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Putative Risk Factors in Developmental Dyslexia: A Case-Control Study of Italian Children

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Abstract

Although dyslexia runs in families, several putative risk factors that cannot be immediately identified as genetic predict reading disability. Published studies analyzed one or a few risk factors at a time, with relatively inconsistent results. To assess the contribution of several putative risk factors to the development of dyslexia, we conducted a case-control study of 403 Italian children, 155 with dyslexia, by implementing a stepwise logistic regression applied to the entire sample, and then to boys and girls separately. Younger parental age at child's birth, lower parental education, and risk of miscarriage significantly increased the odds of belonging to the dyslexia group (19.5% of the variation). These associations were confirmed in the analyses conducted separately by sex, except for parental education, which significantly affected only males. These findings support reading disabilities as a multifactorial disorder and may bear some importance for the prevention and/or early detection of children at heightened risk for dyslexia.

Keywords

developmental dyslexia, multifactorial liability, putative risk factors, case-control study

Developmental dyslexia (DD) is characterized by an impairment of reading abilities in spite of normal intelligence and adequate educational opportunities, typically diagnosed in the first school years, according to the diagnostic criteria of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*) (American Psychiatric Association, 1994). Although DD is moderately heritable with some specific genes suggested as candidates (Scerri & Schulte-Körne, 2010), it is clear that additional factors—whose nature cannot be immediately identified as genetic—increase the risk for developing reading disability and its neuropsychological components. These factors include (a) socioeconomic status (SES), (b) parental education, (c) the home literacy environment, and (d) familial structure and demographic factors (Grigorenko, 2001). Empirical investigations of these factors in relation to the risk for DD, however, have often yielded sparse findings (Grigorenko, 2001). Familial SES appears related to language, verbal abilities, and academic achievement during the primary school years, with high-SES children producing more word types than mid-SES children (Hoff & Tian, 2005; Walker, Greenwood, Hart, & Carta, 1994). Unsurprisingly, SES was also found related to maternal vocabulary and utterances and to teaching practices (e.g., eliciting conversation, teaching by picture cards, telling stories), which in turn predict a child's vocabulary and language development (Hoff & Tian, 2005). Some studies (Friend, De Fries, & Olson, 2008; Kremen et al., 2005; Rosenberg, Pennington, Willcutt, & Olson, 2012) have shown that all these variables can in fact act as mediators of genetic effects. In other words, parental education can moderate the genetic signal on word recognition, spelling, and reading comprehension. A significant impact of familial structure on the development of cognitive and learning abilities was reported by O'Connor, Caspi, De Fries, and Plomin (2000). Likewise, parental separation

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predicted worse learning and preliteracy outcomes as well as more learning difficulties and preliteracy problems in children entering kindergarten and worse academic achievement in adolescents (De Fries, Plomin, & Fulker, 1994; Jee et al., 2008). Melekian (1990) found higher rates of DD among children born to parents younger than 30 years and lower education levels among the mothers of children with DD. Other studies showed that the offspring of younger mothers are at increased risk of cognitive disadvantage and educational underachievement (Fergusson & Lynskey, 1993; Fergusson & Woodward, 1999). These same disadvantages are likely to persist into adolescence and early adulthood (Fergusson & Woodward, 1999). It has been argued, however, that these potentially hazardous factors share a small effect size, so that their ultimate impact on DD may be marginal (Grigorenko, 2001).

The time of incidence of potential risk factors is not limited to infancy and childhood, however. The pre- and perinatal periods can also be critical for reading skills. The number of cigarettes smoked by the mother during pregnancy and a child's language, reading, spelling, and mathematics abilities were found to be related in two independent studies (Batstra, Hadders-Algra, & Neeleman, 2003; Fried, Watkinson, & Siegel, 1997). Nevertheless, after controlling for SES and pre- and perinatal complications, low scores on the reading test were limited to SES, male gender, suboptimal neonatal neurological condition, and the occurrence of infectious diseases early in life (Batstra et al., 2003). Gilger, Pennington, Green, Smith, and Smith (1992) found some evidence of higher rates of miscarriage in families selected through probands with reading disabilities, compared to control families. Worse cognitive, reading, mathematics, and spelling abilities were found both in children who were born extremely premature (gestational age < 28 weeks, or birth weight < 1,000 g; Bowen, Gibson, & Hand, 2002) and among very preterm and/or very low birth weight (VLBW, i.e., < 1,500 g) children (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaand, 2009). On the other hand, a controlled study by Samuelsson et al. (2006) reported reading deficits among VLBW children at age 9, with normalization at follow-up at age 15, implying a catch-up process in reading abilities. A recent review by Michaelsen, Lauritzen, and Motensen (2009) concluded that breast-feeding has a small, significant positive effect on cognitive functions that follows a dose-response trend with the duration of breast-feeding (Anderson, Johnstone, & Remley, 1999).

