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Maternal education and language development at 2 years corrected age in children born very preterm: Results from a European population-based cohort study

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ABSTRACT

Background

Socioeconomic factors influence language development in the general population, but the association remains poorly documented in very preterm (VPT) children. We aimed to assess the impact of maternal education on language development in VPT children, and effect modification by degree of perinatal risk.

Methods

Data were from the European EPICE population-based cohort of children born <32 weeks' gestational age (GA) in 2011/2012. Regions from six countries (Estonia, France, Germany, Italy, Sweden and UK) used a validated short form MacArthur Developmental Communicative Inventories Checklist to assess language at 2-years corrected age (CA). Perinatal variables were collected from clinical records. Developmental language delay (DLD) was defined as a) not combining words; and b) expressive vocabulary <10th percentile of norms for CA and sex. Perinatal risk (low, moderate, high) was determined using GA, small for gestational age and severe neonatal morbidities. We used multivariable modified Poisson models to estimate adjusted risk ratios (aRR) of DLD by maternal education with inverse weighting to account for non-response bias.

Results

Of 2741 VPT children, 24.6% were not combining words and 39.7% had a low expressive vocabulary. Low maternal education increased risks of DLD. Effects were attenuated in the highest perinatal risk group: a) not combining words, aRR=1.88 (95% confidence interval 1.26-2.80) for low perinatal risk versus 1.36 (1.10-1.67) for high perinatal risk; and b) low expressive vocabulary, aRR=1.44 (1.06-1.95) and 1.11 (0.97-1.27) respectively.

Conclusion

Low maternal education affects DLD for all VPT children, although the association appears attenuated among those with highest perinatal risk.

What is already known on this subject?

- Very preterm birth is associated with adverse neurodevelopmental outcomes in childhood, including poor language functioning
- Early language development is influenced by the family social environment, but research has been conducted principally in the general population.

What this study adds?

- In very preterm children, higher perinatal risk and lower maternal educational levels are both associated with DLD at 2 years corrected age, although the effect of maternal education may be stronger for children with lower perinatal risk.
- Very preterm children with mothers who have a low educational level have the highest rates of DLD, illustrating the need to incorporate clinical and social factors to identify children in need of services.

BACKGROUND

Very preterm (VPT) births (< 32 weeks' gestation) represent about 1% of all births or an estimated 50,000 of the 5 million births per year in Europe.¹ Considerable medical advances over recent decades in the fields of obstetrics and neonatology have improved the survival of these children and the number of survivors increases each year. There is a large body of literature investigating the risks of short and long term developmental difficulties for children born VPT, including sensory impairment, neurodevelopmental delays and impaired cognitive, behavioral, motor, and emotional functioning.²⁻³ Such difficulties extend into adulthood and affect long-term health, occupational attainment, family formation and wealth.⁴ In addition, there are multiple studies showing that growing up in a socially disadvantaged environment impacts the child's neurodevelopment in various domains.⁵ As mothers with lower socioeconomic status have a higher incidence of VPT birth, a greater vulnerability to its consequences may exacerbate the social costs of VPT birth and perpetuate the transmission of health inequalities across generations.

Language is a pivotal function, important for developing social relationships and achieving academic success. Some authors have hypothesized that language exposure in early infancy, in terms of vocabulary quantity and quality, is particularly important because it mediates the relationship between the family socioeconomic environment and neurodevelopment in childhood.⁶ There is evidence that language functioning is reduced in school-aged children born VPT compared to term controls.⁷⁻⁹ Children born VPT experience more delays in language development in early childhood than children born at term, assessed through their lexicon size and word combination around 2 years of age.¹⁰⁻¹¹ While there is a solid evidence linking language development to the social environment in the general population, the relationship between the family's socioeconomic background and language development remains poorly documented in the VPT population as studies have been conducted on small and selective samples (i.e. monolingual singletons without severe conditions recruited from a single center study).¹¹⁻¹³

To identify children at risk of delays in language development who would benefit from preventive interventions, more knowledge is needed about the association of social factors with language development among VPT children and whether social factors have a similar impact when well-known clinical risk factors predicting language delay,¹⁴ such as lower gestational

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3 age and severe neonatal morbidities, are present. Our objective was to investigate the
4 association of the family's socioeconomic background, as measured by maternal educational
5 achievement, with expressive language development at 2 years of corrected age (CA) by degree
6 of perinatal risk, in children born VPT in 13 regions of 6 European countries.
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10 **METHODS**

11 **Study design and population**

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14 We used data from the Effective Perinatal Intensive Care in Europe (EPICE) cohort, a
15 population-based, prospective cohort study of children born from 22+0 weeks to 31+6 weeks
16 of gestation in 2011/2012 in 19 regions in 11 European countries.¹⁵ Data were abstracted from
17 obstetrical and neonatal records using a common protocol based on standardised definitions and
18 the children were followed up at 2 years of CA using a parent-report questionnaire.
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25 For this study, we included regions from the 6 countries that had validated instruments in
26 national languages of the short-form MacArthur Developmental Communicative Inventories
27 Checklist (MCDI-SF): Estonia (entire country); France (Burgundy, Ile-de-France and the
28 Northern regions), Germany (Hesse and Saarland); Italy (Emilia-Romagna, Lazio and Marche
29 regions), Sweden (Stockholm County) and the UK (East Midlands, Northern and Yorkshire and
30 the Humber regions). Only children for whom the national language was the main language
31 spoken by the child or at home, either alone or in association with a second language were
32 included in our analysis. Children with difficulties hearing with aids were also excluded. Out
33 of the 5363 live births included in the cohort in these 6 countries, 4638 (87%) were alive at 2
34 years CA and 3101 (67%) participated in the follow up study (see **Figure S1** for the complete
35 flowchart). Our final study sample consisted of 2741 children.
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44 Ethical approvals were obtained in each country as required by national legislation. The
45 European study was also approved by the French Advisory Committee on Use of Health Data
46 in Medical Research and the French National Commission for Data Protection and Liberties.
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54 **Measures**

