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Taylor, Mark J; Lichtenstein, Paul; Larsson, Henrik; Anckarsäter, Henrik; Greven, Corina U; Ronald, Angelica

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Is there a female protective effect against ADHD? Evidence from two representative twin samples.

Mark J. Taylor, PhD*

Department of Medical Epidemiology & Biostatistics, Karolinska Institutet, Stockholm, Sweden

Paul Lichtenstein

Henrik Larsson

Henrik Anckarsäter

Corina U. Greven

Angelica Ronald, PhD

Centre for Brain & Cognitive Development, Department of Psychological Sciences, Birkbeck, University of London, UK

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Abstract

Objective: Attention-deficit/hyperactivity disorder (ADHD) is more common in males than females, yet little is known about why this is the case. We aimed to test for the existence of a 'female protective effect' against ADHD traits in two European twin samples. Specifically, we aimed to test whether co-twins of females displaying extreme ADHD traits would display more ADHD traits than co-twins of males displaying extreme ADHD traits.

Method: Parents of approximately 7,000 pairs of non-identical twins in Sweden, and around 4,000 pairs of twins in England and Wales, completed dimensional assessments of ADHD traits. Probands were selected on the basis of scoring within the highest 10% of the distribution in each sample. Dimensional scores of co-twins of probands, as well as the categorical recurrence rate, were investigated by proband sex.

Results: Co-twins of female probands displayed higher mean ADHD trait scores ($\bar{x}$=0.62-0.79) than co-twins of male probands ($\bar{x}$=0.38-0.55) in both samples. This trend was significant in the Swedish sample ($p<.01$) and when the two samples were merged into a single, larger sample ($p<.001$). When the samples were merged, there was also a significant association between proband sex and co-twin's categorical status, with more co-twins of female probands also being probands than co-twins of male probands.

Conclusions: These findings support a female protective effect against ADHD behaviors in the general population, indicating that females require exposure to a greater degree of etiological factors than males to develop ADHD.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition characterized either by excessive hyperactivity and impulsivity, inattentiveness, or a combination of these symptoms[1]. Epidemiological studies suggest that, overall, ADHD affects between 5-7% of the population[2]. Notably, ADHD appears to be substantially more common in males than females. A study of ten European countries, for instance, indicated that males with ADHD outnumbered females with ADHD by ratios of two to one to sixteen to one[3]. The excess of males with ADHD has been further confirmed by meta-analyses, with four times as many males than females thought to be affected[2,4].

A number of twin studies have established that ADHD is amongst the most heritable of neuropsychiatric conditions[5-9]. The high heritability of ADHD does not vary markedly whether it is conceptualized as a categorical, diagnosed condition[5-6] or treated as a continuous trait in the general population[7-9], thus indicating that severe forms of ADHD may be linked genetically with milder, subclinical traits of ADHD in the general population. Such studies, however, have yet to shed light on the reasons why ADHD appears to be so much more common in males than females.

One possible explanation for the sharp sex discrepancy in ADHD prevalence is a putative 'female protective effect' model. Under this model, females would be predicted to require greater exposure to etiological factors associated with ADHD than males in order to display sufficient ADHD behaviors to warrant a diagnosis, thus meaning that fewer females would be expected to be diagnosed with ADHD than males[10-11]. As such, one would expect more causal factors to be present in the families of females with ADHD, leading to the prediction that ADHD and ADHD behaviors will be more prevalent in the relatives of females with ADHD. The female protective effect is presently receiving considerable attention in relation to autism spectrum disorders (ASD), which are similarly male-biased conditions. In one study, for example, the fraternal co-twins of females displaying a high degree of autistic traits displayed more autistic traits than did co-twins of males with pronounced autistic traits, and were also more likely to display high scores themselves[12].

Very few studies have tested for the existence of a female protective effect against ADHD. A recent Swedish investigation suggested that merely having a female co-twin is associated with displaying a greater degree of ADHD traits than having a male co-twin, although this study did not take account of the degree to which the index twin displayed ADHD symptoms[13]. In one study of a US-based twin sample, traits of ADHD were examined in the co-twins of individuals displaying a high degree of traits of ADHD. Co-twins of females displaying marked ADHD traits displayed significantly greater ADHD-like behaviors than the co-twins of males displaying extreme traits of ADHD[14]. Of note, however, the effect was not present for the co-twins of the most severely affected twins, perhaps owing to the small effect size and lower number of twins displaying the very highest scores. No studies since this 2004 investigation have replicated the female protective effect against ADHD in independent samples.