The studies reviewed above show that environmental risk variables impinge on the development of children's reading abilities, as predicted by the biobehavioral system approach (Fletcher et al., 2002). In a more articulate framework of gene-by-environment interplay and interdependence (Battaglia, 2012; Morton & Frith, 1995; Rutter, 2012), it is conceivable that different ecological niches moderate the strength of the genetic signal, as it appears to be the case also for DD-related neuropsychological phenotypes (Friend et al., 2008; Kremen et al., 2005; Mascheretti et al., 2013). From the bulk of the literature reviewed above, three main points seem to emerge. First, a host of factors may affect reading disability and its neuropsychological components. These putative risk variables, however, are not acting alone and may well be interconnected and reciprocally correlated. Second, the majority of previous investigations have addressed one or a few risk factors at a time, and no study has addressed the role of these indicators together in the same design. This may have affected the estimated effect size. An alternative and more comprehensive analysis may, on the contrary, take into better account the role of the different risk factors. Third, at least some of these putative risk factors may exert their effect during different windows of risk, possibly leading to inconsistent results. The emerging "auxiological epidemiology approach" paradigm, on the contrary, supports the adoption of a "lifetime perspective," which encompasses the analysis of elements of risk that manifest from prenatal life onward (Cameron & Demerath, 2002; Stiles, 2000). There is growing evidence that brain plasticity (Cameron & Demerath, 2002; Stiles, 2000) and functional flexibility (Keller & Just, 2009; Traynor & Singleton, 2010) are critical features of neural development, particularly in the postnatal period. Normal brain development proceeds according to a maturational blueprint that includes both genetic factors and inputs from the environment (Cameron & Demerath, 2002; Stiles, 2000). According to this viewpoint, we adopted a lifetime perspective, which led to the inclusion of several putative risk factors across different developmental periods.

In this case-control study we implemented an alternative design that investigates the contribution of several putative risk factors to the development of DD at different age periods at the same time. Based on available evidence on the determinants of DD, and on the notion that the etiology of complex phenotypes involves multiple risk factors of small effect, we expected that the factors that would emerge as putatively hazardous by our study would exert small effects on the DD-related phenotypes.

Materials and Methods

Sample

Two study groups of children were included in this study. The patient group was drawn from a consecutive pool of Caucasian nuclear families with DD recruited at the Department of Child Psychiatry of the Scientific Institute "Eugenio Medea," Bosisio Parini, Lecco, Italy, and at the Centro Regionale di Riferimento per i Disturbi dell'Apprendimento (CRRDA; Regional Reference Center for the Specific Learning Disability), ULSS 20, Verona, Italy, for molecular genetic studies of DD (Marino et al., 2003; Marino et al., 2004; Marino et al., 2005; Marino et al.,

2007; Marino et al., 2011; Marino et al., 2012; Skiba, Landi, Wagner, & Grigorenko, 2011). Both the Scientific Institute "Eugenio Medea" and the CRRDA are facilities where children are referred mainly by pediatricians and teachers from schools of the same geographical areas for diagnosis and treatment of a wide range of mental disorders, including learning disorders. Probands were selected regardless their family size. The control group (CT) was drawn from a general population sample of Caucasian children aged 3 to 11 years who participated in a study on language abilities (Marino et al., 2011).