57 *Developmental language delay*

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3 Information on language development was collected from the parental questionnaire at 2 years
4 CA. Two dichotomous indicators of developmental language delay (DLD), absence of
5 combining words and low expressive vocabulary,¹⁶ were derived from the adapted versions in
6 national languages of the short-form MCDI-SF. The first indicator of DLD ('not combining
7 words') was defined according to the answer to a single item ("Has your child started to put
8 together words yet, such as "Daddy gone" or "Doggie bite"? with responses coded as: not yet
9 combining words vs often/sometimes). The second indicator ('low expressive vocabulary') was
10 derived from the assessment of vocabulary production (100-word checklist) providing a sub-
11 score ranging from 0-100 based on the number of words the child could say. Using normative
12 data by age and sex,¹⁷ children were classified as having DLD when their vocabulary score was
13 under the 10th percentile (corresponding to 26 and 39 words for boys and girls, respectively, at
14 24 months).¹⁶

25 *Maternal educational level*

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27 The highest level of education achieved by the mother was collected at the 2 year follow up.
28 The International Standard Classification of Education¹⁸ was used, and respondents were then
29 classified into one of nine streams: (0) early childhood education, (1) primary, (2) lower
30 secondary, (3) upper secondary, (4) post-secondary non-tertiary, (5) short cycle tertiary, (6)
31 bachelor degree or equivalent, (7) master degree or equivalent, and (8) doctoral degree or
32 equivalent. To take into account cross-national differences in educational systems, these nine
33 levels were grouped into three categories: (1) low (ISCED 0-2), (2) medium (ISCED 3-5), and
34 (3) high (ISCED 6-8). In cases where the child did not live with the mother and she did not
35 reply to the questionnaire, the guardian's educational level was collected (n=12).

44 *Perinatal risk*

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46 A composite variable was derived from perinatal characteristics to represent three levels of
47 perinatal risk, as defined previously for the cohort¹⁹. High risk was defined as at least one of
48 the following criteria: GA<28 weeks, severe neonatal morbidity (bronchopulmonary dysplasia,
49 defined as need for supplemental oxygen or ventilation at 36 weeks' postmenstrual age,
50 retinopathy of prematurity stages III-V diagnosed before discharge, intraventricular
51 haemorrhage III or IV, cystic periventricular leukomalacia, or necrotising enterocolitis needing
52 surgery), and severe congenital anomaly.²⁰ Low risk included children born at 30-31 weeks GA
53 with no severe morbidity, no congenital anomaly and a birthweight over the 10th percentile for
54 gestational age using intrauterine curves.²¹ All other children were considered moderate risk
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(i.e. not in the high risk group at 28-29 weeks' GA or at 30-31 weeks' GA with birthweight <10th percentile and/or a non-severe congenital anomaly).

Other covariates

The following potential confounders were considered in our analysis: maternal age at birth (<35 vs ≥ 35 year-olds), number of previous births (i.e. parity), whether the mother was foreign born (yes/no),²² the child's CA at assessment (<21 months, 22-26 months, ≥ 27 months), sex, multiple birth (twin or more) and bilingualism. Additional variables were used to describe the sample. The proportions of missing data are provided in **Table S1**; these were low for most variables (<2%) with the highest being 4.5% for mother's country of birth.

Statistical analyses

We compared responders to non-responders at the 2-year follow-up using logistic regression models adjusted for country. Proportions of perinatal and sociodemographic characteristics in the study sample were compared by maternal educational level by performing Wald tests adjusted for country. The prevalence of DLD was estimated for both criteria, overall and stratified by level of maternal educational and perinatal risk. For both DLD indicators, we estimated risk ratios (RRs) for DLD for maternal education level overall and stratified by perinatal risk (low, moderate, high) by performing modified Poisson regression models with a log link and a robust variance estimator²³. Multilevel mixed-effects generalized linear models with random intercepts at the country and the mother levels were included to account for the correlation within countries and twins or higher order births, respectively. Models were adjusted for age at assessment, maternal age, child sex, parity, multiple births, bilingualism, and mother's country of birth. We tested for the presence of multiplicative interactions between maternal education levels and perinatal risk groups for both outcomes by adding a product term to the models. The presence of an interaction was suggested by a P-value <0.10 for at least one of interaction coefficient.

The effects of potential bias due to selective attrition were accounted for using inverse probability weighting (IPW)²⁴ in all analyses. Weights were derived from a logistic regression as the probability of response at 2 years CA derived from relevant sociodemographic and perinatal characteristics.²⁴ Each responder was weighted by the inverse of this probability. Missing data on covariates were first imputed using multiple imputation by chained equations (5 complete datasets generated). All analyses were performed using Stata version 15.0

(StataCorp, College Station, TX, USA), and the LINCOM command was used to compute effect sizes stratified for each level of perinatal risk.

RESULTS

Baseline characteristics by follow-up status are provided in **Table 1**. Non-responders were more likely to have younger mothers, foreign mothers and mothers with a previous birth. They were also more likely to be singleton and have bronchopulmonary dysplasia.

Information on maternal educational level was available for 96.5% (n=2645) of the unweighted sample. Overall, 18.8% of mothers had a lower secondary level of education and 33.9% had completed a postgraduate degree or higher. **Table 2** shows maternal and child characteristics among participants by maternal educational attainment.

In our cohort at 2 years CA, 24.6% (95% confidence interval (CI) 22.8-26.5) of children were not combining words, 39.7% (95%CI 37.6-41.9) had a low expressive vocabulary, and 41.9% (95%CI 39.9-44.0) were not combining words or had low expressive vocabulary. Prevalence of DLD by maternal educational level and by perinatal risk are shown in **Figure 1** and **Table 3**. Children of mothers with low education were more likely to experience DLD at 2 years than other children, based on both DLD criteria (**Figure 1a**): 30.0% of children were not combining words when the mother had a low educational level compared to 21.8% when the mother had high educational level; these proportions were 46.0% and 34.4% for low expressive vocabulary, respectively. DLD was also more prevalent in the highest perinatal risk group for both indicators (not combining words: 29.4%; low expressive vocabulary: 48.1%) compared to the low risk group (18.0% and 34.0%, respectively) (**Figure 1b**).

