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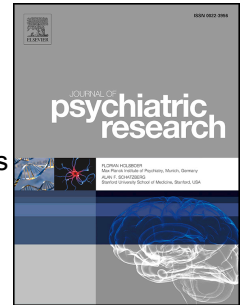
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Reading problems and major mental disorders - Co-occurrences and familial overlaps in a Swedish nation-wide cohort

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Reading problems and major mental disorders - co-occurrences and familial overlaps in a Swedish nation-wide cohort

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Reading problems and major mental disorders - co-occurrences and familial overlaps in a Swedish nationwide cohort

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Authors contributions: MC designed the study together with RP and MC conducted all statistical analyses. MC wrote the first draft of the manuscript and BM, HL, BMDO and RP contributed with important intellectual input to all consecutive drafts. HL and BMDO were responsible for the data collection.

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Abstract

Reading problems often co-occur with ADHD and conduct disorder. However, the patterns of co-occurrence and familial overlap between reading problems and **other** psychiatric disorders have not been systematically explored. We conducted a register-based cohort study including 8,719 individuals with reading problems and their siblings, along with matched comparison individuals. Conditional logistic regressions estimated risks for ADHD, autism, obsessive-compulsive disorder, anorexia nervosa, schizophrenia, bipolar disorder, depression, substance use disorder, and violent/non-violent criminality in individuals with reading problems and their siblings. Diagnoses of psychiatric disorders were physician-assigned and ascertained from the **Swedish** National Patient Register, and crime convictions from the **Swedish** National Crime Register. We found that individuals with reading problems had excess risks for all psychiatric disorders (except anorexia nervosa) and criminality, with risk ratios between 1.34 and 4.91. Siblings of individuals with reading problems showed excess risks for ADHD, autism, schizophrenia, bipolar disorder, depression, substance use disorder, and non-violent criminality, with risk ratios between 1.14 and 1.70. In summary, individuals with reading problems had increased risks of virtually all psychiatric disorders, and criminality. The origin of most of these overlaps was familial, in that siblings of individuals with reading problems also had elevated risks of ADHD, autism, schizophrenia, bipolar disorder, depression, substance use disorder, and non-violent criminality. These findings have implications for gene-searching efforts, and suggest that health care practitioners should be alert for signs of psychiatric disorders in families where reading problems exist.

Keywords; reading problems, psychiatric disorders; epidemiology.

1. Introduction

Developmental reading problems, sometimes referred to as dyslexia or reading disability, were first described 1896 (Morgan, 1896). Today, such problems are part of the broad specific learning disabilities category in *The Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM 5; American Psychiatric Association) and diagnostic criteria include persistent problems with reading that are not better explained by sensory or neurological disorders. It is widely accepted that problems with language awareness and processing form a central part of the underlying mechanisms (Vellutino, 1979). Prevalence estimates vary substantially depending on definition, but reading problems occur in about 10-15% of school-aged children (Vellutino et al., 2004).

Research on the co-occurrence of reading problems and other psychiatric disorders has found that neurodevelopmental disorders, such as ADHD, as well as internalizing psychopathology, are overrepresented (Boada et al., 2012). **In a sample of 209 twins, Willcutt & Pennington (2000a) found that rates of all assessed internalizing and externalizing disorders were elevated among individuals with reading problems. However, the study did not adjust for the potential confounding effect of IQ.** In the same vein, small follow-up studies have shown that children with reading problems are at excess risk of subsequent development of emotional and mood problems (Maughan et al., 2003; Snowling et al., 2007). Furthermore, links between reading problems and schizophrenia have also been reported; reading problems are overrepresented in offspring of parents with schizophrenia (Horrobin et al., 1995), psychotic symptoms are common in individuals with reading problems (Richardson, 1994), reading problems are highly prevalent in individuals with schizophrenia (Revheim et al., 2006), and schizophrenia risk genes are associated with reading problems in the general population (Stefansson et al., 2014). In addition, a **number of** studies have shown that

reading problems occur more often than would be expected by chance in forensic psychiatry (Dåderman et al., 2004) and correctional facilities (Kirk & Reid, 2001; Lindgren et al., 2002).