As a consequence, we aimed to test for the existence of a female protective effect against ADHD behaviors in two independent, large-scale European twin samples. We first tested whether the co-twins of females displaying extreme degrees of ADHD traits would exhibit more continuous ADHD traits than the co-twins of high-scoring males. Second, we sought to test whether high scoring female twins were more likely to have a high-scoring co-twin than high scoring male twins. The one previous study documenting this effect reported that the effect size was small[14]; thus, we not only aimed to test for the female protective effect against ADHD in our two samples independently, but also pooled the two samples to increase power. We expected, in light of existing evidence, to find evidence of a female protective effect against ADHD behaviors[13-14].

Method

Participants

Data were collected from participants in two representative, community-based twin studies. The Child and Adolescent Twin Study in Sweden (CATSS) is a study of twins born in Sweden since 1992. Initially, the twins were contacted in connection with their ninth birthdays[15]. For the present study, data were collected from twins participating in CATSS when they were aged 9. The second sample comprised participants in the Twins Early Development Study (TEDS); TEDS is a sample of twins

born in England and Wales between 1994 and 1996[16]. Data for the present study were collected from TEDS participants when twins were aged 8-years. TEDS and CATSS are representative of the populations of England and Wales, and Sweden respectively[15-16].

Both CATSS and TEDS comprise both monozygotic (MZ) and dizygotic (DZ) twins, although only DZ twins were included in this study owing to the fact that the genetic resemblance of two DZ twins within a pair is the same as the resemblance between two singleton siblings (approximately 50% of their segregating DNA code on average). Both same-sex and opposite-sex DZ twins were included. In CATSS, families of 6817 pairs of DZ twins returned data, while 4309 participating families in TEDS returned data. In CATSS, exclusions were conducted for known brain injuries and chromosomal syndromes (N=113), leaving 6704 DZ twin pairs. Participants in TEDS were excluded for genetic and chromosomal syndromes, extreme perinatal complications, and missing first contact data (N=254), leaving 4055 pairs of DZ twins. Combined, there were 10759 DZ twin pairs across the two samples.

CATSS has ethical approval from the Karolinska Institutet Ethical Review Board, while TEDS has ethical approval from the King's College London, Institute of Psychiatry, Psychology and Neuroscience Ethics Committee.

Measures

Different measures were used to assess traits of ADHD in both samples. In CATSS, the ADHD modules of the Autism-Tics, ADHD, and Other Comorbidities inventory (A-TAC)[17] were administered to parents of the twins over the telephone. There are two ADHD modules, assessing hyperactivity/impulsivity and inattentiveness, comprising a total of 18 items that correspond closely to DSM-IV criteria for ADHD[1]. Each item comprised a question, answered 'yes' (for a score of 1), 'yes, to some extent' (for a score of 0.5), or 'no' (for a score of 0). Thus, the maximum possible score was 18. In the sample of DZ twins used in the present study, the A-TAC ADHD module had strong internal consistency ($\alpha = .92$). A prior study reported strong construct validity for the scale, with 92% sensitivity and 75% specificity for detecting ADHD[18].

Parents of twins participating in TEDS completed the ADHD subscale of the Conners' Parent Rating Scale-Revised (Conners ADHD)[19]. The measure was mailed out to parents of the twins, who completed and returned it. Like the A-TAC, the Conners ADHD measure comprises 18 items that are closely linked with the DSM-IV criteria for ADHD[1]. Each item comprised a statement, in response to which the parents rated, on a 0-3 scale, the extent to which each item was true of their children The maximum possible score was hence 54. In the present study, the Conners ADHD showed strong internal consistency ($\alpha = .91$). Previously, individuals with ADHD have been shown to score more highly on the measure than controls[19], supporting its construct validity.