The distribution of DLD stratified by level of perinatal risk and maternal education is given in **Table 3**. The highest percentage of DLD was reported for children in the high-risk group who had mothers with low education (not combining words: 36.4%; low expressive vocabulary: 52.8%). After adjustment for potential confounding factors (**Table 3**), a low versus a high maternal educational level was related to an elevated risk of DLD for both criteria. There was evidence for multiplicative interaction between maternal education and perinatal risk only for low expressive vocabulary, although estimates of risk were higher for children with low versus high perinatal risk for both DLD criteria. The risk for not combining words for children who

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3 had mothers with low education, compared to those with mothers with high education, was 1.88
4 (95%CI 1.26-2.80) for low perinatal risk, versus RR=1.36 (95%CI 1.10-1.67) for high perinatal
5 risk (p-value for the interaction term 'high risk x low education'=0.252). Similarly, for low
6 expressive vocabulary, RR was 1.44 (95%CI 1.06-1.95) for children with low perinatal risk
7 compared to RR=1.11 (95%CI 0.97-1.27) for children with high perinatal risk (p-value for the
8 interaction term 'high risk x low education' and for low expressive vocabulary=0.056).
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13 14 15 **DISCUSSION**

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18 We used a large population-based cohort of children born very preterm in Europe to investigate
19 delay in expressive language development at 2 years CA in relation to the mother's educational
20 level. We found that almost 42% of children born VPT were classified as having DLD in our
21 study sample with regard to the ability to combine words or their expressive vocabulary. A
22 higher risk of DLD was observed among children whose mothers had low educational levels,
23 corresponding to lower secondary schooling or less, compared to those whose mothers had high
24 educational levels, defined as a bachelor degree or more. DLD was more prevalent among
25 children with higher perinatal risk; maternal educational level affected DLD across all degrees
26 of perinatal risk, but the effect appeared to be attenuated among children at higher risk.
27 Nonetheless, children with high perinatal risk and mothers with a high educational level had
28 similar levels of DLD as children with low perinatal risk and mothers with a low educational
29 level.
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41 Our findings confirm previous research showing that children born VPT experience delays in
42 early language acquisition. About one quarter of children were not combining words around 2
43 years CA and almost 40% had a low expressive vocabulary, which is consistent with previous
44 findings. According to the lexicon size criteria, 24.1% of Italian children born ≤ 33 weeks²⁵ and
45 29.4% of French children born ≤ 34 weeks (EPIPAGE 2 study)¹⁰ were classified under the 10th
46 percentile of the adapted MCDI-SF based on national normative values, while an absence of
47 word combination was 21.6%.¹⁰ Consistent with previous studies,^{8 10 26} we also found an
48 increasing risk for DLD among children with higher perinatal risk, defined in our study as lower
49 GA and/or severe neonatal morbidity. Compared to children born at term, children born VPT
50 are at higher risk for atypical brain development, and developmental impairments in various
51 domains.^{2 3 27} Aggravating factors may be linked to the unnatural sensory environment during
52 the third trimester of pregnancy when language acquisition begins through exposure to
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3 receptive language;^{28 29} the neonatal unit provides less exposure to parental voices and
4 interactions and has elevated levels of other noises.
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8 Maternal educational level had an independent impact on language delay for the VPT children
9 in our study, corroborating previous research.^{12 26 30} The family and social environment of the
10 child in his or her early years has been shown to be crucial for language acquisition and
11 vocabulary development at 2-3 years of age,²² with an increasing effect in early adolescence,¹²
12 but our understanding of the causal pathways remains limited. The home literacy environment,
13 including the availability of books in the home and the time spent reading or sharing picture
14 books daily or engaging in informal play opportunities, has been related to early language
15 skills.^{31 32} Parenting stress and involvement could be a further explanation for social inequalities
16 in language acquisition among children born very preterm.²⁶ Being in a low-income household
17 has been associated atypical brain development in childhood,³³ and financial resources mediate
18 the relationship between maternal education and children's vocabulary size.³⁴ Finally, the type
19 of childcare has been linked to the extent and diversity of vocabulary in early childhood, with
20 consistent findings that care in daycare centers protects against late language acquisition
21 compared to family-based care.^{31 34 35}
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34 Our study produced novel results showing a stronger association between maternal educational
35 level and DLD when perinatal risk was lower. Previous studies exploring the interaction
36 between perinatal risk and social factors have focused on other cognitive outcomes or different
37 populations and produced contradictory results. One study found no interaction with gestational
38 age, although it was not focused only on children born very preterm;²² another found the highest
39 probability of language problems among children with lower GA from the most deprived
40 areas.³⁰ Finally, one study³⁶ found that the association with higher maternal educational level
41 and better cognitive outcomes at 3 to 4.5 years in VPT children increased in the presence of
42 brain injury. Differences in the study populations and risk groups may explain these discordant
43 results. It is important to explore interactions between clinical and social risks in future research
44 as health professionals caring for VPT children need to understand how they interact in order
45 to provide follow-up care and early interventions adapted to risk levels.
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57 The major strength of this study is the use of a large population-based, prospective cohort study
58 of children born VPT in Europe, as well as the use of two different indicators based on common
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3 criteria used in the general population to define DLD.¹⁶ Our study also has some limitations.
4 First, 65% of eligible children were included in the follow-up study and loss to follow-up was
5 more common for children with younger and migrant mothers. We used inverse weighting
6 techniques to adjust for potential bias using data at baseline, but we were not able to fully
7 control for socioeconomic status because this information was not available at birth.
8 Associations with maternal education were strengthened after considering bias due to attrition,
9 suggesting that any remaining bias may be attenuating true effects. We also excluded 353
10 children for whom the main language spoken by the child or at home was different from the
11 national language and our results cannot be generalized to these children. We used common
12 norms to identify children with a low expressive vocabulary because local norms were not
13 available for our age group in all participating countries. We assessed language at two years
14 and delayed language development may not be abnormal at a later time point. However, a recent
15 report shows that DLD, in particular in children born VPT, is stable over childhood.³⁷ Finally,
16 although the ISCED/UNESCO classification¹⁸ aims to standardize educational levels,
17 educational systems differ across countries. To address this limitation, we used a classification
18 adopted in previous European studies of maternal education and perinatal outcome and included
19 country as a random effect.^{38 39}

