Original Contribution

Prenatal Exposure to Perfluoroalkyl Substances and the Risk of Congenital Cerebral Palsy in Children

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Perfluoroalkyl substances (PFASs) are persistent pollutants and endocrine disruptors that may affect fetal brain development. We investigated whether prenatal exposure to PFASs increases the risk of congenital cerebral palsy (CP). The source population for this study includes 83,389 liveborn singletons and mothers enrolled in the Danish National Birth Cohort during 1996–2002. We identified 156 CP cases by linking the cohort to the Danish National Cerebral Palsy Register, and we randomly selected 550 controls using a case-cohort design. We measured 16 PFASs in maternal plasma collected in early or midpregnancy, and 6 PFASs were quantifiable in more than 90% of the samples. We found a higher risk of CP in boys with higher maternal PFAS levels; per 1-unit (natural-log ng/mL) increase, the risk ratios were 1.7 (95% confidence interval: 1.0, 2.8) for perfluorooctane sulfonate and 2.1 (95% confidence interval: 1.2, 3.6) for perfluorooctanoic acid. We also observed a dose-response pattern of CP risk in boys per quartile of maternal level of perfluorooctane sulfonate and perfluorooctanoic acid (P for trend < 0.01). PFASs were associated with both unilateral and bilateral spastic CP subphenotypes. No association between PFASs and CP was found in girls. Prenatal exposures to PFASs may increase the risk of CP in boys, but the finding is novel and replication is needed.

congenital cerebral palsy; movement and posture disorders; perfluoroalkyl substance; perfluorooctane sulfonate; perfluorooctanoic acid

Abbreviations: CP, cerebral palsy; DNBC, Danish National Birth Cohort; PFAS, perfluoroalkyl substance; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

Congenital cerebral palsy (CP) is a group of permanent and nonprogressive movement and posture disorders attributed to early brain lesions (1). CP affects approximately 2–3 per 1,000 births (2, 3), with an incidence as high as 100 cases per 1,000 births among extremely preterm births (4). More than half of the children affected by CP are unable to walk without assistive devices or have comorbidities such as mental retardation and vision impairment (5). Fewer than 10% of cases experienced birth asphyxia or trauma (3), and the etiology of the majority of CP cases remains unexplained (6).

Perfluoroalkyl substances (PFASs) are a group of synthetic chemicals used extensively in food packaging, nonstick pan coatings, fire-fighting foams, paper and textile coatings, and personal care products. PFASs have surfactant properties and are extremely persistent in the environment (7). Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) were the 2 most frequently used PFASs in Denmark during the study period, with biological half-lives of 4–5 years (8). After a drop in manufacturing emission in 2002, PFOS levels in humans were reported to decrease in some countries; however, exposure to substitute PFASs, such as perfluorobutane sulfonate and perfluorononanoic acid, has subsequently increased (9).

Although the low level of PFASs found in the adult population may cause no harm, concerns about the potential
health consequences of PFAS exposure in fetal life have been raised. PFASs can cross the placental barrier (10), affect neuronal cell development (11), change motor function, and lead to delayed learning in animals (12, 13). In addition, PFASs have endocrine disruptive properties (14) and can interfere with thyroid hormone function (15–18), which, during fetal development, may cause mental retardation and neurological deficits (19).

Thus, we hypothesized that prenatal PFAS exposure affects fetal brain development and increases the risk of CP. Within the framework of the Danish National Birth Cohort (DNBC), we measured PFAS concentrations in maternal plasma collected prenatally to examine the association with children’s risk of developing CP.

METHODS

We performed a case-cohort study using data from the DNBC described in detail previously (20). Briefly, from 1996 to 2002, pregnant women were recruited through their general practitioners during gestational weeks 6–12. Approximately 50% of all general practitioners in Denmark participated in the study, and 60% of invited women agreed to participate. Women were ineligible if they did not speak any Danish or did not intend to carry their pregnancies to term. Information was collected through 4 computer-assisted telephone interviews (twice during pregnancy and twice postpartum), and 2 maternal blood samples were taken—1 each in the first and second trimesters (English versions of questionnaires are available online at http://www.bsmb.dk). The study is part of the FETOTOX program (http://www.fetotox.au.dk), which examines neurodevelopmental influences of prenatal exposures to PFASs, and we present our findings for CP in this report.