Data Analysis

Proband Selection

In both samples, one twin was randomly selected as the 'index twin'. All other twins were co-twins. Probands were selected as the index twins scoring within the highest 10% of the A-TAC and Conners ADHD distributions, with such a cut-off designed to maximize statistical power while capturing severe enough cases. Thus, probands in CATSS were selected on the basis of A-TAC scores of 6.5 or more, while TEDS probands were defined as index twins scoring at least 23 on the Conners ADHD. Subsequently, analyses were repeated using more conservative cut-offs of 9.5 on the A-TAC and 28 on the Conners ADHD. These cut-offs were designed to capture the highest scoring 5% of each sample, thus testing for a female protective effect in relation to even more extreme scores. The number of probands, split by sex, is given in Table 1.

Statistical Analysis

To test whether co-twins of female probands would display higher ADHD trait scores than co-twins of male probands, 3x2 between subjects analysis of variance (ANOVA) was employed. Proband status of the index twin (male proband, female proband, or control) was the grouping variable, with co-twins' ADHD trait scores acting as the outcome variable. An omnibus test initially compared scores across co-twins of male probands, female probands, and controls, before planned comparisons compared the

scores of co-twins of male and female probands. All p-values were adjusted within each sample for multiple comparisons using Bonferroni corrections. Effect sizes were summarized using Cohen's *d*.

To test whether sex of the probands was associated with whether or not their co-twin would also be a proband, categorical analyses were employed. Using the above identified cut-offs, co-twins were classified as either 'Affected' (ie scoring above a given cut-off) or 'Unaffected' (ie scoring below a given cut-off). Chi-square tests of association were then used to test whether co-twin status was significantly associated with proband sex. Effect sizes were summarized using odds ratios.

Analyses were first conducted separately in CATSS and TEDS. To bolster statistical power, a third set of analyses was performed on the two samples combined. The Conners ADHD and A-TAC were both heavily, positively skewed and were therefore log transformed prior to analysis (see Table 2). A-TAC and Conners ADHD scores were standardized by sex to control for the effect of co-twin sex, and to account for the use of different measurement scales across the two samples. All analyses were performed in R[20].

Results

Descriptive statistics for the A-TAC and Conners ADHD are given in Table 2.

Analysis of Continuous Scores

Mean standardized scores of co-twins of male probands, female probands, and controls are all shown in Figure 1 for the analyses using the 10% cut-offs. In CATSS, scores differed significantly across the three groups, $F_{2,6688}$=79.35, p<.01, with co-twins of female probands scoring highest ($\bar{x}$=0.62), followed by co-twins of male probands ($\bar{x}$=0.38), and co-twins of controls ($\bar{x}$=-0.05). Specifically, co-twins of female probands displayed significantly higher A-TAC scores than co-twins of male probands, t_{6688}=-2.84, p<.01, with a modest effect size, *d*=.07.

Similarly in TEDS, Conners ADHD scores differed significantly across co-twins of male probands ($\bar{x}$=0.55), co-twins of female probands ($\bar{x}$=0.79), and co-twins of controls ($\bar{x}$=-0.07), $F_{2,4040}$=102.30, p<.001. Planned contrasts, however, indicated that mean Conners ADHD scores were not significantly elevated in co-twins of female probands relative to co-twins of male probands, t_{4040}=-2.36, p=.08, *d*=.07, despite a trend in this direction.

Merging the two samples produced the same pattern; mean ADHD trait scores differed significantly the three groups, $F_{2,10731}$=175.90, p<.001, with co-twins of female probands showing the highest ADHD trait scores ($\bar{x}$=0.69), followed by co-twins of male probands ($\bar{x}$=0.45), and controls ($\bar{x}$=-0.06). The planned contrast confirmed that mean ADHD trait scores were significantly higher for co-twins of female probands than co-twins of male probands, t_{10731}=-3.73, p<.001, *d*=.07.