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35 Both social disadvantage and perinatal risk factors were strong predictors of DLD in early
36 childhood in a large population-based study of children born VPT in Europe. Early
37 interventions for language delay that integrate social and clinical risks may be one strategy for
38 mitigating the longer term consequences of preterm birth. Future research is needed to clarify
39 potential interactions between maternal education and perinatal risks.
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REFERENCES

1. Euro Peristat Project. Euro-Peristat Project. European Perinatal Health Report. Core indicators of the health and care of pregnant women and babies in Europe in 2015 November 2018 [updated 2018. Available from: Available www.europeristat.com.
2. Allotey J, Zamora J, Cheong-See F, et al. Cognitive, motor, behavioural and academic performances of children born preterm: a meta-analysis and systematic review involving 64 061 children. *BJOG : an international journal of obstetrics and gynaecology* 2018;125(1):16-25. doi: 10.1111/1471-0528.14832 [published Online First: 2017/10/13]
3. Twilhaar E, Wade RM, de Kieviet JF, et al. Cognitive outcomes of children born extremely or very preterm since the 1990s and associated risk factors: A meta-analysis and meta-regression. *JAMA pediatrics* 2018;172(4):361-67. doi: 10.1001/jamapediatrics.2017.5323
4. Bilgin A, Mendonca M, Wolke D. Preterm Birth/Low Birth Weight and Markers Reflective of Wealth in Adulthood: A Meta-analysis. *Pediatrics* 2018;142(1) doi: 10.1542/peds.2017-3625 [published Online First: 2018/06/08]
5. Patra K, Greene MM, Patel AL, et al. Maternal Education Level Predicts Cognitive, Language, and Motor Outcome in Preterm Infants in the Second Year of Life. *American journal of perinatology* 2016;33(8):738-44. doi: 10.1055/s-0036-1572532 [published Online First: 2016/02/19]
6. Gilkerson J, Richards JA, Warren SF, et al. Language Experience in the Second Year of Life and Language Outcomes in Late Childhood. *Pediatrics* 2018;142(4) doi: 10.1542/peds.2017-4276 [published Online First: 2018/09/12]
7. Nguyen TN, Spencer-Smith M, Haebich KM, et al. Language Trajectories of Children Born Very Preterm and Full Term from Early to Late Childhood. *The Journal of pediatrics* 2018;202:86-91.e1. doi: 10.1016/j.jpeds.2018.06.036 [published Online First: 2018/07/29]
8. Sanchez K, Spittle AJ, Cheong JL, et al. Language in 2-year-old children born preterm and term: a cohort study. *Archives of disease in childhood* 2019;104(7):647-52. doi: 10.1136/archdischild-2018-315843 [published Online First: 2018/11/25]
9. van Noort-van der Spek IL, Franken MC, Weisglas-Kuperus N. Language functions in preterm-born children: a systematic review and meta-analysis. *Pediatrics* 2012;129(4):745-54. doi: 10.1542/peds.2011-1728 [published Online First: 2012/03/21]
10. Charkaluk ML, Rousseau J, Benhammou V, et al. Association of Language Skills with Other Developmental Domains in Extremely, Very, and Moderately Preterm Children: EPIPAGE 2 Cohort Study. *The Journal of pediatrics* 2019;208:114-20.e5. doi: 10.1016/j.jpeds.2018.12.007 [published Online First: 2019/03/19]
11. Sansavini A, Guarini A, Savini S, et al. Longitudinal trajectories of gestural and linguistic abilities in very preterm infants in the second year of life. *Neuropsychologia* 2011;49(13):3677-88. doi: 10.1016/j.neuropsychologia.2011.09.023 [published Online First: 2011/10/01]
12. Nguyen TN, Spencer-Smith M, Pascoe L, et al. Language Skills in Children Born Preterm (<30 Wks' Gestation) Throughout Childhood: Associations With Biological and Socioenvironmental Factors. *Journal of developmental and behavioral pediatrics : JDBP* 2019 doi: 10.1097/dbp.0000000000000742 [published Online First: 2019/10/16]
13. Stolt S, Savini S, Guarini A, et al. Does the native language influence lexical composition in very preterm children at the age of two years? A cross-linguistic comparison study of

