Early Life

Socioeconomic disadvantage and neural development from infancy through early childhood

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Abstract

Background: Early social experiences are believed to shape neurodevelopment, with potentially lifelong consequences. Yet minimal evidence exists regarding the role of the social environment on children’s neural functioning, a core domain of neurodevelopment.

Methods: We analysed data from 36443 participants in the United States Collaborative Perinatal Project, a socioeconomically diverse pregnancy cohort conducted between 1959 and 1974. Study outcomes included: physician (neurologist or paediatrician)-rated neurological abnormality neonatally and thereafter at 4 months and 1 and 7 years; indicators of neurological hard signs and soft signs; and indicators of autonomic nervous system function.

Results: Children born to socioeconomically disadvantaged parents were more likely to exhibit neurological abnormalities at 4 months [odds ratio (OR) = 1.20; 95% confidence interval (CI) = 1.06, 1.37], 1 year (OR = 1.35; CI = 1.17, 1.56), and 7 years (OR = 1.67; CI = 1.48, 1.89), and more likely to exhibit neurological hard signs (OR = 1.39; CI = 1.10, 1.76), soft signs (OR = 1.26; CI = 1.09, 1.45) and autonomic nervous system dysfunctions at 7 years. Pregnancy and delivery complications, themselves associated with...
socioeconomic disadvantage, did not account for the higher risks of neurological abnormalities among disadvantaged children.

**Conclusions:** Parental socioeconomic disadvantage was, independently from pregnancy and delivery complications, associated with abnormal child neural development during the first 7 years of life. These findings reinforce the importance of the early environment for neurodevelopment generally, and expand knowledge regarding the domains of neurodevelopment affected by environmental conditions. Further work is needed to determine the mechanisms linking socioeconomic disadvantage with children’s neural functioning, the timing of such mechanisms and their potential reversibility.

**Key words:** Neural development, soft signs, neurological abnormality, socioeconomic status

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**Key Messages**
- Early social experiences are believed to shape neurodevelopment, yet minimal evidence exists regarding the role of the social environment on children's neural functioning, a core domain of neurodevelopment.
- Children born to socioeconomically disadvantaged parents were more likely to exhibit neurological abnormalities, and this was not accounted for by perinatal factors.
- Our results suggest that the early childhood environment can adversely affect brain development in ways that are detectable upon neurological examination.

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**Introduction**

Children raised in socioeconomically disadvantaged families exhibit deficits in cognitive and emotional development that are detectable in infancy, and that persist into adulthood. Children’s neurodevelopment is thus highly contingent on early life experiences. However, neurodevelopment also encompasses neural development, and there remains a gap in our understanding of the sensitivity to the environment of this important aspect of children’s development.

Intact neural development is a cornerstone of children’s health. Neural deficits may indicate underlying brain pathologies such as epilepsy, and portend a broad range of disabilities later in life. For example, children with cerebellar malformations presenting with observable deficits during neurological examination experience a high prevalence of motor, cognitive, language and social-behavioural deficits, as well as poor quality of life. Neural deficits such as soft signs are also suspected in the aetiology of multiple forms of neuropsychiatric illness including major depression and schizophrenia. Autonomic nervous system (ANS) deficits are implicated in childhood asthma and obesity, and when they persist into adulthood are linked with both psychiatric and medical conditions.

This study investigates the association between parental socioeconomic disadvantage and children’s neurological abnormalities among participants in the Collaborative Perinatal Project (CPP), a national birth cohort that enrolled women during pregnancy between 1959 and 1966, and followed their offspring through age 7 years. The CPP was a landmark study when it was established, and remains one of the only available resources for epidemiological investigations of neurological problems in children because of its large and diverse sample, and because study physicians (paediatricians or neurologists) performed standardized examinations covering the twelve cranial nerves, reflexes, motor function, sensory perception and the ANS. We hypothesized that offspring born to socioeconomically disadvantaged parents would be more likely to have neurological abnormalities during childhood, which would be consistent with evidence from studies on children’s cognitive development in relation to their family’s socioeconomic status. As previous reports from the CPP and other cohorts have documented an association between perinatal complications and children’s neurological outcomes, we evaluated the extent to which any increase in the risk of neurological abnormalities could be explained by pregnancy and delivery complications that are more common in socioeconomically disadvantaged pregnancies.