All mean ADHD trait scores for co-twins of probands selected under the more severe, 5% cut-offs are given in Table 3. In both CATSS and TEDS, the same trend emerged. In CATSS, mean A-TAC scores differed significantly across co-twins of male probands ($\bar{x}$=0.43), female probands ($\bar{x}$=0.69), and controls ($\bar{x}$=-0.03), $F_{2,6688}$=46.39, p<.01, however mean A-TAC scores for co-twins of female probands were not significantly higher than mean A-TAC scores for co-twins of male probands, t_{6688}=-2.10, p=.16, *d*=.05. The same result emerged for TEDS; while the main effect of index twin status was significant, $F_{2,4040}$=51.63, p<.001, with co-twins of female probands showing the highest mean Conners ADHD scores ($\bar{x}$=0.79), followed by co-twins of male probands ($\bar{x}$=0.62) and controls (-0.04), mean Conners ADHD scores for co-twins of female probands were not significantly higher than mean scores for co-twins of male probands, t_{4040}=-1.10, p=.27, *d*=.03.

Merging the two samples using the 5% cut-offs produced the same pattern of results. Index twin status exacted a significant main effect on the mean ADHD trait scores of co-twins, $F_{2,10731}$=95.90, p<.001, with co-twins of female probands displaying the highest ADHD trait scores ($\bar{x}$=0.73), followed by co-twins of male probands ($\bar{x}$=0.51) and controls ($\bar{x}$=-0.03). Mean ADHD trait scores were significantly elevated in co-twins of female probands compared with co-twins of male probands, t_{10731}=-2.38, p<.05, *d*=.05.

Analysis of Categorical Recurrence

Table 4 shows the number of affected and unaffected co-twins by proband sex for each sample and cut-off. In CATSS, a greater proportion of co-twins of female probands scoring above the 10% also scored above the cut-off (15% of co-twins of female probands compared with 9% of co-twins of male probands. The association was small and non-significant, however, χ^2_1=4.67, p=.06, OR=1.57 (0.34/1.92). Similarly in TEDS, 38% of co-twins of female probands scored above the 10% cut-off compared with 29% of co-twins of male probands, although this association was again small and failed to reach significance, χ^2_1=3.23, p=.14, OR=1.66 (0.43/2.01). Using a 10% cut-off to select probands, the association between proband sex and co-twin status was only significant when CATSS and TEDS were merged, χ^2_1=5.21, p<.05, OR=1.70 (0.52/1.94), with a greater proportion of co-twins of female probands (29%) than co-twins of male probands (22%) showing higher ADHD trait scores.

The findings followed the same pattern when a cut-off that selected 5% of index twins as probands was used. In CATSS, more co-twins of female probands (21%) than co-twins of male probands (12%) were affected, yet this association was not significant, χ^2_1=3.35, p=.14, OR=1.53 (0.28/1.99). The same was true of TEDS; more co-twins of female probands (33%) than co-twins of male probands (22%) were affected, yet this seeming association was not significant, χ^2_1=2.46, p=.24, OR=1.56 (0.29/2.08). Only in pooling together CATSS and TEDS data did a significant association emerge, χ^2_1=6.38, p<-.05, OR=1.54 (0.35/1.86), with a greater proportion of co-twins of female probands (26%) than co-twins of male probands (16%) showing a pronounced degree of ADHD traits.

Discussion

This investigation sought to test whether a female protective effect can account for the substantially elevated prevalence of ADHD in males relative to females[2-4]. The results of this study lend partial credence to a female protective effect hypothesis for ADHD. In line with the results of an existing US study[14] and our hypotheses, there was some evidence to indicate that the co-twins of females displaying an extreme degree of characteristic ADHD behaviors displayed more such behaviors themselves than did the co-twins of males showing an extreme degree of ADHD traits. Further, co-twins of females

with particularly high ADHD trait scores were more likely to display an extreme degree of ADHD behaviors than were the co-twins of males. As such, these findings tentatively indicate that a female protective effect could be a potentially viable model to aid understanding the development of ADHD.

Our findings provide a platform for future research into the genetic basis of ADHD to build upon. While twin studies of ADHD have consistently supported its high heritability[5-9], elucidating the precise genetic mechanisms underpinning ADHD has proven elusive[21]. The female protective effect model provides an opportunity to raise further research questions in such research. For example, genes can be divided into high-impact and low-impact sets[22]. One possibility is that females with ADHD are more likely to inherit higher impact genes associated with ADHD, which are rarer. To illustrate, ASD also more commonly affect males than females[23], and recent twin and family studies support a female protective effect against ASD[12,24]. A genetic study then indicated that females with ASD displayed a higher degree of larger copy number variants, which were more likely to be maternally inherited[11]. Similar studies of ADHD may well prove useful in furthering our understanding of the etiology of ADHD.