- 1
2
3 Italian and Finnish children. *First Language* 2017;37(4):368-90. doi:
4 10.1177/0142723717698006
- 5
6 14. Marston L, Peacock JL, Calvert SA, et al. Factors affecting vocabulary acquisition at age 2
7 in children born between 23 and 28 weeks' gestation. *Developmental medicine and child*
8 *neurology* 2007;49(8):591-6. doi: 10.1111/j.1469-8749.2007.00591.x [published
9 Online First: 2007/07/20]
- 10
11 15. Zeitlin J, Maier RF, Cuttini M, et al. Cohort profile: EPICE (Effective Perinatal Intensive
12 Care in Europe) very preterm birth cohort *International Journal of*
13 *Epidemiology*;Accepted
- 14
15 16. Singleton NC. Late talkers: Why the wait-and-see approach is outdated. *Pediatric Clinics*
16 2018;65(1):13-29.
- 17
18 17. Fenson L, Pethick S, Renda C, et al. Short-form versions of the MacArthur communicative
19 development inventories. *Applied Psycholinguistics* 2000;21(1):95-116.
- 20
21 18. UNESCO Institute for Statistics. International standard classification of education: ISCED
22 2011: UNESCO Institute for Statistics Montreal 2012.
- 23
24 19. Seppanen AV, Bodeau-Livinec F, Boyle EM, et al. Specialist health care services use in a
25 European cohort of infants born very preterm. *Developmental medicine and child*
26 *neurology* 2018 doi: 10.1111/dmcn.14112 [published Online First: 2018/12/07]
- 27
28 20. Draper ES, Manktelow BN, Cuttini M, et al. Variability in Very Preterm Stillbirth and In-
29 Hospital Mortality Across Europe. *Pediatrics* 2017;139(4) doi: 10.1542/peds.2016-
30 1990
- 31
32 21. Zeitlin J, Bonamy AE, Piedvache A, et al. Variation in term birthweight across European
33 countries affects the prevalence of small for gestational age among very preterm infants.
34 *Acta paediatrica* 2017;106(9):1447-55. doi: 10.1111/apa.13899 [published Online
35 First: 2017/05/05]
- 36
37 22. Beauregard JL, Drews-Botsch C, Sales JM, et al. Does Socioeconomic Status Modify the
38 Association Between Preterm Birth and Children's Early Cognitive Ability and
39 Kindergarten Academic Achievement in the United States? *American journal of*
40 *epidemiology* 2018;187(8):1704-13.
- 41
42 23. Zou G. A modified poisson regression approach to prospective studies with binary data.
43 *American journal of epidemiology* 2004;159(7):702-6. doi: 10.1093/aje/kwh090
44 [published Online First: 2004/03/23]
- 45
46 24. Bonnet C, Blondel B, Piedvache A, et al. Low breastfeeding continuation to 6 months for
47 very preterm infants: A European multiregional cohort study. *Maternal & child*
48 *nutrition* 2018;15(1):e12657. doi: 10.1111/mcn.12657 [published Online First:
49 2018/08/24]
- 50
51 25. Sansavini A, Guarini A, Justice LM, et al. Does preterm birth increase a child's risk for
52 language impairment? *Early human development* 2010;86(12):765-72. doi:
53 10.1016/j.earlhumdev.2010.08.014 [published Online First: 2010/09/18]
- 54
55 26. Lean RE, Paul RA, Smyser TA, et al. Social Adversity and Cognitive, Language, and Motor
56 Development of Very Preterm Children from 2 to 5 Years of Age. *The Journal of*
57 *pediatrics* 2018 doi: 10.1016/j.jpeds.2018.07.110 [published Online First: 2018/09/25]
- 58
59 27. Brydges CR, Landes JK, Reid CL, et al. Cognitive outcomes in children and adolescents
60 born very preterm: a meta-analysis. *Developmental Medicine & Child Neurology*
2018;60(5):452-68. doi: 10.1111/dmcn.13685
28. Best K, Bogossian F, New K. Language Exposure of Preterm Infants in the Neonatal Unit:
A Systematic Review. *Neonatology* 2018;114(3):261-76. doi: 10.1159/000489600
[published Online First: 2018/07/06]
29. Pineda RG, Neil J, Dierker D, et al. Alterations in Brain Structure and Neurodevelopmental
Outcome in Preterm Infants Hospitalized in Different Neonatal Intensive Care Unit

- 1
2
3 Environments. *The Journal of pediatrics* 2014;164(1):52-60.e2. doi:
4 10.1016/j.jpeds.2013.08.047
- 5
6 30. Ene D, Der G, Fletcher-Watson S, et al. Associations of Socioeconomic Deprivation and
7 Preterm Birth With Speech, Language, and Communication Concerns Among Children
8 Aged 27 to 30 Months. *JAMA Netw Open* 2019;2(9):e1911027. doi:
9 10.1001/jamanetworkopen.2019.11027 [published Online First: 2019/09/12]
- 10
11 31. Collisson BA, Graham SA, Preston JL, et al. Risk and Protective Factors for Late Talking:
12 An Epidemiologic Investigation. *The Journal of pediatrics* 2016;172:168-74.e1. doi:
13 10.1016/j.jpeds.2016.02.020 [published Online First: 2016/03/13]
- 14
15 32. Hofslundsengen H, Gustafsson J-E, Hagtvet BE. Contributions of the Home Literacy
16 Environment and Underlying Language Skills to Preschool Invented Writing.
17 *Scandinavian Journal of Educational Research* 2019;63(5):653-69.
- 18
19 33. Hair NL, Hanson JL, Wolfe BL, et al. Association of child poverty, brain development, and
20 academic achievement. *JAMA pediatrics* 2015;169(9):822-29.
- 21
22 34. McNally S, McCrory C, Quigley J, et al. Decomposing the social gradient in children's
23 vocabulary skills at 3 years of age: A mediation analysis using data from a large
24 representative cohort study. *Infant Behavior and Development* 2019;57:101326. doi:
25 <https://doi.org/10.1016/j.infbeh.2019.04.008>
- 26
27 35. Grobon S, Panico L, A S. Inégalités socioéconomiques dans le développement langagier et
28 moteur des enfants à 2 ans. *Bull Epidémiol Hebd* 2019;1:2-9.
- 29
30 36. Benavente-Fernández I, Synnes A, Grunau RE, et al. Association of Socioeconomic Status
31 and Brain Injury With Neurodevelopmental Outcomes of Very Preterm Children. *JAMA*
32 *Network Open* 2019;2(5):e192914-e14. doi: 10.1001/jamanetworkopen.2019.2914
- 33
34 37. Putnick DL, Bornstein MH, Eryigit-Madzwamuse S, et al. Long-Term Stability of
35 Language Performance in Very Preterm, Moderate-Late Preterm, and Term Children. *J*
36 *Pediatr* 2017;181:74-79 e3. doi: 10.1016/j.jpeds.2016.09.006 [published Online First:
37 2016/10/18]
- 38
39 38. Poulsen G, Strandberg-Larsen K, Mortensen L, et al. Exploring educational disparities in
40 risk of preterm delivery: a comparative study of 12 European birth cohorts. *Paediatric*
41 *and perinatal epidemiology* 2015;29(3):172-83. doi: 10.1111/ppe.12185 [published
42 Online First: 2015/03/27]
- 43
44 39. Ruiz M, Goldblatt P, Morrison J, et al. Mother's education and the risk of preterm and small
45 for gestational age birth: a DRIVERS meta-analysis of 12 European cohorts. *J*
46 *Epidemiol Community Health* 2015;69(9):826-33. doi: 10.1136/jech-2014-205387
47 [published Online First: 2015/04/26]
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TABLES AND FIGURES