**Method**

**Study sample**

The CPP involved the systematic observation and examination of over 50,000 pregnancies and resulting offspring...
through the first 7 years of life, and focused on prenatal and obstetric antecedents of children’s neurological disorders. The current study included live-born offspring whose mothers completed a social history interview upon study enrolment and participated in at least one assessment of neurological status at birth, 4 months, 1 year and 7 years. Follow-up rates for survivors in the full CPP sample were 88% at 1 year, 75% at 4 years and 79% at 7 years.

Measures

Parental socioeconomic disadvantage
We developed a measure of socioeconomic disadvantage using information collected from the social history interview administered to participants upon their enrolment into the study during pregnancy, which combined information on parental education (more than high school, high school graduate, or less than high school), income relative to the US poverty threshold (> 150% of the poverty threshold, 100–150% of the poverty threshold or less than the poverty threshold), occupation (non-manual, manual or unemployed) and family structure (both parents at home, single or divorced/separated/widowed). Each item was given a score of 0, 1 or 2, with higher scores indicating a higher degree of disadvantage. These scores were then summed to produce a composite measure of socioeconomic disadvantage; we analysed the score in three categories, summed to produce a composite measure of socioeconomic disadvantage to reflect the number of indicators of disadvantage present in each family. Table S1 (available as Supplementary data at IJE online) provides the distribution of the composite measure according to each of its components (e.g. more than 80% of highly disadvantaged families were characterized by parents with less than high school education, low household income, unemployed or manual occupations and father’s absence; in contrast, the overwhelming majority of parents in the low socioeconomic disadvantage category had a high school or greater education, high income, non-manual occupation and were married).

Neurological abnormalities during childhood
The presence of neurological abnormalities during the neonatal period, 4 months, 1 year and 7 years was based on examinations conducted by a paediatrician with training in neurology or by a neurologist with training in paediatrics. The neonatal examination took place when the child was 36–60 hours old, and included inspections for structure and positioning, passive and active movements, ophthalmic examination, muscle tone and reflexes. Examination at 4 months expanded the inspection for structural deformities, posturing, motor skills and response to stimulus. Examination at 1 year added gait, locomotor activities, muscle power and involuntary movements, as well as sensory and autonomic nervous system tests. Examination at 7 years further included a complete testing of cranial nerves, expanded sensory components, speech and intelligence. After completion of the neurological examination, the physician provided a global impression by rating the child’s neurological status as normal, suspicious or abnormal. A rating of abnormal was used when the examiner could make a definite or provisional diagnosis of a recognized syndrome, or when any definite neurological abnormality was identified. Children who were not completely healthy but lacked evidence of a specific neurological syndrome were rated as suspicious, as were children with physical findings often associated with neurological disorders such as haemangiomas on the face or spinal anomalies. The present study combined ratings of suspicious and abnormal.

We also analysed the presence of neurological hard signs and soft signs at 7 years. Hard signs included cranial nerve deficits, abnormal muscle tone or power and abnormal reflexes. Soft signs included motor (fasciculations, myclonus, spontaneous tremor, intention tremor, athetosis, chorea, dystonia, ballismus, tic, mirror movements), coordination (dysmetria, ataxia, dysdiadochokinesia, awkwardness) or sensory abnormalities (fine and gross stereognosis and position sense). Finally, we analysed three measures of autonomic functioning at 7 years: unusual vasomotor symptoms, sweating and sphincter abnormality identified through examination or reported history. Unusual vasomotor symptoms included unusual blotching, obvious dermatographia and unusual changes in skin or temperature. Abnormal sweating was defined by inappropriate sweating within the environmental conditions of examination. Sphincter dysfunction was characterized by inadequate control of bladder or rectal sphincters. Enuresis was not considered abnormal unless accompanied by dribbling.