Studies into the etiology of these associations are rare, but twin studies indicate that the co-occurrence between reading problems and ADHD is driven mainly by a common genetic liability (Light et al., 1995), especially the inattention component of ADHD (Willcutt et al., 2000). Furthermore, in one study, mean levels of symptoms of externalizing psychopathology were elevated in co-twins of twins with reading problems, indicating a familial overlap between these phenotypes (Willcutt & Pennington, 2000a).

More systematic research into the co-occurrence of reading problems and psychiatric disorders is needed, as most prior studies have focused on reading problems and ADHD. No previous studies have examined the co-occurrence of reading problems and all major psychiatric disorders. Moreover, there are no available data regarding the familial origins of the overlap between reading problems and most child- and adult psychiatric disorders. Finally, even though reading problems tend to persist into adulthood, there is a dearth of studies of co-occurring psychiatric disorders in adult populations.

In the current study, we estimated risks of ADHD, autism, obsessive-compulsive disorder (OCD), anorexia nervosa, schizophrenia, bipolar disorder, depression, substance use disorder, and violent/non-violent criminality, in individuals with reading problems and their siblings, using linkage between nation-wide Swedish registers.

2. Materials and Methods

2.2 Swedish registers

Following approval from the Regional Ethics Committee in Stockholm, we linked the Swedish Scholastic Aptitude Test Register (SSATR), the National Patient Register (NPR), the

National Crime Register (NCR), and the Multi-Generation Register (MGR). The key for register linkage was the unique personal identification number (PIN) assigned to each Swedish citizen, including immigrants. The SSATR contains data from the Swedish Scholastic Aptitude Test (SweSAT), which is administered by The Swedish Council for Higher Education. The SweSAT has been used as a selection instrument for tertiary education since 1977 (Carlstedt & Gustafsson, 2005). During the last decade, the number of SweSAT participants has varied between 65.000 and 145.000 individuals yearly, and by 2015, more than 1.4 million individuals had completed the test. Construction, analysis, evaluation, and research on the test is conducted at Umeå University in Sweden. To examine the coverage of the SweSAT, we defined a cohort of individuals born between 1970 and 1980, alive and not emigrated by year 2015 (N=1,178, 514). Out of these, 34.9% (54.4% females) had participated in the SweSAT.

The NPR (Ludvigsson et al., 2011) contains diagnoses assigned by medical doctors according to *The International Statistical Classification of Diseases* (ICD). Inpatient data are available since 1969, and outpatient data since 2001. The MGR contains information about the identity of biological parents of individuals born in Sweden since 1932. With this information, it is possible to identify siblings of individuals with reading problems.

The NCR contains complete crime statistics for individuals aged 15 years and older since 1973, based on convictions in district courts.

2.3 Definitions of disorders and criminality

In the SSATR, there is information about an adapted version of the SweSAT designed for individuals with reading problems. There are two ways that individuals can qualify for taking this adapted test; 1) a documented diagnosis of specific reading disorder (F81.0 in ICD-10) or mixed learning disorder (including problems with reading, spelling, and mathematics; F81.3

in ICD-10), or 2) an official document from a designated licensed speech and language pathologist or special education teacher. The speech and language pathologist/special education teacher needs to formally test word decoding, reading comprehension, phonological awareness, and reading speed with adequate, normed tests. The medical history (including heredity), language development, and school functioning are also documented in an interview. In the official document, the issuer then certifies that the applicant has specific reading problems of a type that requires prolonged test time during the SweSAT. Hence, our definition of reading problems was based on confirmed diagnoses of F81.0, F81.3, or an official reading problems document.

ADHD was defined according to the following diagnoses: F90 (ICD-10) or 314 (ICD-9); autism as F84 (ICD-10) or 299 (ICD-9); OCD as F42 (ICD-10); anorexia nervosa as F50.0-1 (ICD-10); schizophrenia as F20 (ICD-10), 295A-G, 295W, 295X (ICD-9), 295.0-6, 295.8, 295.9 (ICD-8). Bipolar disorder was defined using a validated algorithm (20). Depression was defined according to F32-33, F34.1, F34.8-9, F38.1 (ICD-10), 296B, 300E, 311 (ICD-9), 296.0, 300.4 (ICD-8); and substance use disorder according to F10-16 or F18-20 (ICD-10). We did not distinguish between inpatient/outpatient diagnoses, and we included both primary and secondary diagnoses. Criminality was defined as a violent/non-violent crime conviction record in the NCR.