Table 1 – Baseline characteristics of responders (n=3101) and non-responders (n=1537) at 2 years corrected age

	Non-responders at 2 years	Responders at 2 years	Wald test p-value (adjusted for country)
	n=1,537	n=3,101	
<i>Perinatal characteristics</i>			
Gestational age (%)			
22 weeks	0.07	0	0.207
23-27 weeks	23.2	24.9	
28-31 weeks	76.7	75.0	
Birthweight (%)			
< 1000 grams	26.5	28.2	0.316
Multiple pregnancy (%)	26.5	33.1	0.001
Maternal age at birth (%)			
≥ 35 years old	21.2	31.9	0.000
Previous birth			
0	48.2	59.9	0.000
1	24.9	23.6	
2 or more	26.9	16.6	
Neonatal morbidity (%)			
SGA < 10th	32.3	32.9	0.659
BPD	18.0	13.0	0.018
ROP stage III-V	3.5	3.4	0.466
IVH III°-IV°/cPVL	6.1	5.9	0.584
NEC needing surgery	2.1	1.6	0.918
Severe congenital anomaly (%)	1.2	1.2	0.869
Perinatal risk			
Low level	27.2	26.9	0.554
Moderate level	37.1	38.8	
High level	35.7	34.3	
Male (%)	54.7	52.4	0.375
Mothers born in the country (%)	66.24	81.77	0.000
<i>Countries*</i>			
Estonia	0.1	4.5	0.000
France	7.6	31.8	
Germany	14.4	14.0	
Italy	15.4	23.6	
UK	57.6	20.8	
Sweden	4.9	5.3	

* For example: among children who were not followed at 2 years CA, 0.1% were from Estonia, while among children who were followed up at 2 years CA, 4.5% were from Estonia

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3 Abbreviations: SGA: small for gestational age (i.e. birthweight over the 10th percentile for
4 gestational age using intrauterine curves); BPD: bronchopulmonary dysplasia; ROP:
5 retinopathy of prematurity; IVH: intraventricular haemorrhage; cPVL:cystic periventricular
6 leukomalacia; NEC: necrotising enterocolitis
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Table 2 –Sociodemographic and clinical characteristics by levels of maternal education, sample weighted to account for non-response bias

	Level of maternal education			Wald test p-value adjusted for country
	Low education n=516	Medium education n=1169	High education n=960	
<i>Perinatal characteristics</i>				
Gestational age (%)				
< 28 weeks	25.0	24.6	24.2	0.81
28-31 weeks	75.0	75.4	75.8	
Birthweight (%)				
< 1000 grams	30.1	27.7	26.6	0.79
Multiple pregnancy (%)	30.3	29.8	36.6	<0.001
Maternal age at birth (%)				
≥ 35 years old	27.3	23.1	37.4	<0.001
Previous birth				
0	48.7	54.9	65.8	<0.001
1	24.7	22.9	24.3	
2 or more	26.5	22.3	9.9	
Severe neonatal morbidity (%)				
SGA < 10th	37.6	32.1	31.2	0.51
BPD	12.7	18.8	14.8	0.33
ROP stages III to V	3.3	3.9	2.9	0.43
IVH stages III-IV or cPVL	6.2	7.9	4.9	0.09
NEC needing surgery	1.6	2.0	1.8	0.71
Severe congenital anomaly (%)	1.4	0.9	1.2	0.75
Perinatal risk				
Low level	25.1	27.6	29.2	0.51
Moderate level	40.7	34.9	38.1	
High level	34.3	37.5	32.7	
Male (%)	48.6	50.5	52.7	0.34
Mothers born in the country (%)	71.7	82.9	84.5	<0.001
<i>Information available at follow-up</i>				
Single mother (%)	15.9	12.9	5.1	<0.001
Sibling (%)	62.8	64.7	58.7	0.09
Main childcare (%)				
Parents or other family	84.4	66.9	56.5	<0.001
Daycare, nursery or nanny	11.1	19.6	31.1	
Other	4.5	13.5	12.4	
Corrected age at assessment (%)				
<21 months	1.6	1.3	0.6	<0.001
22-26 months	74.6	83.7	89.7	

	>=27 months	23.8	15.0	9.8	
	Bilingualism (yes)	27.9	20.6	20.4	0.38
	Countries				
	Estonia	2.5	3.1	4.5	-
	France	29.7	22.8	21.9	
	Germany	36.9	4.3	11.9	
	Italy	19.5	23.4	21.4	
	UK	10.7	41.8	32.9	
	Sweden	0.7	4.7	7.2	

Abbreviations: SGA: small for gestational age (i.e. birthweight over the 10th percentile for gestational age using intrauterine curves); BPD: bronchopulmonary dysplasia; ROP: retinopathy of prematurity; IVH: intraventricular haemorrhage; cPVL:cystic periventricular leukomalacia; NEC: necrotising enterocolitis