Pregnancy and delivery complications
We investigated pregnancy and delivery complications as potential explanatory factors for the association between socioeconomic disadvantage and neurological abnormalities. Fetal growth restriction (birthweight < 2500 g or in the bottom decile at each gestational age) and premature birth (< 37 weeks of gestation) were combined into a single measure for analysis. Placental insufficiency was defined as placental hypertrophy, as indicated by a placental:birthweight ratio in the top decile, standardized for gestational age. Placental hypertrophy is suggestive of inadequate placental blood flow (and thus, poor oxygen
supply) and is associated with neonatal white matter injury and neurodevelopmental delay.\textsuperscript{31,32} In the absence of direct measures of fetal hypoxia in the CPP (e.g. blood gas or pH level), two indirect indicators of fetal hypoxia were considered. Possible chronic hypoxia was defined as the presence of gestational diabetes, hypertension or hypotension, preeclampsia or eclampsia.\textsuperscript{33} Acute perinatal hypoxia was defined based on a prediction model for sustained low Apgar scores (below 7 at 1 and 5 min post birth). The prediction model included established and suspected risks for hypoxic conditions: placenta praevia, abruptio placentae, breech/vertex delivery, prolonged duration of second stage labour, meconium presence, post-term delivery, cord tight around neck, knot in cord, prolapsed cord, apnoea, asphyxia, resuscitation at delivery, respiratory distress syndrome, shock during pregnancy and skin cyanosis.\textsuperscript{34} Perinatal hypoxia was classified as present for offspring with predicted probabilities > 5%; the reasoning for this approach is that persistent low Apgar scores in the context of these complications is likely to indicate an underlying hypoxic state.

**Potential confounding factors**

The following self-reported conditions were assessed in the CPP upon mother’s enrolment into the study and were adjusted for in all of the analyses: psychiatric (e.g. mental retardation, organic brain disorder, psychosis and neuroma, alcoholism, drug addiction), neurological (e.g. epilepsy, central nervous system (CNS) infection and tumour, neurological surgery, cerebral palsy), cardiovascular (e.g. rheumatic fever, thrombophlebitis, anaemia, cardiovascular surgery, pericarditis), pulmonary (e.g. tuberculosis, pneumonia, bronchial asthma, pulmonary surgery, pulmonary embolism, sarcoidosis) and metabolic disorders (e.g. diabetes, thyroid disorders, endocrine surgery).

**Statistical analyses**

First, we fitted logistic regression models relating socioeconomic disadvantage to pregnancy and delivery complications, providing an initial indication of whether pregnancy or delivery complications could explain associations with later neurological abnormalities. Second, we fitted logistic regression models for the presence or absence of neurological abnormalities at each follow-up assessment, and for neurological hard signs, soft signs and ANS abnormalities at 7 years, with and without adjusting for pregnancy and delivery complications. As the CPP enrolled women across repeated pregnancies during its enrolment period of 1959–66, we used generalized estimating equations to adjust variance estimates for the presence of correlated observations, implemented in the SAS v9.3 GENMOD procedure;\textsuperscript{35,36} all models included controls for offspring race, sex and CPP study site.

Our approach to the problem of missing data in the CPP was to identify an analysis sample for each time point studied, which comprised all participants with complete data at that time point. This enabled us to use the largest sample size possible for each endpoint, with the trade-off that the analytical sample was reduced due to sample attrition for later endpoints. Therefore in sensitivity analyses we re-analysed the data using the method of inverse probability weighting to adjust for sample attrition (results in Table S2, available as Supplementary data at IJE online).\textsuperscript{37} Finally we conducted sensitivity analyses of the age 7 outcomes, adjusting for socioeconomic disadvantage as reassessed at that follow-up point (results in Table S3, available as Supplementary data at IJE online).

