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Cerebral palsy among children of immigrants in Denmark and the role of socioeconomic status

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ABSTRACT

Background: Children of immigrants in Denmark have excess risk for some of the most well-established risk factors for cerebral palsy (CP).
Objectives: To study differences in risk of CP between children of immigrants and children of Danish-born mothers, and explore whether socioeconomic status drives any potential association.
Methods: A register-based cohort study including 1,274,616 children born in Denmark between 1981 and 2007. Of these, 2807 had a validated CP diagnosis in the Danish CP Register. We estimated the risk of CP as odds ratios (OR) using logistic regression and assessed mediation through socioeconomic status using natural effect models.
Results: In children of Danish-born mothers, 2.2/1000 had CP overall and the prevalence was similar for children of immigrants. However, children of immigrants had lower risk of unilateral spastic CP than children of Danish native-born mothers; OR = 0.59 (95% CI:0.38–0.91) for Western and OR = 0.79 (95% CI:0.61–1.03) for Non-Western immigrants. By contrast, the risk of bilateral spastic CP was higher in children of Non-Western immigrants (OR = 1.27 (95% CI:1.05–1.53)), especially from Turkey and Pakistan compared with children of Danish native-born mothers. The mediation analysis revealed an indirect effect (through maternal educational level and household income) with an OR of 1.06 (95% CI:0.99–1.14) for children of Non-Western immigrants.
Conclusions: While children of immigrants had lower risk of unilateral spastic CP than children of Danish-born mothers, the risk of bilateral spastic CP was increased in children of Non-Western immigrants. Socioeconomic status did not appear to be a significant contributor to the increased risk of bilateral spastic CP.

Abbreviations: CP, cerebral palsy; OR, odds ratio; 95% CI, 95% confidence interval.

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1. Introduction

In Denmark, the number of immigrants from Non-Western countries has increased rapidly since the mid-1980s.[1] Compared to Danish native-born mothers, increased risks of intrauterine-growth-restriction, preterm delivery, and congenital malformations have been reported in Pakistani and Turkish immigrants,[2–4] who constitute some of the largest immigrant groups in Denmark. These adverse birth outcomes are some of the most well-established risk factors for cerebral palsy (CP).[5–7] Moreover, it is well-established that the consanguinity rate is high in immigrants from Pakistan and Turkey,[8,9] and various adverse pregnancy outcomes, including bilateral spastic CP, are common in groups in which consanguinity is frequent ([4,10–13]). Therefore, it is plausible there is an ethnic disparity in the risk of CP.

CP is the most common severe motor disability in childhood[14] affecting about 2 per 1000 live-born children.[15] In Western countries, CP tends to be most prevalent in ethnic minority groups,[16–24] although this may depend upon contextual factors of the host country, e.g., the welfare system and ethnic composition. Only one study has investigated CP in immigrants in a Scandinavian context and found a higher risk of CP in immigrants than in native-born.[23] In this study, specific nationalities and CP subtypes were not assessed, although different CP subtypes may have different etiological profiles. To reduce CP rates, identification of high-risk groups would help to target interventions. Socioeconomic inequalities in the risk of CP have been repeatedly documented,[17,24–26] and it is suggested that socioeconomic inequality is likely fundamental for the ethnic disparity in most health outcomes, since ethnic minority groups often are socioeconomically disadvantaged.[27] Our primary aim was to investigate differences in risk of CP in Denmark between children of immigrants and children of native-born mothers. Secondarily, we aimed to study if maternal educational level or household income mediates the association, if any, between maternal immigrant status and CP.

2. Materials and methods

2.1. Study population

We conducted a register-based study by linkage of the Danish nationwide registers using the unique personal identifier (the CPR-number) assigned to all Danish residents at the time of birth or immigration. We identified 1,282,706 infants in the Danish Medical Birth Registry born in the eastern part of Denmark between 1981 and 1994 or in the entire country between 1995 and 2007, which correspond to the coverage of the Danish National Cerebral Palsy Registry. We excluded children not surviving the first year of life (n = 6925), since CP diagnoses before this age can be transient and are not included in the Danish National Cerebral Palsy Registry.[28,29] Also, we excluded mothers with unknown country of origin (n = 1165). This left us with 1,274,616 children for the main analysis.