Table 3 - Prevalence of DLD and relative risks (RR) for DLD by maternal educational level and level of perinatal risk

	n	% DLD	(95%CI)	RR1 *	(95%CI)	RR2* *	(95%CI)
DLD according to criteria 1: No word combination							
Low perinatal risk							
Low education	129	26.2	(18.6 ; 35.5)	1.92	(1.33 ; 2.78)	1.88	(1.26 ; 2.80)
Medium education	305	17.5	(13.2 ; 22.9)	1.13	(0.99 ; 1.27)	1.14	(1.02 ; 1.26)
High education	267	16.1	(11.9 ; 21.2)	1		1	
Moderate perinatal risk							
Low education	201	26.8	(20.9 ; 33.6)	1.35	(0.98 ; 1.87)	1.51	(1.12 ; 2.05)
Medium education	427	26.9	(22.5 ; 31.7)	1.29	(0.88 ; 1.89)	1.31	(0.92 ; 1.85)
High education	369	20.2	(16.3 ; 24.6)	1		1	
High perinatal risk							
Low education	167	36.4	(29.0 ; 44.5)	1.31	(1.16 ; 1.48)	1.36	(1.10 ; 1.67)
Medium education	382	27.8	(22.7 ; 33.5)	0.91	(0.69 ; 1.19)	0.97	(0.67 ; 1.39)
High education	291	28.9	(23.7 ; 34.8)	1		1	
DLD according to criteria 2: Low expressive vocabulary							
Low perinatal risk							
Low education	109	45.8	(36.4 ; 55.5)	1.54	(1.10 ; 2.16)	1.44	(1.06 ; 1.95)
Medium education	286	33.1	(27.1 ; 39.8)	1.07	(0.83 ; 1.39)	1.04	(0.81 ; 1.34)
High education	262	30.4	(24.8 ; 36.5)	1		1	
Moderate perinatal risk							
Low education	195	41.8	(34.6 ; 49.2)	1.41	(1.14 ; 1.74)	1.32	(1.02 ; 1.69)
Medium education	415	35.9	(31.0 ; 41.1)	1.19	(0.99 ; 1.42)	1.23	(1.02 ; 1.47)
High education	364	29.9	(25.3 ; 34.9)	1		1	
High perinatal risk							
Low education	150	52.8	(44.1 ; 61.4)	1.20	(0.99 ; 1.44)	1.11	(0.97 ; 1.27)
Medium education	366	49.0	(42.9 ; 55.2)	1.09	(0.95 ; 1.27)	1.04	(0.85 ; 1.28)
High education	289	43.8	(37.7 ; 50.1)	1		1	

Estimates computed using the inverse probability of participating at the 2 years of follow-up (IPW approach) based on baseline characteristics

*RR1: adjusted for age at assessment

**RR2: adjusted for age at assessment, sex, maternal age, parity, multiple birth, bilingualism, and country of birth

In models 2, for not combining words, the P-values for interaction terms were 0.45 (low education x moderate perinatal risk), 0.25 (low education x high perinatal risk), 0.34 (medium education x moderate perinatal risk), 0.42 (medium education x high perinatal risk). For low expressive vocabulary, the P-values for interaction terms were 0.38 (low education x moderate perinatal risk), 0.06 (low education x high perinatal risk), 0.30 (medium education x moderate perinatal risk), 0.99 (medium education x high perinatal risk).

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Figure legends

Figure 1 – Prevalence of DLD at 2 years in children born VPT by level of maternal education (a) and by level of perinatal risk (b)

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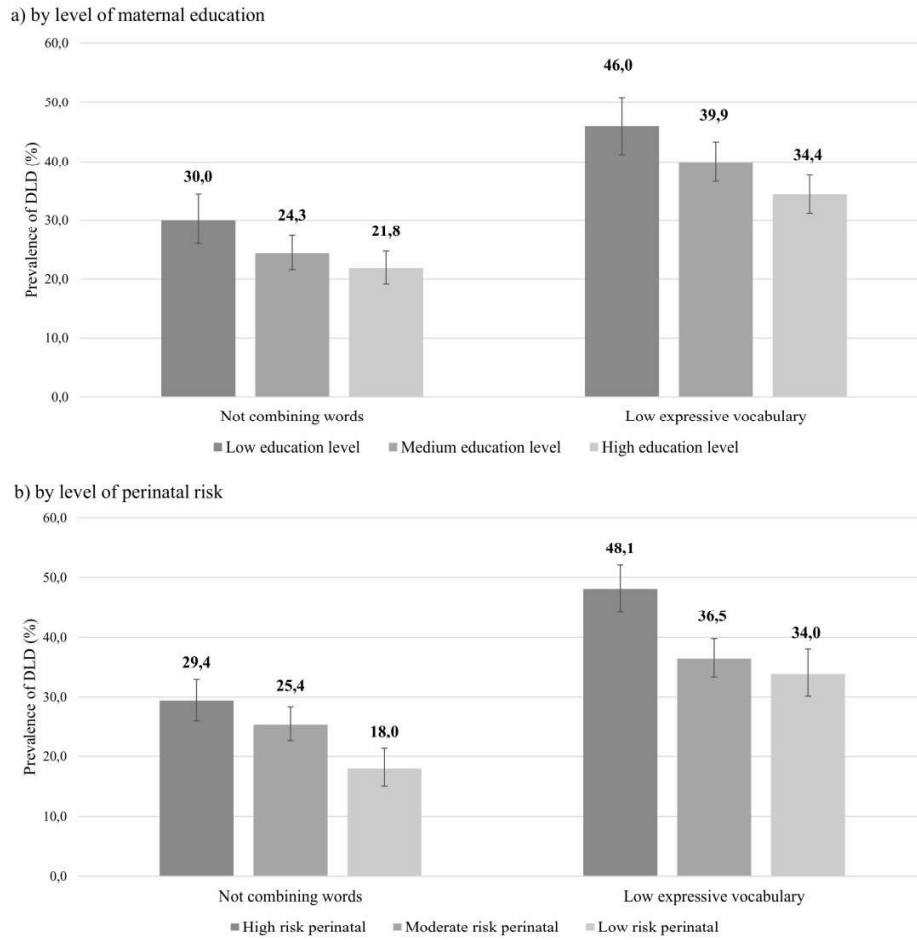