**Results**

**Study sample**

There were 53,724 live births in the CPP cohort (i.e. which survived the neonatal period), 36,443 of which were included in the analysis sample for newborn outcomes. The majority of the reduction in sample size was due to missing data on placental weight (21% missing) or on one or more variables included in the prediction model for acute hypoxia (17% missing). Almost all births (n = 36,156) were from singleton pregnancies; there were 279 pairs of twins and 4 sets of triplets. The distribution of socioeconomic disadvantage in the baseline sample is: 14.8% high socioeconomic disadvantage category, 46.1% medium disadvantage and 39.1% low disadvantage. The baseline sample was 50.7% non-White (75.2% non-White among high disadvantage families, 63.9% among medium disadvantage families and 25.9% among low disadvantage families). The prevalences and sample sizes for the analyses of children’s neurological outcomes at 4 months, 1 year and 7 years are presented overall and according to socioeconomic disadvantage in Table 1. At 7 years, we examined the overlap of the four categories of neurological outcomes. Among children rated as neurologically abnormal, 44% exhibited soft signs (in contrast to 8% of children exhibiting soft signs who were not rated as neurologically abnormal); 17% exhibited hard signs (vs 2%); and 16% had a detectable ANS abnormality (vs 9%). The neurological abnormalities studied were largely not accounted for by frank neuropathology; only a small number of children in the CPP had a recorded diagnosis of cerebral palsy (n = 121) or cerebral spastic paresis (n = 44). Rather, among children rated neurologically abnormal at age 7, 40.2% had a cranial nerve abnormality, 27.0% had abnormal deep tendon reflexes, 7.1% had

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abnormal muscle tone, 3.1% had a muscle power abnormality and 43.8% had neurological soft signs.

### Pregnancy and delivery complications

Socioeconomic disadvantage was associated with possible chronic hypoxia (OR = 1.20; CI = 1.07, 1.35), placental hypertrophy (OR = 1.14; CI = 1.01, 1.29) and fetal growth restriction/prematurity (OR = 1.52; CI = 1.39, 1.66) (Table 2). These associations were independent of maternal medical conditions, several of which were also predictive of pregnancy and delivery complications.

### Neurological abnormalities

The associations of socioeconomic disadvantage with the offspring neurological abnormalities were examined in two logistic regression models for each outcome. Model 1 adjusted for demographic factors and maternal medical conditions; model 2 added pregnancy and delivery complications. At 4 months and 1 year, offspring of socioeconomically disadvantaged parents were more likely to have neurological abnormalities upon paediatric examination, with ORs in the range of 1.20 to 1.35 (Table 3). Adjustment for pregnancy and delivery complications had no impact on these associations.

Socioeconomically disadvantaged offspring were more likely to have neurological abnormalities at age 7 (OR = 1.67; CI = 1.48, 1.89), hard signs (OR = 1.39; CI = 1.10, 1.76) and soft signs (OR = 1.26; CI = 1.09, 1.45) (Table 4). With respect to the ANS outcomes assessed at age 7, socioeconomically disadvantaged was associated with a higher odds of sphincter dysfunction (OR = 1.37; CI = 1.17, 1.60) (Table 5). These associations were not reduced in the models that adjusted for pregnancy and delivery complications.

Results were unchanged in sensitivity analyses using inverse probability weighting to account for attrition and

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**Table 1. Maternal and child characteristics in the Collaborative Perinatal Project sample overall, and by parental socioeconomic disadvantage**