For the DD group recruited at the Scientific Institute "Eugenio Medea," the ascertainment scheme has been reported in details elsewhere (Marino et al., 2003). Briefly, after parental informed consent respondents were recruited if they met the criteria for DD according to *DSM-IV* (American Psychiatric Association, 1994), confirmed by a clinical investigation. Medical assessment included neurological and ophthalmologic examinations and an audiometric test. Respondents were administered a battery of tests that included several neuropsychological tasks standardized in the Italian population (Cornoldi & Colpo, 1995, 1998; Sartori, Job, & Tressoldi, 1995) and the *Wechsler Intelligence Scale for Children, Revised* (WISC-R; Wechsler, 1981) or the *Wechsler Intelligence Scale for Children, Third Edition* (WISC-III; Wechsler, 2006). The criteria used to define affection status were (a) a performance on a timed text-reading test at least 2 standard deviations below the general population mean on either accuracy or speed (Cornoldi & Colpo, 1995, 1998) or (b) an absolute score at least 2 standard deviations below the general population mean on accuracy or speed in a reading list of unrelated words or nonwords (Sartori et al., 1995) and (c) IQ greater than 84 (Wechsler, 1981, 2006). Similarly, the DD group recruited at the CRRDA had to fulfill the previously described diagnostic criteria to be included in the study. Even if some studies report a lack of validity in using the IQ–achievement discrepancy as a criterion for identification of DD (for a recent meta-analysis, see Stuebing et al., 2002), we chose to select children by adopting this criterion because (a) there is substantial evidence that children identified as having significant IQ-achievement discrepancies have the poorest performance on many of the cognitive tests commonly associated with DD (Newman, Wright, & Fields, 1991) and (b) we wanted to exclude from our sample children whose learning difficulties could be better accounted for by a more general cognitive impairment. In our current recruitment scheme, parents are also asked to fill out three self-report questionnaires: (a) one ad hoc questionnaire (11 items) that inquires about potential risk factors (see the Putative Risk Factors: Data Collection and Coding section), (b) the *Conners' Rating Scale–Revised* (Nobile, Alberti, & Zuddas, 2007), and (c) one ad hoc questionnaire that inquires about the presence of a positive family history for Disorders of Speech and Language (DSL) and/or Specific Learning Disability (SLD). Although our consecutive sample currently consists of 412 families ascertained through one child with DD, the self-report questionnaires were introduced more recently, so that 155 children with DD (female 32.3%, $n = 50$) had information sufficient for inclusion in the present study.

The CT group was recruited in kindergartens and primary schools in five different school districts in northern Italy, including one metropolitan area (Milan) and four small- to average-sized urban areas in the province of Lecco. Children were recruited if they met the following criteria: (a) no certification of a handicap and (b) Caucasian ethnicity and (c) Italian spoken at home for at least one generation. Briefly, after parental written informed consent, children were administered an in-depth language assessment of phonological, lexical, and syntactic abilities in comprehension, production, and repetition tasks (Marino et al., 2011), and the WISC-III (Wechsler, 2006) or the *Wechsler Preschool and Primary Scale of Intelligence, Third Edition* (WPPSI-III; Wechsler, 2002), depending on the child's age. For both the WISC-III and the WPPSI-III, only two subtests were administered (i.e., Vocabulary and Block Design, and Information and Block Design, respectively) that show a high correlation (r) with verbal IQ and performance IQ, respectively ($r = .82$ and $r = .73$ for the WISC-III, $r = .70$ and $r = .59$ for the WPSSI-III; Wechsler, 2002, 2006). Parents were also asked to fill out three self-report questionnaires: (a) the *Preschool Child Behavior Checklist 1½–5* (Achenbach & Rescorla, 2000) or the *Child Behavior Checklist 6–18* (CBCL 6–18; Achenbach & Rescorla, 2001), depending on the child's age and (b) the same ad hoc questionnaire inquiring about the presence of a positive family history of DSL and/or SLD among relatives and (c) an ad hoc questionnaire (14 items) to inquire about potential risk factors (see the Putative Risk Factors: Data Collection and Coding section). This yielded a general population sample of 910 children aged 3 to 11 years to be potentially included in this study. Nevertheless, since we sought a comparable age interval in both groups, all children in the preschool years ($n = 234$) were excluded; this yielded an eligible sample of 676 children in their educational years. For the aims of the present study, we applied the following inclusion criteria to the pool of putative CT children: (a) negative family history for DSL and/or SLD and (b) a mean score on Vocabulary and Block Design of 7 or more (corresponding to −1 *SD*) and (c) a *T*-score of 35 or better on the CBCL 6–18 Scholastic Performance Scale and (d) absence of a certification of DD and (e) a performance on the Digit Span subtest of the WISC-III greater than 4 (corresponding to −2 SD), or an absolute score greater than −2 *SD* on accuracy in the Single Word Repetition or on the Single Non-Word Repetition tasks. The application of these criteria left 273 children (49.8% female, $n = 136$) aged 6 to 11 as the final CT group for the present study.