2.2. Maternal immigration status

Statistic Denmark is a Danish governmental organization responsible for providing statistics on the Danish society. We used the definition of country of origin by Statistic Denmark to determine whether the mothers had immigrated to Denmark as a proxy for maternal ethnicity. Mothers born in Denmark were defined as Danish native-born mothers. Immigrants from Western countries included mothers born in Europe except for Denmark, and mothers from Canada, United States, Australia, and New Zealand. Mothers born in other countries were defined as immigrants from Non-Western countries. We also categorized country of origin according to the six largest immigrant groups (Turkey, Lebanon, Pakistan, Somalia, Iraq, and the former Yugoslavia). In some analyses, we pooled immigrants from Turkey and Pakistan to enlarge the statistical power because these two groups have similar risks for adverse birth outcomes[2–4] that are strongly associated with CP.[5–7]

2.3. Cerebral palsy

We obtained CP diagnoses from the Danish National Cerebral Palsy Registry[28,29] where information on CP is based on reporting from Danish pediatric departments and where the Danish National Patient Registry, in which registration is mandatory, is used as a supplementary source. Children with diagnoses of pre- and perinatal acquired CP that were validated by a neuro-pediatrician at age five to six years are included in the Danish National Cerebral Palsy Registry. Children with a CP diagnosis who died after one year of age but before the validation of CP are included in the Danish National Cerebral Palsy Registry if the diagnosis is unquestionable. We assessed all CP cases together, and we assessed two major subtypes separately (i.e.: unilateral spastic and bilateral spastic). We also categoized CP according to the motor impairment (walk without support, walking aids, immobile).

2.4. Covariates

We obtained information on gestational age (<37 vs. ≥37 gestational weeks), maternal age at child's birth (<30 years vs. ≥30 years), and smoking in pregnancy (no vs. yes) from the

Danish Medical Birth Registry.[30] We calculated small-for-gestational-age (SGA) (no vs. yes) as below the 10 percentile of the sex-specific ultrasound estimated curves for normal intrauterine-growth by Marsal et al.[31] with information on gestational age at birth and birth weight obtained from the Danish Medical Birth Registry. We classified congenital malformations (no vs. yes) according to the EUROCAT-classification system using ICD-10 codes from the National Patient Register (minor and chromosomal malformations were excluded, see Appendix A, Table A.1).

We obtained information on maternal education level and household income from population registries in Statistic Denmark.[32] To define educational level, we converted the educational codes derived from the registers to the International Standard Classification of Education (ISCED) codes. We subsequently classified students according to their ongoing education and non-students according to the highest attained educational level in the year of delivery. Women with ≤9 years of education (basic) were compared with more educated women (intermediate or higher), i.e., women with 10 or more years of education. To define household income, we used the sum of the mothers' and fathers' disposable income the year before delivery if the information was available; when this information was not available, we used disposable income from the subsequent year. Household income was divided by the square root of the number of persons in the household to account for the household size[33] and was subsequently classified according to income percentiles for every birth year to account for inflation (0–25% percentile vs. 25–100% percentile).

2.5. Statistical methods

We calculated the prevalence of CP according to maternal country of origin and estimated the risk of CP as odds ratios (OR) using logistic regression with children of Danish-born mothers as reference group. The regression models were adjusted for the child's birth year and robust standard errors were used to account for the potential dependency between siblings when obtaining 95% confidence intervals (95% CI). We examined the risk of bilateral spastic CP according to maternal country of origin in strata of maternal age, smoking status in pregnancy, educational level, and household income. We examined effect modification between maternal country of origin and these variables on the risk of bilateral spastic CP by likelihood ratio tests on multiplicative and additive scales. The statistical power was insufficient to perform stratified analysis for unilateral spastic CP.