<table>
<thead>
<tr>
<th></th>
<th>Total sample</th>
<th>Low percent (n)</th>
<th>Medium percent (n)</th>
<th>High percent (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline sample</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent (n)</td>
<td>100 (36 443)</td>
<td>39.1 (14 250)</td>
<td>46.1 (16 786)</td>
<td>14.8 (5 407)</td>
</tr>
<tr>
<td>4 months</td>
<td>100 (30 463)</td>
<td>40.1 (12 229)</td>
<td>45.4 (13 835)</td>
<td>14.4 (4 399)</td>
</tr>
<tr>
<td>1 year</td>
<td>100 (28 114)</td>
<td>40.2 (11 305)</td>
<td>45.3 (12 725)</td>
<td>14.5 (4 084)</td>
</tr>
<tr>
<td>7 years</td>
<td>100 (23 279)</td>
<td>41.0 (9 539)</td>
<td>44.3 (10 303)</td>
<td>14.8 (3 437)</td>
</tr>
<tr>
<td><strong>Maternal medical conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>8.5 (3 068)</td>
<td>8.4 (1 183)</td>
<td>7.9 (1 310)</td>
<td>10.7 (575)</td>
</tr>
<tr>
<td>Neurological</td>
<td>9.0 (3 025)</td>
<td>9.3 (1 319)</td>
<td>8.5 (1 410)</td>
<td>9.8 (526)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>5.0 (1 800)</td>
<td>4.4 (620)</td>
<td>5.2 (860)</td>
<td>6.0 (320)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>8.3 (2 994)</td>
<td>7.7 (1 093)</td>
<td>8.3 (1 376)</td>
<td>9.8 (525)</td>
</tr>
<tr>
<td>Metabolic</td>
<td>1.8 (641)</td>
<td>2.6 (363)</td>
<td>1.3 (211)</td>
<td>1.3 (67)</td>
</tr>
<tr>
<td><strong>Pregnancy and delivery complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal growth restriction/prematurity</td>
<td>21.2 (7 740)</td>
<td>16.5 (2 345)</td>
<td>23.5 (3 937)</td>
<td>27.0 (1458)</td>
</tr>
<tr>
<td>Placental hypertrophy</td>
<td>9.8 (3 569)</td>
<td>9.1 (1 293)</td>
<td>10.0 (1 683)</td>
<td>11.0 (593)</td>
</tr>
<tr>
<td>Possible chronic hypoxia</td>
<td>11.0 (3 989)</td>
<td>10.5 (1 481)</td>
<td>10.8 (1 802)</td>
<td>13.2 (706)</td>
</tr>
<tr>
<td>Acute perinatal hypoxia</td>
<td>5.8 (2 094)</td>
<td>6.1 (864)</td>
<td>5.6 (931)</td>
<td>5.5 (299)</td>
</tr>
<tr>
<td><strong>Neurological abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth</td>
<td>11.3 (4 132)</td>
<td>11.2 (1 593)</td>
<td>11.3 (1 899)</td>
<td>11.8 (640)</td>
</tr>
<tr>
<td>4 months</td>
<td>10.8 (3 291)</td>
<td>9.3 (1 138)</td>
<td>11.5 (1 590)</td>
<td>12.8 (563)</td>
</tr>
<tr>
<td>1 year</td>
<td>9.2 (2 587)</td>
<td>8.2 (923)</td>
<td>9.9 (1 253)</td>
<td>10.1 (411)</td>
</tr>
<tr>
<td>7 years</td>
<td>16.3 (3 788)</td>
<td>13.5 (1 285)</td>
<td>17.5 (1 807)</td>
<td>20.2 (696)</td>
</tr>
<tr>
<td>Neurological hard signs at 7 years</td>
<td>4.5 (1 035)</td>
<td>4.7 (445)</td>
<td>4.4 (450)</td>
<td>4.1 (140)</td>
</tr>
<tr>
<td>Neurological soft signs at 7 years</td>
<td>13.7 (3 198)</td>
<td>15.7 (1 493)</td>
<td>12.8 (1 315)</td>
<td>11.4 (390)</td>
</tr>
<tr>
<td><strong>Autonomic dysfunction at 7 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasomotor</td>
<td>0.7 (157)</td>
<td>0.7 (70)</td>
<td>0.7 (68)</td>
<td>0.6 (19)</td>
</tr>
<tr>
<td>Sweating</td>
<td>0.7 (172)</td>
<td>0.6 (54)</td>
<td>0.8 (82)</td>
<td>1.0 (36)</td>
</tr>
<tr>
<td>Sphincter</td>
<td>8.8 (2,053)</td>
<td>8.0 (760)</td>
<td>9.0 (927)</td>
<td>10.7 (366)</td>
</tr>
</tbody>
</table>

*First three rows of the table indicate the analysis sample at each time point in the overall Collaborative Perinatal Project sample, and by parent socioeconmic disadvantage. Prevalences of maternal medical conditions and pregnancy and delivery complications are presented in the baseline sample. Prevalences of offspring neurological outcomes are presented in the analysis sample for each time point.*
missing data (Table S2). Finally, we conducted analyses of the age 7 outcomes that further adjusted for socioeconomic disadvantage at the time of the 7-year assessment (Table S3). The associations between socioeconomic disadvantage and age 7 outcomes reported in Tables 4 and 5 were unchanged after adjustment for socioeconomic conditions at age 7, suggesting a lasting influence of early life conditions that is independent of conditions later in childhood. Moreover, adverse socioeconomic conditions at age 7 further (i.e. independently of socioeconomic disadvantage during the prenatal period) increased the risk of neurological abnormalities (OR = 1.31; CI = 1.17, 1.47) and sphincter abnormality (OR = 1.39; CI = 1.20, 1.61) at age 7.