Table 1. Frequencies of the Dichotomous Variables.

	Total Sample (N = 428)		DD Group (n = 155)		Control Group (n = 273)			
Putative Risk Factor	Answer Category 1 (%)	Missing Value (%)	Answer Category 1 (%)	Missing Value (%)	Answer Category 1 (%)	Missing Value (%)	χ^2	p
Maternal smoking during pregnancy	7.0	1.4	5.2	1.3	8.1	1.5	1.285	.257
Risk of miscarriage	5.1	1.2	10.3	1.9	2.2	0.7	13.647	<.001
No breast feeding	22.0	1.2	23.9	0.6	20.9	1.5	0.456	.500
Parental marital status (single, divided, divorced, or widowed)	1.2	0.7	0.6	0.0	1.5	1.1	0.592	.441

Note. DD = developmental dyslexia.

Putative Risk Factors: Data Collection and Coding

Parents in both groups of children filled out paper-and-pencil questionnaires made ad hoc on the basis of an extensive review of the literature (see Introduction). There were 11 items that coincided exactly on the two questionnaires:

1. Maternal smoking during pregnancy ("Has the mother smoked more than one cigarette a day for more than one month during pregnancy?")
2. Risk of miscarriage that required hospitalization ("Has the mother been diagnosed with a risk of miscarriage during pregnancy that required hospitalization?")
3. Gestational weeks at birth ("At what gestational week was the child born?")
4. Birth weight ("What was the child's weight at birth?")
5. Breast feeding ("Did the mother breastfeed her child for at least one month?")
6. Parental marital status during the child's first 3 years
7. Father's age at child's birth (father_age; "What was the father's age at child birth?")
8. Mother's age at child's birth (mother_age; "What was the mother's age at child birth?")
9. SES during the child's first 3 years ("What was father's/mother's employment during the child's first three years?")
10. Father's education level during the child's first 3 years (father_education; "What was the father's educational qualification during the child's first three years?")
11. Mother's education level during the child's first 3 years (mother_education; "What was the mother's educational qualification during the child's first three years?")

"Parental marital status" was coded as a two-level variable, with single-parent families including single, divided, divorced, or widowed parents coded as 1; SES was coded according to the information provided by parents of respondents about their employment, on the basis of the Hollingshead's (1975) 9-point scale for parental occupation (the highest score between mother and father was considered for each respondent); education level was scored according to a 9-point ordinal scale based on the Italian school system (range between 10, corresponding to fifth grade of elementary school, and 90, equivalent to a post-doctoral degree); all dichotomous variables were coded as 0 when answers were no and 1 when answers were yes, except that breast feeding was coded as 0 if the child had been breastfed.

No variable had a missing value frequency greater than 10%. All continuous variables were normally distributed; the only exception was gestational weeks, which showed a leptokurtic distribution (kurtosis = 1.335); in light of its high correlation with birth weight (r = .472, p < .01), this variable was not included in the regression analyses, and birth weight was retained as the only indicator of perinatal potential risk factors. Descriptive statistics are reported in Tables 1 and 2.

Between-Variable Correlations and Data Cleansing

Dichotomous variables. Since a low frequency in an at-risk category (i.e., answers coded as 1) could invalidate the power of the analysis, we decided to remove the variables with at-risk category frequency of less than 5%, which led to the exclusion of parental marital status. The association among the remaining dichotomous variables was tested by contingency table analyses: No significant association was found, and all dichotomous variables were included in analyses.

Table 2. Descriptive Statistics of the Continuous Variables.

	Total Sample (N = 428)		DD Group (n = 155)		Control Group (n = 273)			
Putative Risk Factor	*M*	*SD*	*M*	*SD*	*M*	*SD*	*t* Test	*p*
Birth weight	3307.83	524.96	3369.93	529.80	3273.23	520.00	–1.819	.070
Gestational weeks	38.90	2.04	39.01	1.99	38.84	2.07	–0.830	.407
Mother_age	32.35	4.37	30.78	4.49	33.25	4.04	5.826	<.001
Father_age	34.86	4.92	33.36	5.00	35.73	4.68	4.891	<.001
Mother_education	46.77	16.81	41.16	17.64	49.96	15.46	5.132	<.001
Father_education	44.69	18.61	38.52	18.71	48.20	17.65	5.182	<.001
SES	59.10	18.73	53.82	18.80	62.09	18.04	4.448	<.001

Note. DD = developmental dyslexia.