Finally, we studied if maternal educational level and household income mediate the association between maternal immigrant status and CP by computing natural indirect and direct effect as suggested by Robins and Greenland[34] and Pearl.[35] This method separates the observed effect of ethnicity into a component working only through maternal educational level and household income (the so-called natural indirect effect) and a component working exclusively through other causal pathways (the natural direct effect). Each component is quantified with an OR and the product of these two ORs will be equal to the OR for ethnicity estimated by conventional logistic regression. As an example, the natural indirect OR quantifies the change in the risk of CP from changing ethnicity if ethnicity was only affecting maternal income and education, but nothing else.[36] Specifically, we computed natural effects using natural effect models as suggested by Lange et al. and implemented in the R package medflex. As a technical remark, it is noted that the required auxiliary model for the medflex package was chosen as an additional logistic regression[37–39] and the child's birth year was included as a confounder in the mediation analysis. Unlike traditional methods for mediation analysis, the natural effect models can incorporate mediation through several mediators at once (i.e., both maternal income and education).

In sensitivity analyses, we checked the impact of the following changes to our socioeconomic measures on our results: I) we only used household income the year before the child's birth, II) we used information on educational level the year after the child's birth if educational level was missing in prior years, III) we categorized those with missing information on household income into the '<25% percentile', IV) and we categorized those with missing information on educational level into the 'basic' category.

3. Results

3.1. Characteristics of the study population

The vast majority of mothers were of Danish origin (88.9%, n = 1,133,071), while 3.5% (n = 44,171) emigrated from Western countries, and 7.6% (n = 97,374) emigrated from Non-Western countries. The proportion of births by Non-Western immigrants increased from 5.2% in 1981–1989, to 7.8% in 1990–1999, and then 8.7% in 2000–2007 (results not shown). The proportion of births to Western immigrants was more stable during the study period. Immigrants from Western countries were on average older and more educated than Danish-born mothers, while immigrants from Non-Western countries were younger and less educated than Danish-born mothers. Immigrants were classified in the lowest household income quartile more frequently than Danish-born mothers. Smoking habits varied greatly between the six largest immigrants groups, e.g., 20.3% from Turkey and 1.8% from Pakistan smoked in pregnancy in comparison with 23.0% of the Danish-born mothers. There were more occurrences of SGA-babies among immigrants from Non-Western countries, and a slightly lower occurrence in Western-immigrants compared with Danish-born mothers. Additionally, we found a slightly higher prevalence of preterm delivery in Pakistani and Ex-Yugoslav immigrants compared to Danish-born mothers. Finally, the prevalence of congenital malformations was especially high for Turkish, Pakistani, and Iraqi immigrants (Table 1).

3.2. Maternal immigrant status and the risk of cerebral palsy

In total, 2505 children of Danish-born mothers had CP, corresponding to a prevalence of 2.2 per 1000 live-births for CP

Table 1 – Characteristics of the study population.