2.4 The validity of ICD codes in the NPR

Validation studies have examined ICD diagnoses **in the NPR** against medical files, structural interviews and research diagnoses, and indicate positive predictive values above 90% for schizophrenia and bipolar disorder diagnoses (Sellgren et al., 2011; Ekholm et al., 2005; Dalman et al., 2002; Lichtenstein et al., 2006). Furthermore, recent studies have demonstrated positive predictive values above 90% for OCD and tic disorder (Ruck et al., 2015). While we are unaware of any formal validation studies targeting the other disorders in this study, severe

disorders generally have high positive predictive values (Ludvigsson et al., 2011).

Furthermore, in Denmark, where similar registers are held, a recent study showed that the autism diagnoses in the Danish Patient Register predicted a medical file review diagnosis with 94% certainty (Lauritzen et al., 2010).

2.5 Statistical analyses

First, we examined the risk of psychiatric disorders and criminality in individuals with reading problems. Each individual with reading problems was matched with ten randomly selected comparison individuals from the general population who had the same sex and birth year, and had participated in the SweSAT. **Moreover, using reading problems as a binary independent variable**, we adjusted the associations for IQ (measured with the total SweSAT score, a valid IQ measure; Carlstedt & Gustafsson, 2005). Some studies have attempted to examine the specificity of the association between reading problems and the disorder of interest (e.g. conduct disorder), by statistically adjusting for the presence of other co-occurring psychiatric disorders (Willcutt & Pennington, 2000a; Maughan et al., 2003). In a third model, we therefore mutually adjusted the risk of psychiatric disorders, and criminality for all other psychiatric disorders, and criminality and IQ. **Furthermore, we estimated risks of psychiatric disorders and criminality in individuals scoring above the 10th percentile of the total SweSAT score distribution, to ensure that potential associations would not be specific for individuals with low IQ. The results from these analyses are presented in Supplementary Table 1.**

The risk of psychiatric disorders and criminality was estimated also in siblings of individuals with reading problems. Only siblings who did not have reading problems themselves according to our definition were included in the analyses. For each of these siblings, and for each of their matched comparison individuals, ten comparison siblings matched on sex and birth year were assigned at random. Overlapping familial (genetic and/or environmental) risks

are assumed when individuals with reading problems but not the second disorder of interest (e.g. ADHD) have siblings without reading problems, but an excess risk of ADHD (Szatmari et al., 2007), so we specified the analyses according to these conditions. Risk ratios (RR) with corresponding 95% confidence intervals (CI) were obtained from conditional logistic regressions, and a robust sandwich estimator was applied to adjust for the correlated sibling data. **Finally, we adjusted the sibling analyses for the potential effect of IQ.**

3. Results

Sample characteristics are presented in Table 1. We identified 8,719 individuals with reading problems, with an average age of 23 years at the time of their first SweSAT test.

3.1 Co-occurrence analyses: risks of psychiatric disorders and criminality in individuals with reading problems

As shown in Table 2, the risk of psychiatric disorders (except anorexia nervosa) and criminality was elevated in individuals with reading problems, with risk ratios between 1.37 and 4.91 (RR in Table 2). The magnitude of the risk ratios were higher for childhood-onset psychiatric disorders, such as ADHD (RR 4.91, CI 4.30-5.61) and autism (RR 3.10, CI 2.41-3.77), than for disorders with onset in adolescence or adulthood, such as bipolar disorder (RR 1.94, CI 1.50-2.50) and substance use disorder (RR 1.59, CI 1.42-1.79). IQ explained part of the associations between reading problems and criminality, but was not important for the other associations (RR¹ in Table 2). **All associations remained unchanged when excluding individuals with low IQ (Supplementary Table 1).** In the multivariate model, significant associations between reading problems and ADHD, autism, depression, substance use disorder, and non-violent criminality remained after adjusting for all other psychiatric disorders and IQ, with risk ratios between 1.13 and 3.70 (RR² in Table 2)

3.2 Familial overlap analyses: risks of psychiatric disorders and criminality in unaffected siblings of individuals with reading problems

Table 3 indicates that unaffected siblings of individuals with reading problems had increased risks of ADHD, autism, schizophrenia, bipolar disorder, depression, substance use disorder, and non-violent criminality, with risk ratios between 1.14 and 1.70. **When IQ was adjusted for, the risks of ADHD, schizophrenia, and criminality increased, whereas the risk estimates for the other disorders remained stable (Supplementary Table 2).**