Indeed, while our study did not investigate any specific etiological mechanisms associated with ADHD, our findings suggest that investigating the degree of exposure to etiological factors associated with ADHD in males and females with the condition may be a worthwhile future research direction. While the above example mentioned larger, rarer copy number variants, one might also test whether females with ADHD exhibit a greater number of smaller, common genetic variants. Indeed, in using polygenic scores, which have yielded useful insights in the genetic architecture of ADHD[25], one could investigate whether females with ADHD display a greater degree of genetic variants associated with ADHD than males with ADHD[26].

One could also extend this to causal environmental factors. While twin studies indicate that genetic factors seem to outweigh environmental factors in the etiology of ADHD[5-9], research has implicated certain environmental exposures with ADHD. For instance, lower birth weight is thought to be a causal environmental factor in ADHD[27-28]. It may be that females with ADHD undergo greater exposure to

such factors compared with males; for instance, could females with ADHD display an even lower birth weight than males with ADHD?

The presence of a female protective effect against ADHD behaviors also has implications for clinical practice. If clinicians take account of family history when diagnosing ADHD, it may be beneficial to also account for the sex of any previously affected relatives, under the assumption that relatives of females with ADHD are more likely to exhibit ADHD symptoms than relatives of males with ADHD. The caveat to this assertion, however, is that our findings are based only on twin data. The female protective effect against ADHD needs to be replicated in alternative, non-twin samples before such a conclusion can be decisively drawn. For instance, a recent study of ASD found that siblings of female non-twins with ASD were more likely to have ASD than siblings of male non-twins[24]. Such studies of non-twin relatives are now needed in relation to ADHD.

It does need to be noted that the overall size of the effects reported here, where significant, were small. Indeed, significant findings only emerged for the more severe cut-off of 5% to select probands when the two samples used were merged to create a larger sample. The small effect size seen here is consistent with that reported previously[14], and so it is quite clear that subsequent studies testing the female protective effect model of ADHD are going to need to depend on large samples.

The small female protective effect seen here does, nevertheless, stress the need not to discount alternative explanations for the increased number of males with ADHD relative to females. There is very limited research considering phenotypic differences between males and females with ADHD. For instance, one study investigated sex differences in ADHD across ten European countries, and reported that females with ADHD displayed more emotional difficulties[3]. Furthermore, the DSM-IV criteria for ADHD, upon which our measures were based, are based exclusively on observations of males[1, 29-30].

In addition to the caveat of the small effect size, our study did have further limitations that need taking into account. Proband status was ascertained through use of dimensional questionnaire measures, as opposed to in-depth assessments of ADHD. The use of this approach would, however, have come at the cost of the large sample size. As alluded to above, only twins were used in this study. While we

removed MZ twins to ensure that the genetic relatedness of the relatives in our sample was similar to fraternal siblings, it is important to know whether these findings extend to non-twin relatives in future. In defence of our use of a twin sample, on the other hand, there is evidence to indicate that ADHD traits are not elevated in twins relatives to singletons[31]. Finally, we did not examine the dimensions of hyperactivity/impulsivity and inattentiveness separately. This was intentional; we already had conducted numerous statistical tests, necessitating adjustment of p-values for multiple comparisons. The inclusion of further comparisons would likely have yielded non-significant results, nonetheless future studies of the female protective effect against ADHD should examine the two core ADHD symptom domains separately.

To a certain degree, this study indicates that females are protected against behaviors characteristic of ADHD. While our findings do not speak to any specific mechanisms through which this effect may operate, this study indicates that further research on the female protective effect model is warranted in relation to ADHD, with a view to identify the specific biological basis of this effect. If the effect holds across multiple epidemiological methods, then it represents a plausible explanation for why fewer females than males develop ADHD, as well as assisting in the diagnostic process.