Figure 1 – Prevalence of DLD at 2 years in children born VPT by level of maternal education (a) and by level of perinatal risk (b)

250x250mm (300 x 300 DPI)

SUPPLEMENTAL MATERIAL

Figure S1- Flowchart of the study selection

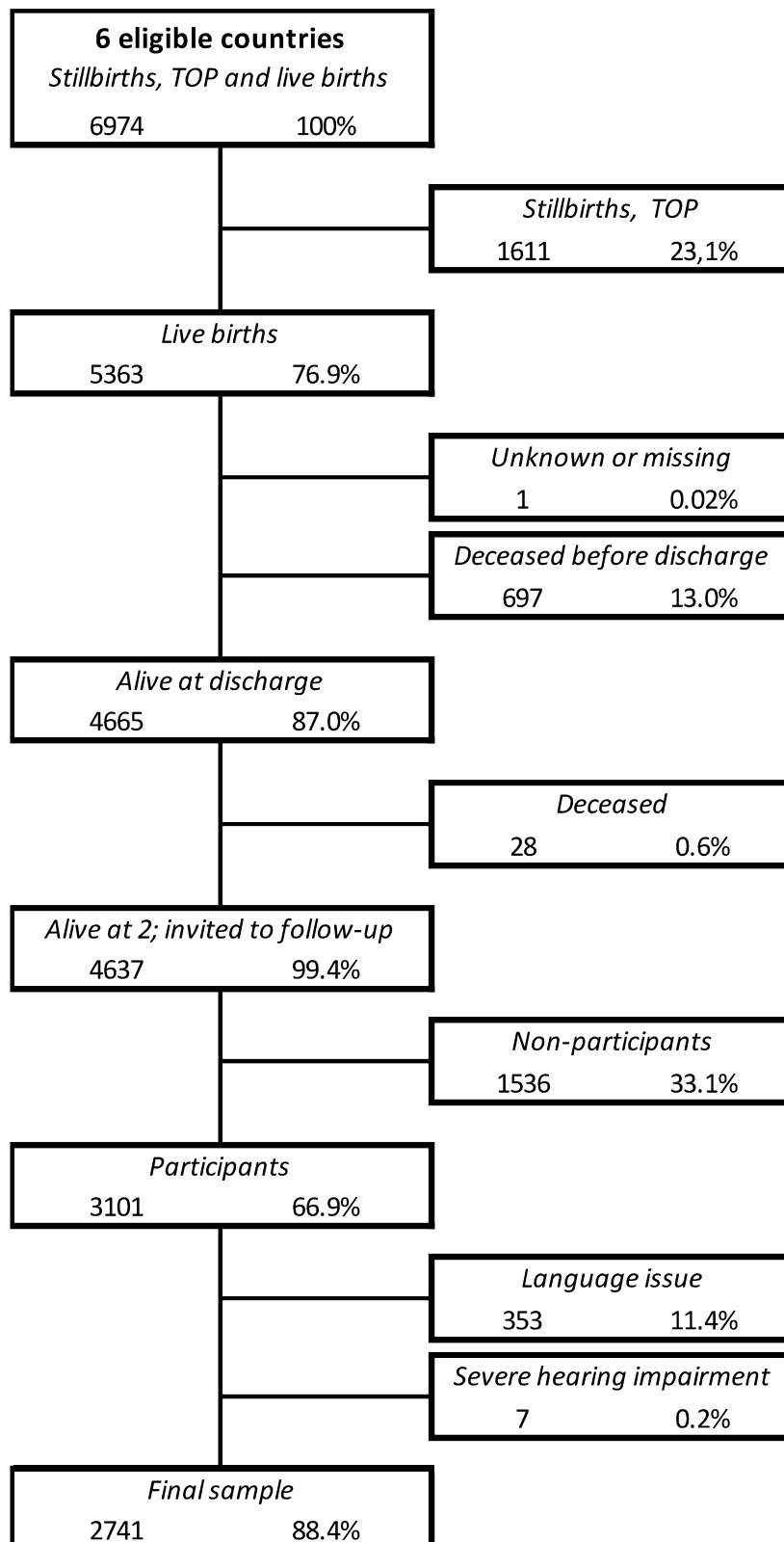


Table S1 – Percentage of missing data for main variables in the analyzed sample (n=2741)

	% of missing
<i>Outcomes</i>	
Word combination	1.8
Expressive vocabulary	5.8
<i>Perinatal characteristics</i>	
Gestational age (%)	0
Birthweight (%)	0
Multiple pregnancy (%)	0
Maternal age at birth (%)	0.3
Previous birth	1.2
Neonatal morbidity (%)	
SGA < 10th	0
BPD	0
ROP stages III to V	1.4
IVH stages III-IV or cPVL	0.7
NEC needing surgery	0
Severe congenital anomaly (%)	0
Perinatal risk	2.5
<i>Socioeconomic and demographic characteristics</i>	
Maternal education level	3.5
Boy (%)	0
Single mother (%)	0.8
Sibling (%) – (after excluded France)	0.8
Main childcare (%)	0.7
Foreign mothers born in the country (%)	4.5
<i>Follow up information</i>	
Corrected age at assessment (%)	0.1
Bilingualism (yes)	0

Abbreviations: SGA: small for gestational age (i.e. birthweight over the 10th percentile for gestational age using intrauterine curves); BPD: bronchopulmonary dysplasia; ROP: retinopathy of prematurity; IVH: intraventricular haemorrhage; cPVL: cystic periventricular leukomalacia; NEC: necrotising enterocolitis