4. Discussion

We found that individuals with reading problems had increased risks of ADHD, autism, OCD, bipolar disorder, depression, substance use disorder, and criminality. Risks were generally higher for childhood-onset disorders than for adolescent and adult-onset disorders. The increased risks remained after adjusting for IQ, and in a multivariate model, associations between reading problems and ADHD, autism, depression, substance use disorder, and non-violent criminality remained after adjustment for all psychiatric disorders, as well as IQ.

The familial overlap analyses showed that excess risks of ADHD, autism, schizophrenia, bipolar disorder, depression, substance use disorder, and non-violent criminality were also present in unaffected siblings of individuals with reading problems.

4.1 Co-occurrence analyses: risks of psychiatric disorders and violent criminality in individuals with reading problems

Prior reports evidence an overrepresentation of ADHD (Willcutt & Pennington, 2000a; Willcutt & Pennington, 2000b; Carroll et al., 2005) depression (Willcutt & Pennington, 2000a; Maughan et al. 2003; Snowling et al., 2007; Carroll et al., 2005; Boetsch et al., 1996), antisocial behavior (Carroll et al., 2005), and conduct disorder (Carroll et al., 2005) in **childhood and adolescent** samples with reading problems. Our findings are consistent with earlier studies regarding overlaps between reading problems and ADHD and depression, and extend the literature with several new findings; the excess risks of OCD, bipolar disorder, substance use disorder, and criminality have not been previously documented in samples with reading problems. The associations between reading problems and substance use disorder, and criminality, are however in keeping with prior small studies suggesting that reading problems are common in populations under drug treatment (Yates, 2013) forensic psychiatric care (Dåderman et al., 2004) and prison care (Kirk & Reid, 2001; Lindgren et al., 2002).

When the effect of IQ was accounted for, the associations between reading problems and criminality decreased, whereas all other associations remained. **Furthermore, none of the associations decreased when individuals with low IQ were excluded. These findings** suggest that the associations between reading problems and major psychiatric disorders exist above and beyond that which they share with general cognitive ability, **and that these associations are not specific for individuals with low IQ.**

Two studies have reported mixed results when they assessed the specificity of associations between reading problems and psychopathology by controlling for co-occurring psychiatric disorders. Whereas the association between reading problems and conduct disorder seems to be largely explained by co-occurring ADHD (Willcutt & Pennington, 2000a; Maughan et al.,

1996), the association between reading problems and depression is not (Willcutt & Pennington, 2000a; Maughan et al., 2003). In the multivariate model in our study, the associations between reading problems and ADHD, autism, depression, substance use disorder, and non-violent criminality remained after controlling for all other psychiatric disorders, whereas the other associations decreased. Hence, our results are in line with prior approaches (Willcutt & Pennington, 2000a; Maughan et al., 2003) and add evidence that autism, substance use disorder, and non-violent criminality are also specific correlates of reading problems that cannot be better explained by co-occurrence of reading problems and ADHD, and ADHD and for example substance use disorder (Biederman et al., 1995; Wilens et al., 1997).

These findings may have implications for clinicians working in school health care and health care services, warranting alertness to signs of psychiatric disorders in individuals with reading problems. Moreover, practitioners in psychiatric settings and correctional facilities should consider screening for reading problems, as such problems may have a negative impact on broad patient/client functioning.

4.2 Familial overlap analyses: risks of psychiatric disorders and criminality in siblings to individuals with reading problems

We replicated the previously reported familial overlap between reading problems and externalizing problems, as siblings of individuals with reading problems had elevated risks of being diagnosed ADHD. We also extend current knowledge with new findings; excess risks of autism, schizophrenia, bipolar disorder, depression, substance use disorder, and (non-violent) criminality have not been previously reported **in sibling studies**.

The observed familial overlap between reading problems and schizophrenia is further corroborated by molecular genetic studies, where schizophrenia risk loci associates with

reading problems in the general population (Stefansson et al., 2014). Moreover, reading problems are common in offspring of parents with schizophrenia (Rieder & Nichols, 1979), lending further support to the notion of a familial overlap between reading problems and schizophrenia.