Characteristics	Maternal country of origin n (%)								
	Denmark n = 1,133,071	Western n = 44,171	Non-Western n = 97,374	Turkey n = 22,436	Lebanon n = 9680	Pakistan n = 9239	Somalia n = 8766	Iraq n = 7243	Former Yugoslavia n = 5225
Preterm birth (<37 gw), n (%)	67,325 (5.9)	2577 (5.8)	5617 (5.8)	1341 (6.0)	460 (4.8)	588 (6.4)	342 (3.9)	361 (5.0)	354 (6.8)
Missing, n (%)	9 (<0.1)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
Congenital malformations[a], n (%)	62,921 (8.0)	2365 (7.4)	6048 (8.2)	1272 (9.2)	689 (8.5)	458 (9.0)	734 (8.6)	653 (9.4)	270 (8.5)
Missing, n (%)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
Small for gestational age, n (%)	171,642 (15.2)	6534 (14.8)	18,648 (19.2)	3869 (17.2)	1920 (19.8)	2294 (24.8)	2093 (23.9)	1224 (16.9)	893 (17.1)
Missing, n (%)	8485 (0.75)	751 (1.7)	1356 (1.4)	196 (0.9)	106 (1.1)	91 (1.0)	149 (1.7)	117 (1.6)	90 (1.7)
Maternal age, mean (sd)	29.0 (4.8)	29.5 (5.3)	27.9 (5.6)	25.9 (5.1)	26.4 (5.3)	27.6 (5.3)	29.2 (5.4)	28.5 (5.4)	26.3 (5.5)
Missing, n (%)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
Smoking in pregnancy[b], n (%)	201,206 (23.0)	5922 (17.0)	7087 (8.6)	3370 (20.3)	1146 (12.6)	113 (1.8)	223 (2.6)	199 (2.8)	928 (24.4)
Missing, n (%)	38,692 (4.4)	1971 (5.6)	4501 (5.5)	841 (5.1)	487 (5.3)	352 (5.7)	566 (6.5)	334 (4.7)	237 (6.2)
Basic educational level, n (%)	263,084 (23.2)	5773 (13.1)	34,840 (35.8)	11,039 (49.2)	4209 (43.5)	3204 (34.7)	3236 (36.9)	2378 (32.83)	1760 (33.7)
Missing, n (%)	6693 (0.6)	9780 (22.1)	22,095 (22.7)	6391 (28.5)	1184 (12.2)	2611 (28.3)	1838 (21.0)	1378 (19.0)	1126 (21.6)
0–25% household income percentile, n (%)	252,458 (22.3)	15,925 (36.1)	55,749 (57.3)	11,514 (51.3)	6994 (72.3)	5702 (61.7)	7113 (81.1)	5378 (74.3)	2505 (47.9)
Missing, n (%)	2732 (0.24)	2869 (6.5)	4771 (4.9)	688 (3.1)	286 (3.0)	425 (4.6)	428 (4.9)	434 (6.0)	304 (5.8)

Abbreviations: n, number of children. gw, gestational week. sd, standard deviation.

[a] Information on congenital malformations is available for children born in 1994 and onwards.

[b] Information on smoking is available for children born in 1991 and onwards.

overall, and 0.8 per 1000 and 1.1 per 1000 for unilateral and bilateral spastic subtypes, respectively (Table 2). No difference in the risk of CP overall was observed, but children of immigrants from Western and Non-Western countries had 40% and 20% reduced risk of unilateral spastic CP, respectively, compared with children of Danish-born mothers; OR = 0.59 (95% CI: 0.38–0.91) and OR = 0.79 (95% CI: 0.61–1.03). By contrast, the risk of bilateral spastic CP was higher in children of immigrants from Non-Western countries compared with children of Danish-born mothers; OR = 1.27 (95% CI: 1.05–1.53). This seemed mainly to be driven by an increased risk of bilateral spastic CP in children of Turkish and Pakistani immigrants who both had 70% higher risk than the Danish-born group (OR = 1.70 (95% CI: 1.23–2.35) and OR = 1.67 (95% CI: 0.97–2.87), Table 2). The unadjusted estimates did not differ from the estimates adjusted for birth year. Furthermore, children with bilateral spastic CP were more functionally disabled if their mothers had a Non-Western origin than a Danish origin (Fig. 1).

The increased risk of bilateral spastic CP in children of Non-Western immigrants, including immigrants from Turkey and Pakistan, was restricted to children born to mothers with intermediate or higher educational level (p-values for effect modification on both scales ≤0.02). The risk of bilateral spastic CP by maternal country of origin did not differ across maternal age groups, smoking status, or income groups (Appendix A, Table A.2).

3.3. *The association between maternal immigrant status and bilateral spastic cerebral palsy mediated through socioeconomic status*

Only children of mothers with Danish and Non-Western origin with complete information on socioeconomic measures were included in the mediation analyses (N = 1,200,984). We included an interaction term for maternal immigrant status and educational level in the working model when assessing maternal educational level as mediator. The ORs for the natural indirect effects were all almost one indicating that the mediating effect of household income or maternal educational level of the association between immigrant status and bilateral spastic CP was negligible (Table 3). As an example, The proportion of the total risk of CP among children of immigrant mothers explained by the socioeconomic pathway was 5% (4 divided by 87).

