, birth weight < 2500 g, mother's age <25, child does not live with both parents, one or two parents not in job/education, one or two parents of non-Danish origin, concerns about mother's mental health in the first six months after delivery) were also significantly higher in families with short than long education, all p-values < 0.01. Table 3 column 1-2 shows OR (95% Cl) for child mental disorders by parental education. The OR estimates increased for each step of diminishing educational duration. The association attenuated slightly when adjusted for the control variables, but it remained graded and significant.

Mediation analyses: In the restricted study population (n=15,432) a total of 830 children (5.4%) were reported with concerns regarding the parent-child-relation. The proportion of parent-child-relationship concern was 3.5% in the group with the highest parental education and 3.9%, 6.3%, 6.2% and 11.8% in the subsequent groups (p<0.01), showing a strong and graded association between parental education and parent-child-relations. Table 3 column 3-5 shows the results of the mediation analysis. The unadjusted analysis showed a graded and significant relationship between parental education and diagnosed mental disorders. Concern about the parent-child-relation was a significant predictor of diagnosed mental disorders, OR=2.06 (1.57-2.70). Adjustment for the control variables attenuated the association between parental education and diagnosed mental disorder but the association remained graded and significant. The association remained almost unchanged after

inclusion of concern about the parent-child-relation in the statistical model, i.e. concern about the parent-child-relation did not mediate or explain the association between parental education and diagnosed mental disorders.

Analysis of effect modification: Table 4 shows the combined effect of parental education and concerns about the parent-child-relation. The adjusted OR for diagnosed mental disorders between 11th month and 8th birthday was significantly elevated in the two categories with the shortest education, in particular 3.24 (2.03-5.16) in the group with combined vocational education and concerns about parent-child-relations (n=241) and 2.49 (1.42-4.38) in the group with combined primary school and concerns about parent-child-relations (n=177).

Discussion

Main findings: This is one of the first studies which demonstrate a strong and graded association between parents' education and the prevalence of diagnosed mental disorders in childhood, i.e. problems that lead to clinical referrals and diagnoses within hospital settings.³ Problematic parentchild-relations in infancy resulted in a twofold increased risk of being diagnosed with a mental disorder. Problematic parent-child-relations did not explain the association between parents' education and diagnosed mental disorders. Low education and problematic parent-child relations were independent risk factors which tended to reinforce the effect of each other, demonstrated by a threefold increased risk of mental disorder among children exposed to both risks: low parental education and problematic parent-child-relation. Since education is a valid and appropriate indicator of SES, we consider this finding as a strong indicator of social inequality in childhood mental disorders.

The finding of a social inequality among young children diagnosed in clinical settings corresponds with other studies of mental health problems in general populations.^{4, 7, 9} The finding of a social inequality in problematic parent-child-relations also corresponds with other studies²²⁻²³ and so does the finding of problematic parent-child-relations in infancy as predictor of mental health problems later in childhood.^{9, 15-21}

There are several and concurrent possible explanations to the increased risk of mental disorders among children of parents with short education. According to current understanding of the origin of mental disorders and the role of gene-environment interaction over time, children of parents of low education may be at risk of a genetic transmission of mental health problems related to the parents' low educational attainment. These include neuro-developmental disorders such as disorders of attention deficit and inattention, ADHD, autism-spectrum disorders and learning disorders.³¹ Equally important, parents with short education are exposed to many psychosocial and economic challenges which may hamper their functions as caregivers.^{7, 10, 32} Parental SES has repeatedly been found influencing the child's executive functions of inhibitory control, cognitive flexibility, working memory and the child expressive language abilities.³³

The parent-child relation is a potential mediator of stress exposures since the parent-child-relation is suggested to be involved in the overall trajectories linking SES and child mental health problems.¹³ Children born of mothers exposed to severe stress in pregnancy have a highly increased risk of behavioural and emotional problems in their postnatal life.³⁴ Moreover, biomarkers of long-term adrenocortical activity and chronic stress have been found among children from low SES-groups.¹⁴ Finally, the high exposure to psycho-social stressors in families of low SES corresponds with the sociological hypotheses about the harmful effects of stress-inducing conditions caused by lower access to material and social resources.^{32, 35-36}

Limitations: The risk of selection bias in this study was low; first because of a high coverage of health visitors' home visits in Denmark; second because of the linkage to complete national health and sociodemographic registers; third because the referrals to public hospitals in Denmark are free of charge to the family and occur without selection. Due to a comprehensive health care system, the vast majority of children in need of psychiatric assessment and treatment are referred. The study population included a large and diverse community-based population, almost complete from 16 municipalities in the capital region of Copenhagen, representing a mixture of metropolitan, urban, and rural areas. There were no significant differences in the composition of the eligible and the applied study population regarding sociodemographic and perinatal characteristics. The restricted study population used in the mediation analyses had the same composition, except for a slightly larger proportion of families with both parents engaged in the labour market or educational system.