Turning to the excess sibling-risk of bipolar disorder; this finding is novel in epidemiological settings, but nevertheless in keeping with one study reporting that children of parents with bipolar disorder perform worse than controls on standard reading tests (McDonough-Ryan et al., 2002), indicating that shared familial risks might play a role in this association.

The familial overlap we observed between reading problems and depression is not completely consistent with the only prior study in this area (Willcutt & Pennington, 2000a), where no significantly elevated levels of depressive symptoms in co-twins of individuals with reading problems were found, even though the mean level was somewhat higher compared with controls. Reasons behind this discrepancy might be related to insufficient statistical power in the previous report, and/or to the difference in how depression was measured; we relied on inpatient and outpatient diagnoses, whereas the prior study used parent-reports (Willcutt & Pennington, 2000a). Age might also play a role in this difference, as the prior study concerned children and adolescents. Furthermore, as physician-assigned diagnoses are likely to represent more severe phenotypic expressions than parent-reports, it is not surprising that a putative familiarity in the association between reading problems and depression/internalizing problems **is** attenuated when parent-reports are used.

Furthermore, substance use disorder was also overrepresented in siblings of individuals with reading problems. We are not aware of prior studies in **this** field suggesting **either** a genetic or **an** environmental overlap between these problems, and more research is clearly needed.

Finally, there **was** less evidence for increased sibling-risks of OCD, anorexia nervosa, and violent criminality. However, point estimates exceeded 1 for OCD, indicating possible associations that we did not have sufficient statistical power to detect at conventional levels of statistical significance. We observed no evidence of excess risks of anorexia nervosa or violent criminality, meaning that shared familial factors do not seem to be part of the mechanisms behind the excess risks of violent criminality observed in the co-occurrence analyses. Instead, a possible explanation could be that the academic difficulties associated with reading problems may put individuals at risk of becoming more risk-taking and delinquent than their peers.

We were not able to directly assess the extent to which the observed familial overlap between reading problems and psychiatric disorders and criminality was due to genetic or environmental factors. Still, findings from the sibling-analyses suggest that future polygenic risk score approaches should **consider to include** reading problems, which may further improve the genetic liability-based prediction of ADHD, autism, schizophrenia, bipolar disorder, depression, substance use disorder, and criminality. **However, it is important to note that the familial overlap might reflect different underlying mechanisms for different disorders, including an importance of shared environmental factors. Also, one disorder could act as a risk factor for another disorder. Clearly, this important question should be addressed further in more informative data sets.**

4.3 Strengths and limitations

We believe that our study has several strengths; the data is nation-wide and constitutes the largest reading problems sample we are aware of to date. Furthermore, the measurements of psychiatric disorders relied on physician-assigned diagnoses, most of which are thoroughly validated. Also, the matched cohort design efficiently rules out potential cohort effects.

Nonetheless, four limitations should be considered when interpreting the results. First, we lacked quantitative data about reading problems, for example regarding severity or other characteristics. Second, the cohort of individuals with reading problems was selected on participation in the SweSAT, that is, on academic ambition. As a result, findings from this study may not be fully generalizable to the full spectrum of individuals with reading problems. However, we believe that this selection process may also constitute a strength, as reading problems in individuals who aspire to higher studies are probably more specific, that is, less dependent on IQ, than “typical” reading problems. Moreover, **it seems plausible** that individuals with reading problems and academic ambition are less likely to suffer from psychiatric comorbidities than individuals with reading problems who have not participated in SweSAT and therefore might lack academic ambition for various reasons. Hence, the magnitude of the observed associations are likely an underestimation of the true population effects. Third, the statistical power was limited in some analyses. **Fourth**, reading problems are more common among males than females (Rutter et al., 2004), but because females are overrepresented in Swedish tertiary education, our sample consisted of predominantly women. **Finally, we were not able to control for the potential effect of socio-economic status, due to lack of robust measures.** In conclusion, we found that individuals with reading problems are at increased risk of a wide range of psychiatric disorders and violent criminality, and there is a familial overlap between reading problems and ADHD, autism, schizophrenia, bipolar disorder, depression, non-violent criminality, and substance use disorder. These findings have implications for molecular genetic research and highlight the need for clinical alertness for signs of psychiatric disorders in families where reading problems exist. Based on results from our sibling analyses, we conclude that reading problems are most closely related to the two major childhood-onset disorders, i.e., ADHD and autism, and the three most classic adolescent and adult-onset disorders, i.e., schizophrenia, bipolar

disorder, and depression, but in addition also to substance use disorder and non-violent criminality.