3.4. *Sensitivity analyses*

A higher proportion of immigrants than Danish-born mothers had missing values on socioeconomic measures (22.8% vs. 0.6%) and were excluded in the stratified and mediation analyses. Changing the categorization of socioeconomic measures did not affect our findings in respect to effect modification (results not shown). However, only using household income the year before child's birth in the mediation analysis attenuated the direct effect on bilateral spastic CP (Appendix, Table A.3), while other changes in categorization of socioeconomic variables had no impact on the direct and indirect effects (Appendix, Table A.4–6).

Table 2 – Prevalence and odds ratio of cerebral palsy according to maternal immigrant status.

Mother's country of origin	N	All CP n = 2807		Unilateral spastic CP n = 939		Bilateral spastic CP n = 1469	
		Per 1000 live births (n)	OR[a] (95% CI)	Per 1000 live births (n)	OR[a] (95% CI)	Per 1000 live births (n)	OR[a] (95% CI)
Denmark	1,133,071	2.2 (2505)	1 (ref.)	0.8 (859)	1 (ref.)	1.1 (1290)	1 (ref.)
Western	44,171	1.9 (84)	0.87 (0.70–1.09)	0.5 (20)	0.59 (0.38–0.91)	1.0 (46)	0.94 (0.70–1.26)
Non-Western	97,374	2.2 (218)	1.04 (0.90–1.20)	0.6 (60)	0.79 (0.61–1.03)	1.4 (133)	1.27 (1.05–1.53)
Turkey	22,436	2.8 (63)	1.25 (0.95–1.63)	0.4 (10)	0.60 (0.32–1.12)	2.0 (45)	1.70 (1.23–2.35)
Lebanon	9680	1.7 (18)	0.83 (0.51–1.33)	0.7 (7)	0.92 (0.44–1.93)	0.9 (9)	0.90 (0.46–1.73)
Pakistan	9239	3.2 (30)	1.42 (0.94–2.15)	0.8 (7)	1.04 (0.50–2.20)	2.1 (19)	1.67 (0.97–2.87)
Somalia	8766	2.6 (23)	1.29 (0.84–1.97)	1.1 (10)	1.38 (0.74–2.58)	1.5 (12)	1.46 (0.79–2.70)
Iraq	7243	2.2 (16)	1.09 (0.67–1.79)	0.8 (6)	0.99 (0.44–2.22)	1.4 (10)	1.50 (0.80–2.79)
Former Yugoslavia	5225	2.5 (13)	1.10 (0.64–1.90)	0.8 (4)	1.04 (0.39–2.77)	1.5 (8)	1.29 (0.64–2.58)

Abbreviations: CP, cerebral palsy. n, number of children. OR, odds ratio. 95% CI, 95% confidence interval.
[a] Multiple logistic regression adjusted for child's birth year.