The major strengths of the study were the large sample size and the complete follow-up in Danish national registers. The outcome included all ICD-10 diagnoses of mental and developmental disorders, assigned to children referred to in- or outpatient, or emergency settings at hospitals. Hereby, our study included children with the most severe mental health problems. Several of the register-based diagnoses in the present study have been validated, showing overall good validity.^{3, 29, 37-38} It was a strength of this study that the diagnostic assessments of mental disorders were based on clinical examinations leading to a final diagnostic conclusion by experienced medical doctors in accordance with the ICD-10 criteria.³

Another virtue of the study was the careful confounder control of the association between parental education and diagnosed mental disorders. Other SES measures such as income and occupational social class might have been included, but we considered educational attainment to be the most valid and stable indicator of SES. Income fluctuates considerably and is to some degree a function of educational attainment. Employment (having a job) is a different entity, although related to SES, and

we decided to include employment in the statistical models because it may be a confounder of the education-child health association. Among the potential confounder variables recorded in the Danish registries, several were considered but not included in the final analyses, because they did not show associations with the independent variable and/or the outcome variable. We included maternal age as confounder control, but not paternal age, because father's age is strongly correlated with mother's age which would cause collinearity; moreover, approximately one in eight infants do not live with their father. Still, there may be unmeasured confounding such as parental mental health and insufficient control for other aspects of family environment.

The data from the health visitors' records have not been formally validated, but the health visitors promote the comparability and validity of these data by use of detailed instructions for completion of their records.²⁶ The predictive validity of Danish health visitors' concern about parent-child relations has previously been explored showing a more than twofold increased risk of mental disorders at age 1 ½ years in children for whom the health visitor had expressed concern within the first ten months of the child's life.^{19-20, 39}

Implications: This study highlighted that both low SES and poor parent-child relations were independent risk factors for diagnosed mental disorders in the child's first eight years of living. Our study did not explain the mechanisms behind these associations. It seems likely that low SES families have a higher risk of poor parenting practice, ¹² poor parental responsivity, ¹³ and accumulated stress ¹⁴ which may explain the social inequality in diagnosed mental disorders. Research in this area is needed to further elucidate the key determinants of parental practices and guide preventive intervention accordingly.^{9, 12, 23, 40}

Health visitors meet families and infants with high risk of severe child mental disorders. This insight is a strong argument for early intervention within the general child health surveillance to ameliorate

the risk of developmental psychopathology in vulnerable infants and their families. Among the most severe and impairing child mental disorders, neuro-developmental disorders such as mental retardation, autism spectrum disorders and ADHD have their onset in early childhood.³¹ Findings from this study suggested that paying attention to developmentally vulnerable infants in families of low parental education and relationship problems has potentials to optimize preventive strategies to these children. Health visitors and other practitioners can use this knowledge when identifying children in need of preventive efforts. Funding: There was no external funding of this research.

Conflict of interest: The authors declare that they have no conflict of interest.

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Data sharing: The data underlying this article will be shared on reasonable request to the Principal Investigator, Dr. Trine Pagh Pedersen (tppe@sdu.dk).

Key points

- In this community-based cohort of more than 40,000 children, 4.0% had at least one diagnosed mental disorder between 11 months and their 8th birthday
- There was a twofold increased risk of diagnosed mental disorders among children of parents with short education
- Children with problematic parent-child-relations in infancy also showed a twofold increased risk of diagnosed mental disorders.
- Problematic parent-child-relations in infancy reinforced the effect of low parental education on diagnosed mental disorders.
- Health visitors who meet families and infants at risk of severe child mental disorders can use this new insight when identifying children in need of preventive efforts.

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Table 1 Descriptive information about the eligible, the applied and the restricted study population

Variables		Eligible study	Applied study	Restricted study	Difference between non-included
		population ^a	population ^b	population ^c	(N=25,330) and restricted study
		n=47,021	n=40,762	n=15,432	population (n=15,432), P-value
Exposure variable	Higher education, %	52.6	53.4	53.9	0.3982
Outcome variable	Any child mental disorder between	4.4	4.0	4.0	0.9498
	11^{th} month and 8^{th} birthday, %				
Control variables	Sex, % boys	51.3	51.3	51.9	0.2912
	Born before 37 th week, %	6.8	6.4	6.2	0.2070
	Birth weight < 2500 g, %	5.0	4.7	4.6	0.7320
	Mother < 25 years, %	14.0	11.7	12.8	0.7603
	Child lives with both parents, %	87.0	88.3	88.0	0.1516
	Two parents in job or education, %	81.9	82.9	85.0	<0.0001
	Two parents of Danish origin, %	73.5	73.5	74.8	0.1695
	Concern about mother's mental				
	health 0-6 months after delivery, %	28.3	27.5	27.3	0.4124

^a All newborn from 1st January 2002 to 31st December 2010 in 16 municipalities in the capital region of Copenhagen, Denmark.