Conflict of interest

HL has served as a speaker for Eli-Lilly, and has received a research grant from Shire – are unrelated to the current work

References

- American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC.
- Boada, R., Willcutt E.G., Pennington, B.F., 2012. Understanding the comorbidity between dyslexia and attention-deficit/hyperactivity disorder. *Top. Lang. Disord.* 32, 264-284.
- Biederman, J., Wilens, T., Mick, E., Milberger, S., Spencer, T.J., Faraone. S.V., 1995. Psychoactive substance use disorders in adults with attention deficit hyperactivity disorder (ADHD): effects of ADHD and psychiatric comorbidity. *Am. J. Psychiatry* 152,1652-1658.
- Boetsch, E.A., Green, P.A., Pennington, B.F., 1996. Psychosocial correlates of dyslexia across the life span. *Dev. Psychopathol.* 8, 539-562.
- Carlstedt, B., Gustafsson, J.E., 2005. Construct validation of the Swedish scholastic aptitude test by means of the Swedish enlistment battery. *Scand. J. Psychology* 46, 31-42.
- Carroll, J.M., Maughan, B., Goodman, R., Meltzer, H., 2005. Literacy difficulties and psychiatric disorders: Evidence for comorbidity. *J. Child. Psychol. Psychiatry* 46, 524-532.

- Dalman, C., Broms, J., Cullberg, J., Allebeck, P., 2002. Young cases of schizophrenia identified in a national inpatient register-are the diagnoses valid? *Soc. Psychiatry Psychiatr. Epidemiol.* 37, 527-531.
- Dåderman, A.M., Lindgren, M., Lidberg, L., 2004. The prevalence of dyslexia and AD/HD in a sample of forensic psychiatric rapists. *Nord. J. Psychiatry* 58, 371-381.
- Ekholm, B., Ekholm, A., Adolfsson, R., Vares, M., Osby, U., Sedvall, G.C., Jönsson, E.G., 2005. Evaluation of diagnostic procedures in Swedish patients with schizophrenia and related psychoses. *Nord. J. Psychiatry* 59, 457-464.
- Horrobin, D.F., Glen, A.I.M., Hudson, C.J. 1995. Possible relevance of phospholipid abnormalities and genetic interactions in psychiatric disorders: the relationship between dyslexia and schizophrenia. *Med. Hypotheses* 45, 605-613.
- Kirk, J., Reid, G., 2001. An examination of the relationship between dyslexia and offending in young people and the implications for the training system. *Dyslexia* 7, 77-84.
- Lauritsen, M.B., Jørgensen, M., Madsen, K.M., Lemcke, S., Toft, S., Grove, J., Schendel, D.E., Thorsen, P., 2010. Validity of childhood autism in the Danish Psychiatric Central Register: findings from a cohort sample born 1990–1999. *J. Autism Dev. Disord.* 40, 139-148.
- Lichtenstein, P., Bjork, C., Hultman, C.M., Scolnick, E., Sklar, P., Sullivan, P.F., 2006. Recurrence risks for schizophrenia in a Swedish national cohort. *Psychol. Med.* 36, 1417-1425.
- Light, J.G., Pennington, B.F., Gilger, J.W., DeFries, J.C., 1995. Reading disability and hyperactivity disorder: Evidence for a common genetic etiology. *Dev. Neuropsychol.* 11, 323-335.

Lindgren, M., Jensen, J., Dalteg, A., Meurling, A.W., Ingvar, D.H., Levander, S., 2002.

Dyslexia and AD/HD among Swedish prison inmates. *J. Scand. Studies Criminol. Crime Prev.* 3, 84-95.

Ludvigsson, J.F., Andersson, E., Ekbom, A., Feychting, M., Kim, J.L., Reuterwall, C., Heurgren, M., Otterblad, Olausson, P., 2011. External review and validation of the Swedish national inpatient register. *BMC Public Health* 11,450.

Maughan, B., Pickles, A., Hagell, A., Rutter, M., Yule, W., 1996. Reading problems and antisocial behaviour: developmental trends in comorbidity. *J. Child Psychol. Psychiatry* 37, 405-418.