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Table 1 Number of probands

	TEDS		CATSS		Merged Samples	
Cut-Off	N Male	N Female	N Male	N Female	N Male	N Female
5%	146	63	227	95	373	158
10%	291	138	450	201	741	339

TEDS: Twins Early Development Study; CATSS: Child and Adolescent Twin Study in Sweden

Table 2 Descriptive statistics

Measure	Cronbach's α	Possible Range of Scores	$\bar{x}$ Full Sample (SD)	$\bar{x}$ Males (SD)	$\bar{x}$ Females (SD)	Skew
A-TAC [a]	.92	0-18	2.10	2.54 (3.54)	1.62 (2.73)	2.34
Conners ADHD [b]	.91	0-54	10.84 (9.00)	12.67 (9.71)	9.04 (7.85)	1.37

[a] *Mean A-TAC scores were significantly higher for males than females in the full sample,* $t_{6539.22}=11.90$, $p<-.001$, $d=.29$

[b] *Mean Conners ADHD scores were significantly higher for males than females in the full sample,* $t_{3843.64}=13.08$, $p<.001$, $d=.42$

A-TAC: Autism-tics and other comorbidities inventory; Conners ADHD: ADHD subscale of the Conners' Parent Rating Scale

Table 3 Analysis of continuous traits of ADHD in co-twins

	CATSS	TEDS	Merged Samples
Co-Twin of Male Proband $\bar{x}$	0.43 (1.18)	0.62 (0.89)	0.51 (1.08)
Co-Twin of Female Proband $\bar{x}$	0.69 (1.23)	0.79 (1.02)	0.73 (1.15)
Co-Twin of Control $\bar{x}$	-0.03 (0.98)	-0.04 (0.99)	-0.03 (0.99)
Omnibus ANOVA	$F_{2,6688}=46.39$, $p<.01$	$F_{2,4040}=51.63$, $p<.001$	$F_{2,10731}=95.90$, $p<.001$
Planned Contrast	$t_{6688}=-2.10$, $p=.16$, $d=.05$	$t_{4040}=-1.10$, $p=.27$, $d=.03$	$t_{10731}=-2.38$, $p<.05$, $d=.05$

Analyses in this table based on using a cut-off that selected highest scoring 5% of index twins as probands

CATSS: Child and Adolescent Twin Study in Sweden; TEDS: Twins Early Development Study; Merged Samples: analyses of both CATSS and TEDS, merged into a single dataset

Omnibus ANOVA: comparison of all three conditions (co-twins of male probands, co-twins of female probands, and co-twins of controls); planned contrast: comparison of co-twins of male probands and co-twins of female probands