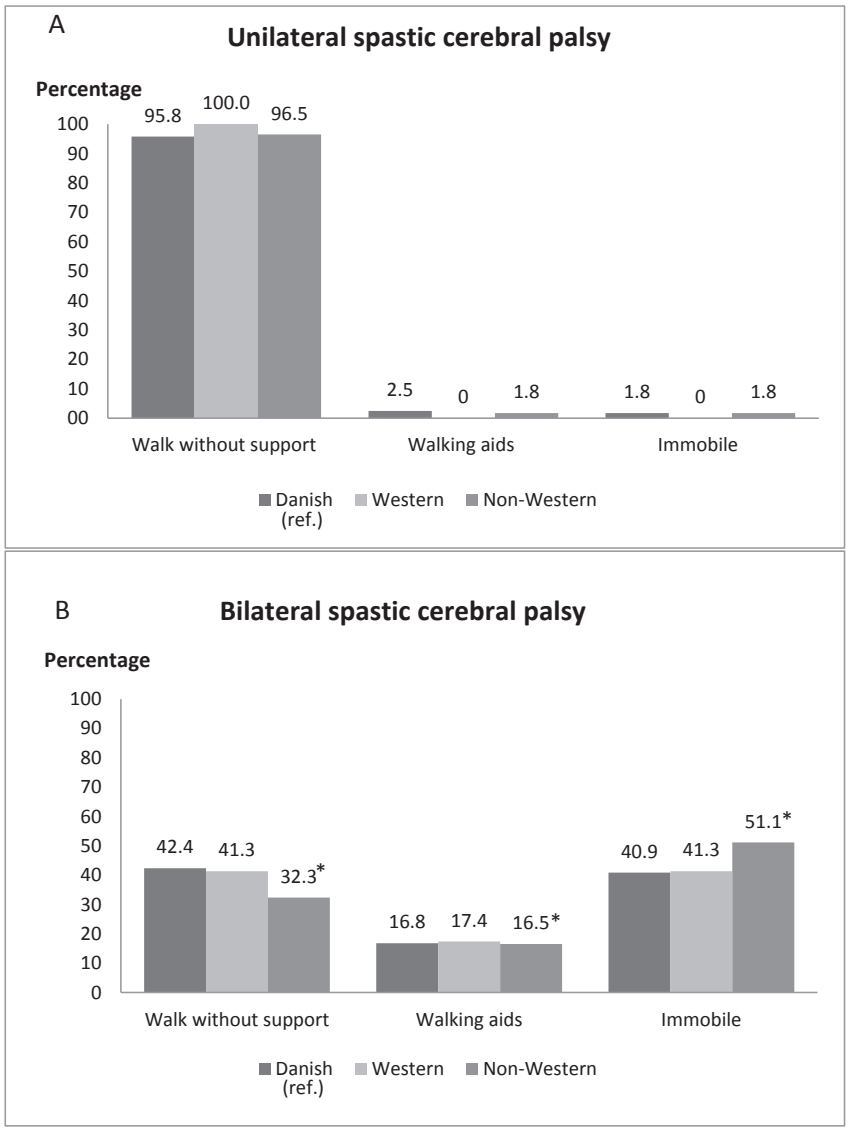

Fig. 1 – Distribution of motor function in children with unilateral (A) and bilateral (B) spastic cerebral palsy. *Among bilateral spastic CP, statistically significant differences in motor function in children of Non-Western immigrants compared with children of Danish-born mothers (p = 0.03).

Table 3 – Natural direct, natural indirect and total effects of maternal immigrant status on bilateral spastic cerebral palsy.

Potential mediators	Natural direct effect OR[a] (95% CI)	Natural indirect effect OR[a] (95% CI)	Total effect OR[a] (95% CI)
Immigrants from Non-Western countries (n = 75,214) vs. Danish-born (n = 1,125,770)			
Household income	1.19 (0.97–1.47)	1.11 (0.71–1.72)	1.32 (1.07–1.61)
Maternal educational level[b]	1.39 (1.12–1.72)	0.99 (0.94–1.05)	1.38 (1.13–1.68)
Maternal educational level[b] and household income	1.29 (1.04–1.61)	1.06 (0.99–1.14)	1.38 (1.13–1.67)
Immigrants from Turkey and Pakistan (n = 22,656) vs. Danish-born (n = 1,125,770)			
Household income	1.62 (1.19–2.20)	1.04 (1.02–1.07)	1.69 (1.25–2.30)
Maternal educational level[b]	1.94 (1.31–2.85)	0.97 (0.84–1.12)	1.88 (1.38–2.55)
Maternal educational level[b] and household income	1.80 (1.23–2.62)	1.04 (0.89–1.20)	1.87 (1.39–2.51)

Abbreviations: OR, odds ratio. 95% CI, 95% confidence interval.
[a] Mediation analysis using the imputation-based approach. Multiple logistic regression adjusted for child's birth year.
[b] Interaction-term between maternal country of origin and educational level is included in the model.