**Discussion**

We sought to determine whether children’s neural development is impaired in the context of socioeconomic disadvantage. Using data from a large national birth cohort, children of lower socioeconomic status parents were more likely to
exhibit neurological abnormalities at 4 months and 1 year, and neurological abnormalities, hard signs, soft signs and autonomic nervous system dysfunctions at 7 years. These ages encompass a critical period for forming complex neuronal networks, with potentially lifelong consequences.38,39

### Limitations

Neurological abnormalities were based partly on study physicians’ global ratings of children’s neurological status. Study procedures were standardized throughout the CPP,40 and global ratings of neurological abnormalities

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**Table 4.** Results of logistic regression analyses of neurological outcomes at 7 years according to parental socioeconomic disadvantage, maternal medical conditions, and pregnancy and delivery complications in the Collaborative Perinatal Project (n = 23,279).

<table>
<thead>
<tr>
<th></th>
<th>Neurological abnormalities</th>
<th>Neurological hard signs</th>
<th>Neurological soft signs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1 OR (CI)</td>
<td>Model 2 OR (CI)</td>
<td>Model 1 OR (CI)</td>
</tr>
<tr>
<td>Parental socioeconomic disadvantage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.67 (1.48, 1.89)</td>
<td>1.62 (1.43, 1.83)</td>
<td>1.39 (1.10, 1.76)</td>
</tr>
<tr>
<td>Medium</td>
<td>1.33 (1.21, 1.46)</td>
<td>1.31 (1.19, 1.44)</td>
<td>1.21 (1.03, 1.43)</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Maternal medical conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>1.18 (1.05, 1.34)</td>
<td>1.17 (1.03, 1.32)</td>
<td>1.05 (0.86, 1.30)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1.03 (0.88, 1.20)</td>
<td>1.01 (0.86, 1.18)</td>
<td>0.92 (0.69, 1.23)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0.97 (0.85, 1.10)</td>
<td>0.96 (0.84, 1.10)</td>
<td>1.09 (0.87, 1.35)</td>
</tr>
<tr>
<td>Metabolic</td>
<td>1.51 (1.20, 1.90)</td>
<td>1.26 (1.00, 1.59)</td>
<td>1.95 (1.43, 2.67)</td>
</tr>
<tr>
<td>Neurological</td>
<td>1.05 (0.93, 1.19)</td>
<td>1.05 (0.93, 1.19)</td>
<td>1.02 (0.83, 1.26)</td>
</tr>
<tr>
<td>Pregnancy and delivery complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal growth restriction/prematurity</td>
<td>1.49 (1.37, 1.62)</td>
<td>1.42 (1.22, 1.64)</td>
<td>1.37 (1.25, 1.50)</td>
</tr>
<tr>
<td>Placental hypertrophy</td>
<td>1.21 (1.08, 1.36)</td>
<td>1.02 (0.83, 1.26)</td>
<td>1.03 (0.91, 1.17)</td>
</tr>
<tr>
<td>Possible chronic hypoxia</td>
<td>1.27 (1.14, 1.41)</td>
<td>1.21 (1.01, 1.45)</td>
<td>1.16 (1.03, 1.31)</td>
</tr>
<tr>
<td>Acute perinatal hypoxia</td>
<td>1.21 (1.05, 1.40)</td>
<td>1.37 (1.07, 1.75)</td>
<td>1.15 (0.98, 1.34)</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, 95% confidence interval.

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**Table 5.** Logistic regression analyses of parental socioeconomic disadvantage and offspring autonomic function abnormalities at 7 years in the Collaborative Perinatal Project (n = 23,279).