Table 3. Spearman's Correlations Among the Continuous Variables.

	1	2	3	4	5	6	7
1. Gestational weeks	1	.472**	–.076	–.061	.006	.018	.001
2. Birth weight		1	–.056	–.022	–.041	.021	–.031
3. Mother_age			1	.722**	.317**	.311**	.257**
4. Father_age				1	.213**	.212**	.212**
5. Mother_education					1	.596**	.591**
6. Father_education						1	.604**
7. SES							1

Table 3 shows the correlations for continuous variables. Mother_age and father_age were highly correlated, and mother_education and father_education were substantially correlated. Therefore, we calculated the mean parental age at the child's birth (parental age) and the mean parental education level during the child's first 3 years (parental education) to obtain more concise and comprehensive variables. Therefore, the variables in the analyses were as follows:

1. Maternal smoking during pregnancy
2. Risk of miscarriage
3. Birth weight
4. Breast feeding
5. Parental age
6. SES
7. Parental education

Supplementary Table 1 (all supplementary materials are available at http://jid.sagepub.com/content/by/supplemental-data) shows the nonparametric correlations between putative risk factors. No substantial associations were found, except between SES and parental education. Although this association is not surprising, we kept the two variables separated in the following analyses, given the exploratory nature of the study and the absence of any data on the effect of environmental factors in DD for the Italian population.

Statistical Analyses

To evaluate the contribution of this set of covariates in modifying the probability of belonging to the DD or the CT group, we carried out a stepwise logistic regression using the forward selection procedure with SPSS 17.0. Moreover, to evaluate if the contribution of these putative hazards differed in males and females, we repeated the same analysis separately for boys and girls.

The DD and CT groups did not differ for birth order ranking (Pearson χ^2 = 5.574, df = 3, p = .134). The two groups differed for age (M = 126.51, SD = 32.76 and M = 102.52, SD = 17.85 months, respectively, p < .001); however, since the groups did not differ for birth order and all variables were referring to the child's first 3 years of life, age was not included as a covariate in the model.

Results

The descriptive statistics for neuropsychological variables for the DD and CT groups are shown in Supplementary Table 2 and Supplementary Table 3, respectively. The DD group seems to have more concern for speed than for accuracy on reading tasks, as expected in transparent, regular languages such as Italian (Supplementary Table 2). Moreover, CT children do not show any deficits in cognitive skills that are related to DD (i.e., Digit Span subtest, Single Word/Non-Word Repetition tasks) and are not

Table 4. Binary Logistic Regression: Forward:LR Method Predicting Developmental Dyslexia Diagnosis.

Model Predictor	Hosmer–Lemeshow test χ^2 (*p*)	Cox R^2	Nagelkerke R^2	Wald (*df*)	*p*	OR	95% CI for OR	
							Lower	Upper
Step 1	5.393 (.409)	.078	.108					
Parental education				30.356 (1)	<.001	0.962	0.948	0.975
Step 2	14.766 (.064)	.117	.160					
Parental age				15.742 (1)	<.001	0.893	0.844	0.944
Parental education				17.056 (1)	<.001	0.970	0.956	0.984
Step 3	11.337 (.183)	.142	.195					
Risk of miscarriage				10.145 (1)	.001	6.166	2.013	18.885
Parental age				15.229 (1)	<.001	0.893	0.844	0.945
Parental education				16.746 (1)	<.001	0.969	0.955	0.984

Table 5a. Binary Logistic Regression: Forward:LR Method Predicting Developmental Dyslexia Diagnosis in Boys.

Model Predictor	Hosmer–Lemeshow test χ^2 (*p*)	Cox R^2	Nagelkerke R^2	Wald (*df*)	*p*	OR	95% CI for OR	
							Lower	Upper
Step 1	6.843 (.336)	.133	.179					
Parental education				28.182 (1)	<.001	0.949	0.931	0.968
Step 2	6.084 (.530)	.163	.219					
Risk of miscarriage				6.338 (1)	.012	8.825	1.620	48.081
Parental education				28.284 (1)	<.001	0.948	0.929	0.967
Step 3	4.798 (.779)	.190	.255					
Parental age				6.970 (1)	.008	0.902	0.836	0.974
Risk of miscarriage				6.432 (1)	.011	9.574	1.671	54.865
Parental education				17.405 (1)	<.001	0.956	0.937	0.977

Table 5b. Binary Logistic Regression: Forward:LR Method Predicting Developmental Dyslexia Diagnosis in Girls.