Source population

The DNBC source population for this study was 1) live-born singletons at risk of CP; 2) infants born to women who participated in the first telephone interview conducted during the 16th week of gestation (interquartile range, 14–19 weeks); and 3) infants of mothers from whom we collected blood during the first or second trimester of pregnancy. From 101,041 pregnancies originally enrolled in the DNBC, we excluded unsuccessful pregnancies (n = 6,207), nonsingleton births (n = 2,080), births with unknown birth outcomes (n = 25) or missing birth dates (n = 99), mothers who emigrated (n = 51) or died (n = 3), and women who missed the first telephone interview (n = 4,578) or did not provide a blood sample during pregnancy (n = 4,609). This left us with 83,389 mother-child pairs (42,737 boys) as the source population.

Congenital cerebral palsy

We identified 156 children in the DNBC source population who were diagnosed with congenital CP according to the Danish National Cerebral Palsy Register. The linkage of DNBC and Danish National Cerebral Palsy Register was updated up to September 23, 2010. The Danish National Cerebral Palsy Register is a population-based registry that contains records of individuals with validated CP diagnoses since 1925 (2, 21). Since 1978, the register has used the definition of CP from the Surveillance of Cerebral Palsy in Europe (5) as a group of permanent movement and/or posture disorders caused by nonprogressive interference/lesion/abnormality in the developing/immature brain. The motor disorders are described as unilateral or bilateral manifestations, and the main affected brain areas are the white matter (resulting in spastic CP), basal ganglia (resulting in dystonic/dyskinetic CP), or cerebellum (resulting in ataxic CP). The distributions of clinical subgroups of the 156 CP cases in this study are as follows: 137 spastic, 13 dystonic, 2 ataxic, 2 choreatic, and 2 unclassified. Cases of CP were validated by a pediatric neurologist and an obstetrician on the basis of reviews of the children’s medical records and information collected from all hospitals and pediatric departments in Denmark.

Control selection

We randomly selected 550 children (440 boys) by sex from the source population to be the population control group. More male than female controls were sampled because the population control group was also designed as a comparison group for other outcomes we targeted, including attention deficit hyperactivity disorder and autism—diseases that are both 4 times more prevalent among boys. In addition, we oversampled an additional 50 controls at random from 3,866 children who were born preterm (before 37 weeks of gestation), but we used these preterm controls only for secondary analyses. A flowchart of subjects’ selection and sampling fractions of cases and controls is shown in Figure 1.

PFAS exposure

Plasma concentrations of perfluorinated chemicals were analyzed at the Department of Environmental Science at Aarhus University (Aarhus, Denmark). In the DNBC, 2 maternal blood samples were collected and sent by mail to Statens Serum Institut (Copenhagen, Denmark) and then separated and stored in freezers at −80°C or in liquid nitrogen. Blood samples were transported and subjected to outdoor temperatures for 4–48 hours, but most samples arrived within 28 hours. We used 0.1 mL of stored maternal plasma for PFAS analyses; 86% of samples for both cases and controls were collected at the first antenatal visit during the first trimester, and 14% were collected at the second antenatal visit in the second trimester.

Solid phase extraction technique was used to extract and purify PFASs from plasma samples, and PFAS concentrations were measured by liquid chromatography–tandem mass spectrometry. All samples were measured in a random sequence of case or control status by laboratory personnel blinded to participant information. Nine maternal plasma samples (4 cases, 5 controls) were either not available from the biobank or failed the PFAS extraction and purification process and were therefore excluded. For quality control, we analyzed 6 blood samples (2 each with low, average, and high concentrations of PFOS/PFOA) that were not part of this study but had previously been analyzed at the 3M
toxicology laboratory with similar analytical techniques (10, 22). In addition, 15 samples that were included in this study had previously been analyzed in the 3M toxicology laboratory (10, 23). Correlations between PFOA and PFOS values measured at the 2 laboratories were compared.