<table>
<thead>
<tr>
<th></th>
<th>Vasomotor abnormality</th>
<th>Sweating abnormality</th>
<th>Sphincter abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1 OR (CI)</td>
<td>Model 2 OR (CI)</td>
<td>Model 1 OR (CI)</td>
</tr>
<tr>
<td>Parental socioeconomic disadvantage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.34 (0.79, 2.29)</td>
<td>1.33 (0.78, 2.27)</td>
<td>1.03 (0.65, 1.65)</td>
</tr>
<tr>
<td>Medium</td>
<td>1.30 (0.91, 1.85)</td>
<td>1.28 (0.90, 1.82)</td>
<td>0.86 (0.59, 1.24)</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Maternal medical conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>0.54 (0.27, 1.09)</td>
<td>0.54 (0.27, 1.10)</td>
<td>1.15 (0.68, 1.93)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1.16 (0.57, 2.38)</td>
<td>1.16 (0.57, 2.37)</td>
<td>1.47 (0.83, 2.59)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0.69 (0.36, 1.32)</td>
<td>0.67 (0.35, 1.28)</td>
<td>1.14 (0.69, 1.90)</td>
</tr>
<tr>
<td>Metabolic</td>
<td>3.04 (1.35, 6.85)</td>
<td>2.82 (1.23, 6.51)</td>
<td>1.11 (0.35, 3.52)</td>
</tr>
<tr>
<td>Neurological</td>
<td>0.61 (0.33, 1.15)</td>
<td>0.62 (0.33, 1.17)</td>
<td>1.08 (0.65, 1.79)</td>
</tr>
<tr>
<td>Pregnancy and delivery complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal growth restriction/prematurity</td>
<td>1.19 (0.80, 1.76)</td>
<td>1.21 (0.85, 1.71)</td>
<td>1.13 (1.01, 1.27)</td>
</tr>
<tr>
<td>Placental hypertrophy</td>
<td>1.45 (0.91, 2.31)</td>
<td>1.25 (0.80, 1.96)</td>
<td>1.03 (0.88, 1.20)</td>
</tr>
<tr>
<td>Possible chronic hypoxia</td>
<td>1.15 (0.69, 1.92)</td>
<td>1.19 (0.76, 1.86)</td>
<td>1.03 (0.89, 1.20)</td>
</tr>
<tr>
<td>Acute perinatal hypoxia</td>
<td>0.89 (0.43, 1.82)</td>
<td>0.62 (0.29, 1.32)</td>
<td>0.99 (0.81, 1.21)</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, 95% confidence interval.

*aAll models controlled for maternal race, offspring sex and study site.*
were recorded after comprehensive neurological examination. Neurological examination items used in the CPP were found to have high test-retest and inter-rater reliabilities in other samples, and abnormalities observed in the CPP were predictive of mental and behavioural disorders in adolescence and adulthood, suggesting their sensitivity for detecting clinically relevant problems. A major objective of the CPP was to study children’s neurological development, and the neurological examinations performed do not differ substantially from current practice. The clinical ANS examinations generated rather coarse measures of ANS functioning, unlike heart rate variability or skin conductance. We investigated pregnancy and delivery complications as potential explanatory variables in the association between socioeconomic disadvantage and offspring neurological outcomes; though there was no evidence of mediation, we cannot definitively rule out intrauterine mechanisms. Our measures of fetal hypoxia were indirect (i.e. did not assess oxygen saturation in fetal blood), and the prenatal exposures analysed might not be sensitive to subtle impacts on neural development.

The CPP could not identify neurological conditions that have genetic origins, which could have introduced bias to the extent that such conditions were more common in disadvantaged families and were not captured by the maternal medical history. Attrition during the course of the study may have biased results; our sensitivity analyses correct for bias caused by factors measured in the CPP, but not unmeasured factors. Finally, as the CPP was conducted between 1959 and 1974, it is useful to consider the extent to which analyses of this historic study remain generalizable to contemporary circumstances. The socioeconomic assessments were validated at the time the CPP was conducted, and have been shown to have long-term associations with adult physical and mental health outcomes. More broadly, are the neurodevelopmental consequences of early life socioeconomic disadvantage the same today as in the 1960’s? In terms of exposure, the proportion of children under 6 years of age raised in households below the federal poverty threshold is higher today (e.g. 22.2% in 2013) than it was at the time the CPP was conducted (e.g. 16.6% in 1970). Whether or not the conditions of child poverty have changed since the era in which the CPP was conducted, and thus whether the implications of economic disadvantage for child development are the same or potentially worse, is a question than warrants this study’s replication in more recent cohorts.