Model Predictor	Hosmer–Lemeshow test χ^2 (*p*)	Cox R^2	Nagelkerke R^2	Wald (*df*)	*p*	OR	95% CI for OR	
							Lower	Upper
Step 1	0.000	.037	.054					
Risk of miscarriage				6.084 (1)	.014	6.049	1.447	25.280
Step 2	10.074 (.260)	.064	.093					
Risk of miscarriage				5.307 (1)	.021	5.568	1.292	23.995
Parental age				4.679 (1)	.031	0.905	0.827	0.991

reported to have any scholastic problems, as shown by their scores on the CBCL 6–18 Scholastic Performance Scale (Supplementary Table 3).

Table 4 shows the results of the logistic regression: Because of some missing values, the model was run on 94.2% ($n = 403$) of the respondents. The Hosmer–Lemeshow test showed an improvement of fit at each step together with a rise in the amount of explained variance ranging from 10.8% to 19.5%, according to the Nagelkerke R^2. The final model yielded two small negative associations with parental age and parental education (OR = 0.893 and OR = 0.969, respectively) and a quite strong positive association with risk of miscarriage (OR = 6.166). Correlation coefficients among selected variables were low, ranging from –0.045 to –0.224; these results suggest the absence of multicollinearity.

As shown in Tables 5a and 5b, the associations were confirmed in the analyses conducted separately by sex, except for lower parental education level, which was significant only in the male subsample.

Discussion

Although there is consistent evidence of strong familial aggregation in DD—partly attributable to genetic factors—a notable proportion of variation in liability remains to be explained by elements whose nature does not appear as immediately genetic. This fits with both the expectations of a multifactor model of liability (Bishop, 2009; Rutter, Moffitt, & Caspi, 2006) and the results of numerous genetically informed studies (Scerri & Schulte-Körne, 2010). Despite the amount of data addressing one or a few risk factors at a time, there are no published systematic comparisons between normally developing children and children with DD for different common and identified risk factors. Here, we addressed this lack of data by providing an alternative design in which several identified elements, acting both pre- and postnatally were contemporaneously injected into regression models, in normal readers and children with DD.

Taken together, our data indicate that lower parental education, younger parental age at birth, and having risked miscarriage during pregnancy additively increase the offspring's risk for DD. These findings may bear some importance in the prevention and/or early detection of children at heightened risk for DD. Moreover, having analyzed several risk factors together has probably led to more parsimonious and actual estimates of effect size than previous studies. According to the notion that the etiology of DD involves multiple risk factors, each bearing on a continuously distributed liability, it should be expected that each single identified risk factor accounts for only a tiny proportion of variance. In addition to these general comments, some specific considerations are in order.

The disadvantages of having less educated parents could be related to parental suboptimal reading abilities (van Bergen, de Jong, Plakas, Maassen, & van der Leij, 2012) and to the quality of their teaching practices. Recent data show a positive relationship among maternal education, talking styles during interactions with the child, and later children's lexical development and reading skills (Hoff & Tian, 2005; van Bergen et al., 2012). Our finding of an effect of lower parental education among males, however, may imply a protective role—which has been hypothesized since early infancy (Aksglaede, Juul, Leffers, Skakkebaek, & Andersson, 2006)—played by the female sexual hormones on cognitive functions (Massinen et al., 2009). Moreover, this finding should also be discussed in light of the three males to one female sex ratio in our sample. Our figures replicate the data of several studies in which the ratio of males to females with DD is slightly above one-to-one both in research-defined samples and in school-identified children (Jimenéz et al., 2011; Share & Silva, 2003; Shaywitz, Shaywitz, Fletcher, & Escobar, 1990).

Concerning the role of parental education level, Fergusson and Woodward (1999) commented on the social, economic, and personal factors associated with teenage parenthood as an element of stress. Moreover, the quality of parenting and early family life associated with younger maternal age can impinge negatively on offspring's reading abilities, whereby young mothers provide less verbally stimulating environments (Fergusson & Woodward, 1999).