Statistical analysis

PFAS concentrations were analyzed as continuous variables (with or without natural-log transformation) and were also categorized into quartiles according to the distribution among population controls; the lowest quartile was used as the reference group. We used generalized linear models with a log link function based on a Poisson distribution to estimate risk ratios and 95% confidence intervals for PFAS exposures and CP, taking into account inverse probability weights derived from the sampling fractions of cases and controls. Convergence problems arose when we estimated risk ratios using a log-binomial regression. Because the outcome is rare, the risk ratio estimates from a log-Poisson regression are expected to approximate the estimates from a log-binomial regression. Trend tests were performed using median values of PFAS concentrations in each quartile as a continuous variable.

In addition, we fit generalized additive models to examine a potential nonlinear relationship between maternal plasma PFASs and CP with a smoothing function of PFAS concentrations without imposing a given parametric form. Five knots was set as the upper limit of the number of degrees of freedom, and we compared model fit and visually inspected plots of the smoothed data. We did not find evidence for nonlinearity between PFAS values and CP.

Because PFASs are hormonally active (24), we conducted separate analyses for boys and girls. We also performed stratified analyses by term and preterm birth status; in this analysis, we added the preterm controls additionally selected from the DNBC. We also evaluated the relationship of PFASs by subtype of spastic CP (i.e., unilateral or bilateral manifestation).

Final models were adjusted for potential confounders that were previously described as risk factors of CP or factors associated with PFAS exposures, including maternal age at child’s birth, parity, socioeconomic status (derived from the mother’s and father’s educational levels and occupations), maternal smoking and alcohol intake during pregnancy, and mother’s self-reported psychiatric illnesses, in addition to child’s sex. To determine maternal psychiatric illnesses, we asked women if they had seen a doctor or psychologist because of depression, anxiety, a childhood psychiatric

Figure 1. Flow chart of study population selection in the Danish National Birth Cohort (DNBC), Denmark, 1996–2002. Unsuccessful pregnancies include miscarriage, stillbirth, induced abortion, hydatidiform mole, and ectopic pregnancy. The sampling fraction of cerebral palsy (CP) cases is 1. The sampling fractions of the control group are 0.0103 for boys and 0.0027 for girls.
disorder, family problems/life crisis, or other mental health problems. Additionally, other potential confounders, such as gestational week of blood sampling, child’s birth year, father’s age at child’s birth, mother’s prepregnancy body mass index (weight [kg]/height [m]²) value, season of conception, and maternal fever or infections during pregnancy were evaluated but not included in final models because they changed effect estimates of interest by less than 1%. Using propensity scores, we further adjusted for some dietary factors (e.g., fish and organic food consumption) and household attributes (e.g., ownership and size) that may be common sources of exposure to PFASs and other endocrine-disrupting compounds, such as bisphenol A and phthalates (25, 26).

We focus on 6 of 16 PFASs with the following proportions of samples above the lower limit of quantitation: 100% for PFOS, 100% for PFOA, 98% for perfluorohexane sulfonate, 96% for perfluorooctane sulfonate, 92% for perfluorononanoic acid, and 90% for perfluorodecanoic acid (see full PFAS panel with quantitation limits in Web Table 1, available at http://aje.oxfordjournals.org/). To account for PFAS values below the lower limit of quantitation when PFASs were analyzed as continuous variables, we used multiple imputations (27) with the MI procedure in SAS, version 9.2, statistical software (SAS Institute, Inc., Cary, North Carolina), including 6 PFASs and all covariates (all potential confounders including dietary and household factors) in the model. Five simulated complete data sets were generated after imputation, and we used standard analytical procedures to combine the results.

Correlations between PFAS concentrations were assessed by using a Pearson correlation matrix (Web Table 2). To examine whether any single PFAS may be of particular importance, we simultaneously included all PFASs in 1 model. To ensure that individuals with extreme exposure values did not disproportionately influence our results, we conducted sensitivity analyses excluding observations greater than 3 times the 75th percentile for each PFAS.