4. Discussion

4.1. Main findings

Children of immigrants from Western and Non-Western countries had a lower risk of unilateral spastic CP compared with children of Danish native-born, but the risk of bilateral spastic CP was higher in children of Non-Western immigrants, particularly those who emigrated from Turkey and Pakistan. Our mediation analysis suggested that the socioeconomic inequality pathway did not contribute to the higher risk of bilateral spastic CP among the children of Non-Western immigrants.

4.2. Comparison with other studies and interpretation of findings

A Canadian study found that immigrants had an overall lower risk of having a child with CP compared with native-born. However, the ethnic composition in Canada is quite different from Denmark, and in analyses including the largest immigrant groups in Denmark (immigrants from the Middle-East, South-East, and Africa) no differences in CP risk were observed when compared to the Canadian native-born group.[20] In contrast, studies from Sweden and the United Kingdom found higher prevalence of CP overall in immigrants or descendant of immigrants than in native-born populations.[19,21,23] In addition, the functional limitations of CP appeared to be more severe in immigrant children compared with native-born children in Sweden.[23] Consistent with our findings, a study from the United Kingdom showed that Pakistani immigrants and descendants had a lower prevalence of unilateral spastic CP than other ethnic groups, including native-born. Moreover, the Pakistanis group tended to have a higher prevalence of bilateral spastic CP, although the estimate for the difference was statistically imprecise, presumably due to low statistical power.[21]

The opposite findings regarding the risk of unilateral and bilateral spastic CP indicate that the CP subtypes to a large extent have distinct etiological profiles, which also has been indicated in other studies.[40–42] Furthermore, different causal mechanisms may be in play for children of immigrants and Danish-born mothers. Although there is considerable uncertainty about the etiology of CP, it is well-recognized that multiple factors, operating in the pre- and perinatal periods, cause CP.[7,43] Prenatal factors appear to play the greatest role in children with CP born at term, of which most have unilateral spastic CP.[40,44] Therefore, it can be speculated the reduced risk of unilateral spastic CP among children of immigrants is attributable to lifestyle factors in pregnancy. However, our finding in respect of smoking during pregnancy, which is associated with increased risk of CP,[45] did not support this, because immigrants from Turkey smoked as often as Danish-born mothers, and children of Turkish immigrants had the lowest risk of unilateral spastic CP.

Various risk factors for CP, such as diabetes,[46] obesity,[47] preeclampsia, uterine rupture,[47] and birth complications[48] tend to cluster in some immigrant groups and are socioeconomically skewed.[32] We found that socioeconomic status is not a significant contributor to the increased risk of bilateral spastic CP in children of Non-Western immigrants. In agreement with this, two large population-based studies from the United States found that the increased risk of CP in blacks persisted after adjustment for maternal education or insurance status.[17,24] However, these studies did not distinguish between CP subtypes, and it is not straightforward to generalize the findings from the United States to a Danish setting.

It is suggested that many ethnic minority groups experience institutional discrimination which may contribute to ethnic disparities in various health outcomes.[27,49] In Scandinavia, health care is free of charge, and all residents have, in principle, equal access to health care. Nevertheless, studies from Scandinavia have shown that pregnant and delivering immigrant women are at a higher risk of receiving suboptimal health care due to linguistic, social and cultural barriers, which lead to increased risk of perinatal and maternal death.[48,50,51] Therefore, it is possible that suboptimal prenatal and obstetric care for immigrants also will increase the risk of pregnancy and birth complications that contribute to the increased risk of bilateral spastic CP.

Children born to consanguineous parents i.e., blood related parents, are at higher risk of autosomal recessive disorders.[4] Studies have linked consanguinity with increased risk of CP[10–12] and suggested an autosomal recessive genetic origin of spastic bilateral CP.[13,52,53] Unfortunately, consanguinity has not been registered systematically in Denmark until recently. However, data from Norway have shown that consanguineous parenthood is commonly practiced in immigrants from Pakistan and Turkey with a prevalence of 47% and 23% in 1967–2005,[8] though the prevalence was decreasing over time.[9] A Danish register-based study supports that children of immigrants from Turkey and Pakistan, in particular, have a high risk of consanguinity related diseases.[2] Nevertheless, before we can draw any conclusions on whether consanguinity might explain the high risk of bilateral spastic CP in children of Pakistani and Turkish immigrants, we need large studies linking information on consanguineous parenthood with CP.