Maughan, B., Rowe, R., Loeber, R., Stouthamer-Loeber, M., 2003. Reading problems and depressed mood. *J. Abnorm. Child Psychology* 31, 219-229.

McDonough-Ryan, P., DelBello, M., Shear, P.K., Ris, M.D., Soutullo, C., Strakowski, S.M., 2002. Academic and cognitive abilities in children of parents with bipolar disorder: a test of the nonverbal learning disability model. *J. Clin. Exp. Neuropsychology* 24, 280-285.

Morgan WP (1896). A case of congenital word blindness. *BMJ* 2,1378.

Revheim, N., Butler, P.D., Schechter, I., Jarlbrzikowski, M., Silipo, G., Javitt, D.C., 2006.

Reading impairment and visual processing deficits in schizophrenia. *Schizophr. Res.* 87, 238-245.

Richardson, A.J., 1994. Dyslexia, handedness and syndromes of psychosis-proneness. *Int. J. Psychophysiol.* 18, 251-263.

Rieder, R.O., Nichols, P.L., 1979. The offspring of schizophrenics. 3. Hyperactivity and neurological soft signs. *Arch. Gen. Psychiatry* 368, 665-674.

Rutter, M., Caspi, A., Fergusson, D., Horwood, L.J., Goodman, R., Maughan, B., Moffitt, T.E., Meltzer, H., Carroll, J., 2004. Sex differences in developmental reading disability: new findings from 4 epidemiological studies. *JAMA* 292, 2007-2012.

Rück, C., Larsson, K.J., Lind, K., Perez-Vigil, A., Isomura, K., Sariaslan, A., Lichtenstein, P., Mataix-Cols, D., 2015. Validity and reliability of chronic tic disorder and obsessive-compulsive disorder diagnoses in the Swedish National Patient Register. *BMJ Open* 5, e007520.

Sellgren, C., Landén, M., Lichtenstein, P., Hultman, C.M., Långström, N., 2011. Validity of bipolar disorder hospital discharge diagnoses: file review and multiple register linkage in Sweden. *Acta Psychiatr. Scand.* 124, 447–453.

Snowling, M.J., Muter, V., Carroll, J., 2007. Children at family risk of dyslexia: a follow-up in early adolescence. *J. Child Psychol. Psychiatry* 48, 609-618.

Stefansson, H., 2014. CNVs conferring risk of autism or schizophrenia affect cognition in controls. *Nature* 505, 361-366.

Szatmari, P., White, J., Merikangas, K., 2007. The use of genetic epidemiology to guide classification in child and adult psychopathology. *Int. Rev. Psychiatry* 19, 483-496.

Vellutino, F.R., 1979. The validity of perceptual deficit explanations of reading disability: a reply to Fletcher and Satz. *J. Learn. Disabil.* 12, 160-167.

Vellutino, F.R., Fletcher, J.M., Snowling, M.J., Scanlon, D.M., 2004. Specific reading disability (dyslexia): What have we learned in the past four decades? *J. Child Psychol. Psychiatry* 45, 2-40.

Wilens, T.E., Biederman, J., Mick., E., Faraone, S.V., Spencer, T., 1997. Attention deficit hyperactivity disorder (ADHD) is associated with early onset substance use disorders. *J. Nerv. Ment. Dis.* 185, 475-482.

Willcutt, E.G., Pennington, B.F., 2000a. Psychiatric comorbidity in children and adolescents with reading disability. *J. Child. Psychol. Psychiatry* 41, 1039-48.

Willcutt, E.G., Pennington, B.F., 2000b. Comorbidity of reading disability and attention-deficit/hyperactivity disorder differences by gender and subtype. *J. Learn. Disabil.* 33, 179-191.

Willcutt, E.G., Pennington, B.F., DeFries, J.C., 2000. Twin study of the etiology of comorbidity between reading disability and attention-deficit/hyperactivity disorder. *Am. J. Med. Genet.* 96, 293-301.

Yates, R., 2013. Bad mouthing, bad habits and bad, bad, boys: an exploration of the relationship between dyslexia and drug dependence. *Ment. Health Subst. Use* 6, 184-202.

Table 1. Characteristics of the cohort of individuals with reading problems.