**RESULTS**

Table 1 presents the demographic characteristics of the participants. Table 2 shows the median and interquartile ranges of maternal plasma PFAS concentrations in cases and controls separately for boys and girls. We found a high correlation between the PFOS/PFOA levels measured in the current study and previous measurements performed at the 3M toxicology laboratory (Pearson’s r = 0.94 for PFOS and 0.95 for PFOA) in our quality control assessment.

We estimated increased risk of CP per natural-log increase in maternal PFOS, PFOA, and PFHpS in all boys and in boys born at term (Table 3). We found positive associations between PFAS concentrations and CP in boys for both spastic unilateral and bilateral subphenotypes of CP (Web Table 3). We found no associations between PFASs and CP in all girls or in girls born at term (Table 3). Results are very imprecise for boys born preterm (i.e., per natural-log ng/mL increase in PFOS, risk ratio = 1.1, 95% confidence interval: 0.3, 5.0; and per natural-log ng/mL increase in PFOA, risk ratio = 1.4, 95% confidence interval: 0.3, 7.0), and data are too sparse to estimate effects in girls born preterm.

Higher risks were observed among boys in higher quartiles of PFOS, PFOA, and perfluorooctane sulfonate compared with boys in the lowest quartile (Figure 2). Simultaneous adjustment for all PFASs in 1 model weakened most PFAS and CP associations, but high PFOS concentrations remained positively associated with CP risk (Web Table 4). The use of propensity scores to additionally adjust for common sources of exposure to PFASs and other endocrine-disrupting chemicals did not remove the observed associations (i.e., elevated CP risks in boys among the highest quartile of PFOS (risk ratio = 2.7; 95% confidence interval: 1.4, 5.3) or PFOA (risk ratio = 2.1; 95% confidence interval: 1.1, 4.0) compared with the lowest quartile). Additional sensitivity analyses comparing results with or without natural-log transformation of PFAS values and excluding extreme...
PFAS values from the analyses did not change our findings (data not shown).

**DISCUSSION**

We found a dose-response–like association between prenatal exposure to PFAS and the risks of CP in boys, and similar associations were seen for spastic unilateral or bilateral CP subphenotypes. No associations between PFASs and CP were found in girls, but the statistical power to estimate effects for girls was low because of small numbers. Recent evidence in animal and human studies suggests that PFASs interfere with maternal hormone function during pregnancy (14–18); deficiency of thyroid hormone during critical periods of brain development can damage the nervous system and cause neurodevelopment disorders such as CP (28–29).

Two previous studies used subsets of the DNBC samples and found no associations between prenatal exposures to PFOS/PFOA and scales of motor function and coordination of children at ages 18 months (23) and 7 years (30). However, the study endpoints were self-reported by mothers and potentially prone to nondifferential measurement errors. More recently, in a birth cohort from Taiwan, trained physical therapists were asked to evaluate children’s neurodevelopment, and the authors reported higher prenatal PFOS levels associated with lower gross motor function in children at 2 years of age (31), but the predictive value of the scores that were used may be low at these young ages.

Our study shows that PFAS exposures were correlated with CP risk only in boys, which could be a chance finding, but a possible sex-specific mechanism should be further investigated. There is some evidence suggesting that PFASs are sex-specific endocrine disruptors in vitro (24) and in adults (15),

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**Table 2. Median Maternal Plasma Perfluoroalkyl Substance Concentrations in Cases and Controls, by Child’s Sex, Danish National Birth Cohort, 1996–2002**