4.3. Methodological considerations

A major strength of this study was the large population-based cohort with data from national registries, including CP diagnoses validated by neuropediatricians with phenotypic subtypes of CP. We used country of origin derived from administrative registers, which in general are considered to be of high quality. Even though we assessed specific nationalities, country of origin remains a crude measure of ethnicity that combines heterogenic groups.[54] We studied both education and income as they capture different but related aspects of socioeconomic status, which may affect health differently.[54] However, we should be aware that these measures do not necessarily have a uniform meaning and effect on different ethnic groups.[54] Also, the data quality of socioeconomic status may vary according to immigrant status, e.g., poor registration of education attained before migration to Denmark may account for the great number of missing values in immigrants.[55] About 4% of the immigrants had no recorded income the year before the child's birth because they immigrated the same year as the child was born. A sensitivity

analysis suggested that the direct effect would have been biased towards the null if the categorization exclusively had been based on income the year prior to the child's birth.

The Danish National Cerebral Palsy Registry is assessed as almost complete for the study population since the Danish National Patient Register was used to identify additional cases not submitted to the CP register from pediatric departments.[28,29] However, barriers for immigrants, such as language, in the health care system[48,50] may result in the mildest CP cases being overlooked and not recorded in any health register. This could possibly contribute to the lower risk of unilateral spastic CP we saw in children of immigrants. If the same is the case for socioeconomically disadvantaged groups, low case attainment may also contribute to an explanation of the effect modification showing an elevated risk of bilateral spastic CP in the well-educated immigrants, but not in immigrants with basic educational level. However, low case attainment can hardly explain the entire difference observed.

While ethnicity is not modifiable in itself and thus is not strictly conforming to the counterfactual setup, our mediation analyses can still be interpreted as follows: if an intervention could change the socioeconomic factors in, e.g., the Non-Western group to the levels found in the Danish-born group there would still be considerable ethnic disparities in CP risk (cf. the direct effect of Table 3).[56] From a clinical perspective, it could be argued that it is of more interest to investigate to what extent the ethnic disparities are mediated by factors such as small-for-gestational-age and preterm birth. However, this is not straightforward since stratifying or adjusting for these factors can induce major distortions due to collider stratification bias, because it is likely that small-for-gestational-age and preterm birth share pathological causes with CP.[57–59]

5. Conclusion

Findings from this large register-based study document ethnic disparities in the risk of CP in children born in Denmark during 1981–2007. Our findings showed children of immigrants from both Western and Non-Western countries had a lower risk of unilateral spastic CP, but children of immigrants from Non-Western Countries, and especially from Turkey and Pakistan, had a higher risk of bilateral spastic CP than children of Danish-born mothers. The increased risk of bilateral spastic CP did not appear to be mediated through socioeconomic status. However, before being able to set up interventions to reduce ethnic inequality in the risk of CP and other birth outcomes, more insights into the role of consanguinity, health behavior, and suboptimal prenatal and obstetric care for immigrants are needed.

Conflicts of interest

None.

Contributors' statements

Tanja Gram Petersen conceptualized and designed the study, carried out all analyses and takes responsibility for the integrity of the data and the accuracy of the data analyses, contributed substantially to interpretation of the work and drafted the manuscript.

Katrine Strandberg-Larsen conceptualized and designed the study, contributed substantially to interpretation of the work, and drafted the manuscript.

Ingeborg Forthun, Theis Lange, Sarah Fredsted Villadsen, Anne-Marie Nybo Andersen, and Peter Uldall conceptualized and designed the study, contributed substantially to interpretation of the work, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.01.007.

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