	Individuals with reading problems
Characteristic	n (%)
	8,719 (100)
Sex	
Female	5,072 (58.2)
Years of age at first SweSAT test, mean (range)	
23 (16-61)	
Birth year	
1949-1960	103 (1.2)
1961-1970	454 (5.2)
1971-1980	1,241 (14.2)
1981-1990	3,359 (38.5)
1991-1998	3,561 (40.9)
SweSAT test year (first test)	
1996-2000	694 (8.0)
2001-2005	1,408 (16.2)
2006-2010	2,206 (25.8)
2011-2015	4,357 (50.0)

Table 2. Crude (RR) and adjusted (RR^{1,2}) risk ratios with 95% confidence intervals (CI) of psychiatric disorders in individuals with reading problems, compared with matched comparison individuals. Statistically significant risk ratios are bolded.

	Individuals with reading problems (N=8,699)	Matched comparison individuals (N=86,991)			
	n (%)	n (%)	RR (CI)	RR ¹ (CI)	RR ² (CI)
ADHD	334 (3.84)	703 (0.81)	4.91 (4.30-5.61)	4.83 (4.21-5.52)	3.67 (3.18-4.25)
Autism	101 (1.16)	339 (0.39)	3.01 (2.41-3.77)	3.43 (2.73-4.32)	1.60 (1.25-2.05)
OCD	64 (0.74)	457 (0.53)	1.40 (1.08-1.83)	1.38 (1.06-1.80)	0.92 (0.69-1.21)
Anorexia nervosa	48 (0.55)	441 (0.51)	1.09 (0.81-1.47)	1.20 (0.89-1.62)	0.92 (0.67-1.25)
Schizophrenia	12 (0.14)	82 (0.09)	1.47 (0.80-2.69)	1.36 (0.74-2.51)	0.96 (0.51-1.80)
Bipolar disorder	72 (0.83)	374 (0.43)	1.94 (1.50-2.50)	2.05 (1.59-2.66)	1.08 (0.82-1.42)
Depression	631 (7.25)	3,393 (3.90)	1.94 (1.78-2.12)	2.04 (1.87-2.23)	1.66 (1.50-1.83)
Substance use disorder	338 (3.89)	2,156 (2.48)	1.59 (1.42-1.79)	1.55 (1.37-1.74)	1.18 (1.04-1.34)
Violent criminality	124 (1.43)	917 (1.05)	1.37 (1.13-1.65)	1.19 (0.98-1.44)	0.91 (0.74-1.11)
Non-violent criminality	684 (7.9)	5,265 (6.05)	1.34 (1.23-1.46)	1.23 (1.13-1.34)	1.13 (1.04-1.24)

RR¹, risk ratios adjusted for SweSAT score, as a proxy for IQ. RR², risk ratios from a multivariate model where all associations were adjusted for all psychiatric disorders, criminality, and IQ. A total of 18 individuals with reading problems (0.003%) were not matched with any comparison individuals due to incomplete demographic information.

Table 3. Risk ratios (RR) with 95% confidence intervals (CI) of psychiatric disorders and crime convictions in non-affected siblings to individuals with reading problems, compared with matched siblings of non-affected comparison individuals. Statistically significant risk ratios are bolded.

	Siblings of individuals with reading problems	Siblings of comparison individuals	
	n (%)	n (%)	RR (CI)
ADHD	232 (2.14)	1,535 (1.42)	1.53 (1.33-1.74)
Autism	129 (1.10)	968 (0.83)	1.31 (1.09-1.57)
OCD	75 (0.67)	635 (0.57)	1.18 (0.94-1.49)
Anorexia nervosa	43 (0.39)	420 (0.38)	1.02 (0.76-1.38)
Schizophrenia	33 (0.30)	195 (0.17)	1.70 (1.21-2.39)
Bipolar disorder	63 (0.57)	453 (0.41)	1.39 (1.09-1.79)
Depression	483 (4.64)	3,834 (3.69)	1.28 (1.16-1.40)
Substance use disorder	334 (3.10)	2,749 (2.55)	1.22 (1.09-1.37)
Violent criminality	228 (2.07)	2,213 (2.01)	1.03 (0.89-1.19)
Non-violent criminality	877 (8.51)	7,834 (7.61)	1.14 (1.05-1.23)