<table>
<thead>
<tr>
<th>Perfluoroalkyl Substance</th>
<th>Carbon Chain Length</th>
<th>% Quantifiable in All Samples</th>
<th>Median Perfluoroalkyl Substance Concentration, ng/mL (Interquartile Range)</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>CP Cases (n = 86)</td>
<td>Controls (n = 435)</td>
<td>CP Cases (n = 66)</td>
</tr>
<tr>
<td>PFOS</td>
<td>8</td>
<td>100</td>
<td>28.90 (22.40–40.00)</td>
<td>27.60 (20.00–35.60)</td>
<td>27.50 (19.38–37.20)</td>
</tr>
<tr>
<td>PFOA</td>
<td>8</td>
<td>100</td>
<td>4.56 (3.32–6.04)</td>
<td>4.00 (2.98–5.34)</td>
<td>3.90 (3.30–5.58)</td>
</tr>
<tr>
<td>PFHxS</td>
<td>6</td>
<td>98</td>
<td>0.96 (0.72–1.30)</td>
<td>0.92 (0.67–1.23)</td>
<td>0.90 (0.67–1.26)</td>
</tr>
<tr>
<td>PFNA</td>
<td>9</td>
<td>92</td>
<td>0.46 (0.38–0.58)</td>
<td>0.44 (0.35–0.55)</td>
<td>0.39 (0.33–0.53)</td>
</tr>
<tr>
<td>PFHpS</td>
<td>7</td>
<td>96</td>
<td>0.33 (0.23–0.45)</td>
<td>0.30 (0.21–0.41)</td>
<td>0.29 (0.21–0.42)</td>
</tr>
<tr>
<td>PFDA</td>
<td>10</td>
<td>90</td>
<td>0.18 (0.12–0.24)</td>
<td>0.17 (0.13–0.23)</td>
<td>0.16 (0.11–0.21)</td>
</tr>
</tbody>
</table>

Abbreviations: CP, cerebral palsy; PFDA, perfluorodecanoic acid; PFHpS, perfluoroheptane sulfonate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

a Number of carbons in the fully fluorinated alkyl chain.

b Concentrations for 9 samples (4 cases and 5 controls) were missing because samples were not available from the biobank or failed the extraction process.

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**Table 3. Risk Ratios for Congenital CP in Children According to Maternal Perfluoroalkyl Substance Concentrations During Pregnancy, by Child’s Sex and Among Term Births, Danish National Birth Cohort, 1996–2002**

<table>
<thead>
<tr>
<th>Prenatal Exposure</th>
<th>All Boys</th>
<th>All Girls</th>
<th>Boys Born at Term</th>
<th>Girls Born at Term</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted RR</td>
<td>95% CI</td>
<td>Adjusted RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>PFOS</td>
<td>1.7</td>
<td>1.0, 2.8</td>
<td>0.7</td>
<td>0.4, 1.4</td>
</tr>
<tr>
<td>PFOA</td>
<td>2.1</td>
<td>1.2, 3.6</td>
<td>0.8</td>
<td>0.4, 1.5</td>
</tr>
<tr>
<td>PFHxS</td>
<td>1.2</td>
<td>0.9, 1.7</td>
<td>1.1</td>
<td>0.6, 1.9</td>
</tr>
<tr>
<td>PFNA</td>
<td>1.2</td>
<td>0.6, 2.5</td>
<td>0.6</td>
<td>0.3, 1.2</td>
</tr>
<tr>
<td>PFHpS</td>
<td>1.5</td>
<td>1.0, 2.2</td>
<td>0.9</td>
<td>0.6, 1.5</td>
</tr>
<tr>
<td>PFDA</td>
<td>1.1</td>
<td>0.7, 1.7</td>
<td>0.6</td>
<td>0.3, 1.1</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CP, cerebral palsy; PFDA, perfluorodecanoic acid; PFHpS, perfluoroheptane sulfonate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; RR, risk ratio.

a Per 1 natural-log unit (ng/mL) increase.

b A total of 152 cases (86 boys) and 545 controls (435 boys) were used in analyses.

A total of 110 term cases (65 boys) and 530 term controls (422 boys) were used in analyses.

Adjusted for maternal age at delivery, socioeconomic status, parity, alcohol consumption during pregnancy, smoking during pregnancy, and mother’s psychiatric illnesses.
and motor functions in PFAS-exposed mice were impaired in a sex-related manner (13). The vulnerability of different brain areas during different developmental windows may also differ by sex (32). Moreover, the male brain is suggested to be more vulnerable to white matter injuries and intraventricular hemorrhage (33), and males are, in general, at higher risk of CP (34). CP risks were elevated among boys born at term to mothers with higher PFAS levels, but results are imprecise for boys born preterm. It should, however, be taken into consideration that gestational age may be a mediator in the causal pathway between PFAS exposure and CP (35), and stratification on preterm birth status could potentially introduce collider bias that could lead to either overestimated or underestimated risks (36, 37).