By focusing on specific time windows, these results may also shed light on some time-sensitive neurobiological mechanisms that underpin reading development. For instance, parental education and parental age referred to the ages of 0 to 3 years; this is a time when new synapses, myelination, and the expansion of brain connectivity produce dramatic growth curves (Cameron & Demerath, 2002; Stiles, 2000). On the other hand, risk of miscarriage points toward a window of risk to DD that may begin with the prenatal period. Inasmuch as miscarriage reflects the effects of an antigenically hostile uterine environment (Gilger et al., 1992), it could be argued that this variable maps a suboptimal intrauterine environment. This could in turn interfere with early brain development and ultimately affect a child's acquisition of reading abilities.

Moreover, Italian is a transparent language (whereby there is clear grapheme-to-phoneme correspondence). This means that children who are diagnosed as dyslexic in Italy are on average more likely to be severely affected than children diagnosed as having DD in other linguistic environments (Marino et al., 2004). Thus, these results could be looked at as quite conservative and hint at parental education level, parental age at the child's birth, and having risked miscarriage during pregnancy as more suitable elements for studies on the investigation of the multifactorial liability underlying DD because they allow for cross-linguistic comparison of the results. These results may further suggest that in a highly transparent orthography with a majority of surface DD profile, reading impairments may be partly the result of aggravating environmental factors. Indeed, the orthographic deficits among children with the surface DD profile are associated with poor home literacy (Jiménez, Rodríguez, & Ramírez, 2009). Children from disadvantaged social backgrounds, such as those with less educated and younger parents, may not only be less exposed to written material but also be given less help in overcoming their reading deficiency than children from better educated and more supportive environments (Sprenger-Charolles, Siegel, Jiménez, & Ziegler, 2011). Thus, the combination of neuropsychological deficits and lack of reading opportunity could lead to the orthographic deficit observed in surface DD profile (Sprenger-Charolles et al., 2011).

There are at least five potential limitations. First, a larger sample size may have increased statistical power to detect effects in additional variables. Replications with larger samples, the inclusion of more sophisticated risk factors, and the

analysis of how these putative risk factors may interact with other predictors of DD are warranted. Second, this study is cross-sectional owing to the outcome variable, and retrospective owing to risk factors. Obviously, a longitudinal design employing direct assessments of parents and households would ensure better reliability of both outcome and risk variables. Third, although we selected a number of reasonable risk elements based on an extensive review of the available literature, several of these variables remain composite and heterogeneous in nature. For instance, there are many facets of possible hazard nested within a distal measure, such as SES and parental education level. A new methodology in genetically informed designs will be needed to address the complex nature of generic and distal risk variables and their ultimate impact on adaptation and maladaptation (Petronis, 2010). Overall, our results further support the idea that more proximal measures of putative risk factors (e.g., parental education) could be better markers of reading abilities than distal variables (Nobile et al., 2010). Fourth, since it is possible to make a diagnosis of DD only at the end of the second year of primary school, and in the CT there were also children attending the first and the second year of elementary school (n = 53), there could be some false negatives in this group. Nevertheless, we included our CT children according to their performance on two cognitive skills related to DD (i.e., phonology and memory), and the percentage of dyslexic children in the Italian general population is about 3% to 5%; the margin for error is therefore very small (i.e., about 1–3 children). Fifth, since we selected our case-sample by adopting the IQ–achievement discrepancy as an inclusion criterion, our data may be not be generalizable to all children in a population. Future studies based on broader inclusion criteria and on the new *DSM-5* criteria will help clarifying this issue.

Conclusion

In our analysis of putative risk factors we found some relationships between identified risk agents acting at different time windows and DD. Their nature appears at first sight to be biological, in the case of risk of miscarriage, or sociocultural, as for parental education. However, current approaches to multifactorial diseases show that such type of clear-cut distinctions can often be misleading, as the causal architecture of many factors that appear environmental, can in fact be partially genetic (Moffitt, Caspi, & Rutter, 2005; van Bergen et al., 2012). Moreover, DD remains a complex phenotype that is likely to be underpinned by several phenotypic subcomponents (Gabrieli, 2009). A constellation of genetic and environmental agents are likely to act in concert and determine several, likely distinct etiopathogenetic pathways in DD. In the endeavor toward the identification of these factors, we must bear in mind that only part of the causal process may ultimately become accessible (Rutter et al., 2006).

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MM in a coinventor on a patent application filed by Laval University relating to novel markers for mental disorders. He has been a consultant for GlaxoSmithKline (GSK) and Eli Lilly and has received research funding from GSK, Eli Lilly, and AstraZeneca that is not related to the material of this study.

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