^b Study population with full information on all applied variables.

^c Subset of the study population (children born in 2002, 2008, 2009 and 2010) with data about the potential mediator variable problematic parent-child relation.

Table 2 Descriptive information about the study population: the applied variables by parental education, N=40,762.

	Parental education at birth						
Variable	5+ years	Higher	Highschool	Vocational	Primary	Total	
	university	education	education	education	school	population	
	(n=11,374)	(n=10,414)	(n=4,679)	(n=10,509)	(n=3,786)	(n=40,762)	
Child mental disorder diagnosed from	2.9	3.5	3.7	5.0	6.0	4.0	
$11^{ ext{th}}$ month to $8^{ ext{th}}$ birthday, %							
Born before 37 th week, % ^a	6.0	5.9	6.0	7.2	7.1	6.4	
Birth weight < 2500 g, % ^a	4.2	4.1	4.1	5.5	5.9	4.7	
Mother's age < 25 years, % ^a	1.6	3.6	24.3	17.2	44.0	12.7	
Child does not live with both parents, % a	5.7	8.1	12.6	14.9	29.7	11.7	
<2 parents in job or education, % ^a	9.1	11.1	22.3	18.3	48.3	17.1	
<2 parents of Danish origin, % ^a	16.9	21.0	36.3	22.6	49.8	24.7	
Concern about mother's mental health in	23.9	26.7	28.2	28.6	36.4	27.5	
the first six months after delivery, % $^{\rm a}$							
Concerns about parent-child-relationship	3.5	3.9	6.3	6.2	11.8	5.4	
at 8-10 months, % ^{a, b}							

^a p<0.01. ^b Data only available for the restricted study population, N=15,432

Table 3 OR (95% CI) for diagnosed mental disorders from 11th month to 8th birthday by parental education.

	OR (95% CI) for diagnosed mental disorder from 11 th month to 8 th birthday					
	Applied study po	pulation, n=40,762	Restricted study population, n=15,432			
	Column 1	Column 2	Column 3	Column 4	Column 5	
Parental education at birth	Unadjusted	Adjusted ^a	Unadjusted	Adjusted ^a	Inclusion of	
					mediator variable ^b	
5+ y university education	1	1	1	1	1	
Higher education	1.23 (1.05-1.43)	1.22 (1.05-1.43)	1.23 (0.97-1.57)	1.24 (0.97-1.58)	1.24 (0.97-1.58)	
High school education	1.30 (1.08-1.57)	1.28 (1.06-1.55)	1.09 (0.79-1.51)	1.05 (0.75-1.46)	1.04 (0.75-1.45)	
Vocational education	1.78 (1.55-2.05)	1.66 (1.43-1.92)	1.74 (1.39-2.18)	1.63 (1.29-2.06)	1.62 (1.28-2.04)	
Primary school	2.17 (1.83-2.58)	1.83 (1.49-2.23)	2.14 (1.63-2.82)	1.76 (1.28-2.43)	1.71 (1.24-2.36)	
Concern about parent-child-						
relations at 8-10 months			2.06 (1.57-2.70)		1.59 (1.19-2.11)	

^a Adjusted for gestational age, birth weight, mother's age, family composition, parents' employment, parents' origin, mother's mental health status in the first six months

after delivery. ^b Adjusted for the above variables and concern about parent-child relations at 8-10 months. Estimates in *italics* are statistically significant

Table 4 Adjusted ^a OR (95% CI) for diagnosed mental disorders from 11th month to 8th birthday by

combinations of parental education and concern about parent-child-relations at 8-10 months, n=15,432

	Concern about parent-child-relations at 8-10 months			
Parental education at birth	No	Yes		
5+ years university	1	1.45 (0.66-3.16)		
Higher education	1.24 (0.97-1.59)	1.65 (0.79-3.46)		
Highschool education	1.07 (0.76-1.50)	1.18 (0.42-3.28)		
Vocational education	1.56 (1.23-1.99)	3.24 (2.03-5.16)		
Primary school	1.74 (1.24-2.44)	2.49 (1.42-4.38)		

^a Adjusted for gestational age, birth weight, mother's age, family composition, parents' employment, parents' origin,

mental health status in the first half year of the child's life. Estimates in *italics* are statistically significant