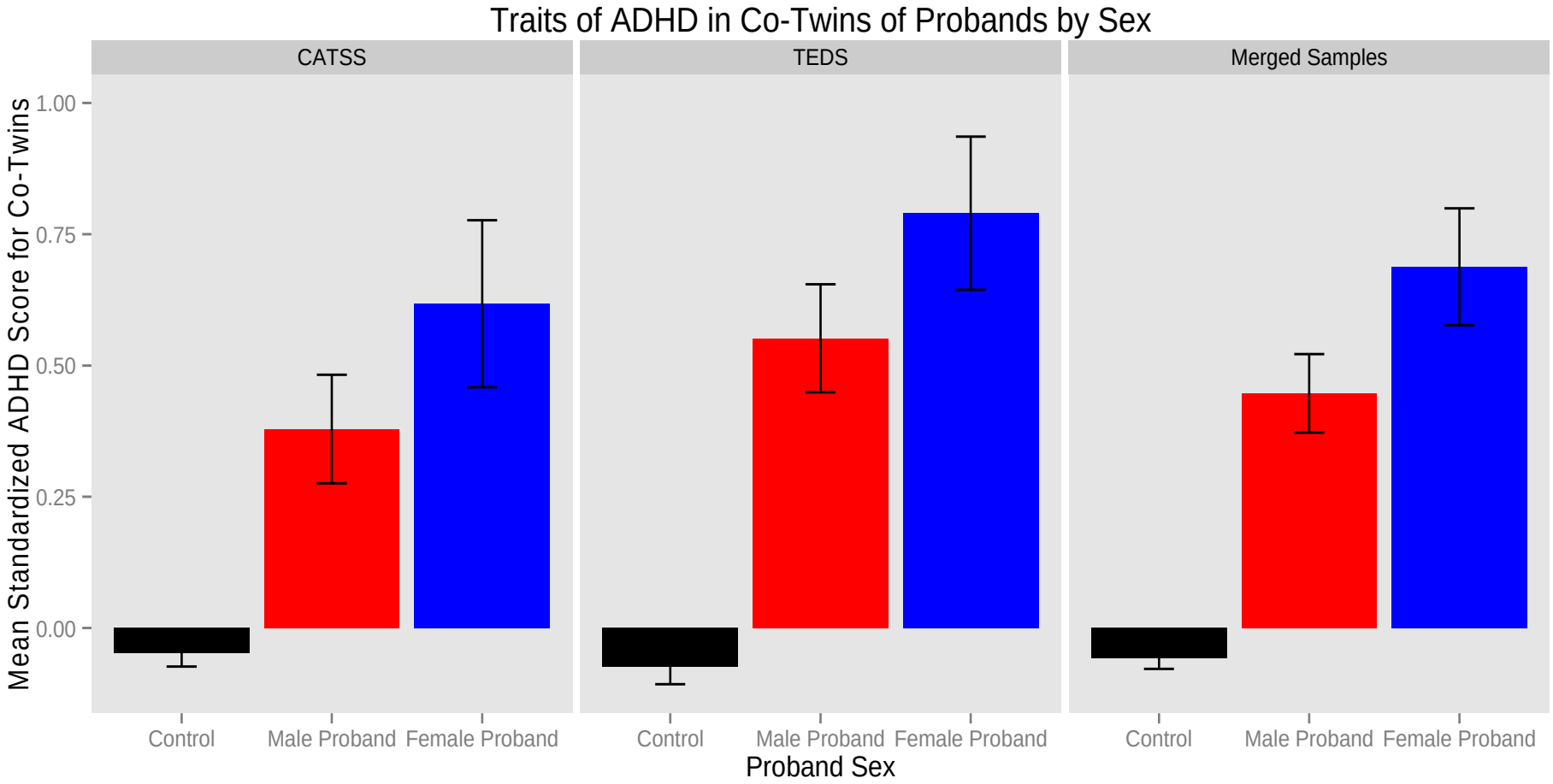
Table 4 Analyses of categorical recurrence rates

CATSS					
	5%			10%	
	'Affected' Co-Twin	'Unaffected' Co-Twin		'Affected' Co-Twin	'Unaffected' Co-Twin
Male Proband	28 (12%)	199 (88%)	Male Proband	40 (9%)	410 (91%)
Female Proband	20 (21%)	75 (79%)	Female Proband	30 (15%)	171 (85%)
	χ^2_1=3.35, p=.14, OR=1.53 (0.28/1.99)			χ^2_1=4.67, p=.06, OR=1.57 (0.34/1.92)	
TEDS					
	5%			10%	
	'Affected' Co-Twin	'Unaffected' Co-Twin		'Affected' Co-Twin	'Unaffected' Co-Twin
Male Proband	32 (22%)	114 (78%)	Male Proband	83 (29%)	208 (71%)
Female Proband	21 (33%)	42 (67%)	Female Proband	52 (38%)	86 (62%)
	χ^2_1=2.46, p=.24, OR=1.56 (0.29/2.08)			χ^2_1=3.23, p=.14, OR=1.66 (0.43/2.01)	
Merged Samples					
	5%			10%	
	'Affected' Co-Twin	'Unaffected' Co-Twin		'Affected' Co-Twin	'Unaffected' Co-Twin
Male Proband	60 (16%)	313 (84%)	Male Proband	163 (22%)	578 (78%)
Female Proband	41 (26%)	117 (74%)	Female Proband	97 (29%)	242 (71%)
	χ^2_1=6.38, p<.05, OR=1.54 (0.35/1.86)			χ^2_1=5.21, p<.05, OR=1.70 (0.52/1.94)	

CATSS: Child and Adolescent Twin Study in Sweden; TEDS: Twins Early Development Study; Merged Samples: analyses of both CATSS and TEDS merged into a single dataset

5% and 10% indicate which cut-off was used to select probands in each analysis (highest scoring 10% of each sample or highest scoring 5% of each sample)

Figure 1 Mean ADHD trait scores of co-twins by proband sex



CATSS: Child and Adolescent Twin Study in Sweden; TEDS: Twins Early Development Study