The social context of neurological development
Socioeconomic disadvantage was associated with an increased risk of neurological abnormalities beginning at 4 months of age, persisting through age 7 years. These abnormalities include demonstrable neurological deficits suggestive of localizable lesions, and subtle problems in sensory, motor and autonomic development that may be clinically unremarkable but could impede the child’s adaptation and learning. This association was not evident in newborns, perhaps because the neurological system is under-developed at birth, leaving the coverage of the newborn neurological examination to primitive reflexes and brief inspection.

The association between socioeconomic disadvantage and ANS dysfunction at age 7 is consistent with the theory that social and environmental stressors have enduring consequences for the development of the endocrine, immune and autonomic nervous systems which regulate physiological responses to stressors. For example, socioeconomic disadvantage has been shown to change the baseline activity and stress responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in sympathetic hyper-arousal at baseline and suboptimal responsiveness under stress.

In adjusted analyses, children of disadvantaged parents were more likely to exhibit neurological hard signs and soft signs. These neurological problems have been associated with childhood cognitive deficits, and increased risks for attention deficit hyperactivity disorder and internalizing and externalizing symptoms. They are also implicated in the neurodevelopmental origins of severe forms of psychopathology such as mood and anxiety disorders, schizophrenia and autistic spectrum disorders.

Potential mechanisms
We hypothesized that pregnancy and delivery complications would partly explain the association between socioeconomic disadvantage and offspring neural deficits. This hypothesis was not supported, as the associations between disadvantage and offspring neurological abnormalities were maintained in analyses adjusting for such complications. Nonetheless, we do not rule out the existence of other intrauterine pathways bridging parental socioeconomic conditions and child neurodevelopment, such as pathways linked to nutritional deficits that may be overrepresented in the context of socioeconomic disadvantage (e.g. folate deficiency). Maternal substance use during pregnancy could also be an important factor. The CPP did not assess maternal alcohol or drug use during pregnancy, but did assess cigarette smoking; however, further adjustment for maternal smoking during pregnancy had no impact on the estimated effects for socioeconomic disadvantage (data not shown).
Physiological responses to maternal stress during pregnancy, including socioeconomic disadvantage, include higher blood cortisol and proinflammatory cytokines crossing the placenta, which could adversely affect the development of the HPA axis, limbic system and prefrontal cortex. Supporting these pathways, Buss et al. reported reduced grey matter volume in regions controlling cognitive function in a sample of 6–9-year-old children exposed to maternal pregnancy-related anxiety. Within pregnancy there was evidence for a sensitive period, as these reductions were only observed when exposure occurred at 19 weeks of gestation, but not at later time points. Maternal stress is also associated with epigenetic changes in offspring, producing in animal models an epigenetic profile consistent with neuropsychiatric dysfunction. In addition to intrauterine mechanisms, the associations we observed could be due to, or compounded by, postnatal factors such as maternal depression or anxiety and other aspects of the early childhood environment including child maltreatment.

**Conclusion**

Exposure to socioeconomic disadvantage during early childhood is associated with neural deficits that are detectable upon physical examination. This finding confirms that aspects of the child’s environment at the very beginning of life may impede both peripheral and central nervous system development, as well as lower and higher cortical functions of the brain, with potentially long-term consequences for children’s health. Future research should explore the specific domains of neural functioning that are most susceptible to socioeconomic disadvantage and, considering that the nervous system has the greatest degree of plasticity during infancy and early childhood, the extent to which the abnormalities we identified can be reversed.

**Supplementary Data**

Supplementary data are available at IJE online.

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**Conflict of interest:** None declared.

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