The maternal PFAS values measured in our study are comparable to those previously reported during a similar time period in the US general population (38). The PFAS values below the lower limit of quantitation in our studies were estimated from multiple imputations, but the influence of estimation errors would be small for PFAS quartiles. Because concentrations for several PFASs were moderately correlated, it is difficult to disentangle whether specific compounds or the combination of substances are driving the associations. PFOS remained positively associated with CP after adjustment for the other types of PFAS in the same model. A recent in vitro assay found mixture-specific effects of 5 PFASs tested simultaneously for their ability to interfere with androgen receptors (14). Further experimental studies are needed to examine mechanisms of how different PFASs act on biological targets.

This study has several strengths. First, PFAS values were measured in prospectively collected maternal plasma samples. PFASs have a long biological half-life in humans, and it has previously been shown that PFAS measurements in serum and plasma samples are very comparable (22). High correlations between maternal and cord blood PFAS concentrations have been reported and suggest that PFAS in maternal plasma is also a valid marker of fetal exposure (10). Moreover, participants were selected from a well-defined nationwide cohort with a sufficient duration of follow-up (approximately 10 years, on average, in the DNBC) to catch all congenital CP cases, and CP cases were ascertained from records of the Danish National Cerebral Palsy Registry with unique civil registration numbers used for linkage. Because follow-up does not require the subject’s active participation, selection bias due to differential response is not an issue. CP diagnoses were validated by experts’ review of the children’s medical records, which reduces disease misclassification. However, children must survive to at least 1 year of age to be diagnosed in the Danish National Cerebral Palsy Register; therefore, we likely underestimated the number of severe CP cases who died in pregnancy, at birth, or during early infancy. If PFAS exposure reduces fetal/neonatal survival (17, 39), survival bias might occur, and we would expect an attenuation of the observed results.

We have no data for other endocrine-disrupting compounds; therefore, we could not evaluate possible confounding by organophosphates, bisphenol A, and phthalates. However, additional adjustment for dietary factors and household

Figure 2. Associations of congenital cerebral palsy in boys and maternal perfluoroalkyl substance (PFAS) concentrations (in quartiles) during pregnancy. The 25th, 50th, and 75th quartile distributions are 20.40, 27.40, and 35.60 for perfluorooctane sulfonate (PFOS); 3.01, 4.00, and 5.42 for perfluorooctanoic acid (PFOA); 0.21, 0.30, and 0.41 for perfluorohexane sulfonate (PFHxS); 0.35, 0.43, and 0.56 for perfluorononanoic acid (PFNA); 0.21, 0.30, and 0.41 for perfluorohexane sulfonate (PFHxS); and 0.12, 0.17, and 0.23 for perfluorodecanoic acid (PFDA) (in ng/mL), respectively. The lowest quartile was used as the reference group. Risk ratio (diamonds) and 95% confidence intervals (vertical bars) are adjusted for maternal age at delivery, mother’s socioeconomic status, parity, maternal alcohol intake and smoking during pregnancy, and mother’s psychiatric illnesses. P values for trend are as follows: <0.01 for PFOS, <0.01 for PFOA, 0.21 for PFHxS, 0.10 for PFNA, 0.03 for PFHpS, and 0.12 for PFDA. P for trend was modeled on the basis of the midpoint of each category.
characteristics (25, 26) as proxies for common sources of exposure to endocrine-disrupting chemicals did not change our results and conclusions. Nonparticipation in the DNBC cohort would raise concerns if exposure has an influence on the selection of mothers who are at higher risk of having children with CP, and selective participation may also limit the generalizability of our results (40).

In summary, we found that prenatal exposure to some PFASs may increase the risk of CP in children. This finding raises concerns, because PFASs are ubiquitous and persistent in the environment, and CP has long-lasting impacts on patients, caregivers, and society. If this finding is causal, we have identified a potential preventable risk factor for CP, but further studies using other data sources are needed to reach such a conclusion.

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