Journal of Attention Disorders
2016, Vol. 20(11) 934–945

DOI: 10.1177/1087054713506261
jad.sagepub.com
SAGE

Variation in Latent Classes of Adult Attention–Deficit Hyperactivity Disorder by Sex and Environmental Adversity

Jane L. Ebejer[1,2], Sarah E. Medland[2], Julius van der Werf[1], Michael Lynskey[2,3], Nicholas G. Martin[2], and David L. Duffy[2]

Abstract

Objective: The findings of genetic, imaging and neuropsychological studies of attention-deficit hyperactivity disorder (ADHD) are mixed. To understand why this might be the case we use both dimensional and categorical symptom measurement to provide alternate and detailed perspectives of symptom expression. **Method:** Interviewers collected ADHD, conduct problems (CP) and sociodemographic data from 3793 twins and their siblings aged 22 to 49 (M = 32.6). We estimate linear weighting of symptoms across ADHD and CP items. Latent class analyses and regression describe associations between measured variables, environmental risk factors and subsequent disadvantage. Additionally, the clinical relevance of each class was estimated. **Results:** Five classes were found for women and men; few symptoms, hyperactive-impulsive, CP, inattentive, combined symptoms with CP. Women within the inattentive class reported more symptoms and reduced emotional health when compared to men and to women within other latent classes. Women and men with combined ADHD symptoms reported comorbid conduct problems but those with either inattention or hyperactivity-impulsivity only did not. **Conclusion:** The dual perspective of dimensional and categorical measurement of ADHD provides important detail about symptom variation across sex and with environmental covariates. *(J. of Att. Dis. 2016; 20(11) 934-945)*

Keywords

adult ADHD, inattention, impulsivity, conduct problems

Introduction

ADHD is a behavioral disorder that typically manifests during early childhood and continues into adulthood in approximately 50% of cases (Ebejer et al., 2012; Mannuzza, Klein, & Moulton, 2003). The three subtypes of ADHD—inattention, hyperactivity-impulsivity, and combined inattentive and hyperactive-impulsive symptoms—are the core behavioral features of this disorder. For a diagnosis, at least six symptoms of inattention and/or hyperactivity-impulsivity must be present for a 6-month period to a degree that is developmentally inappropriate. However, we and others (Das, Cherbuin, Butterworth, Anstey, & Easteal, 2012; Ebejer et al., 2012) have previously found that more than half the adults within community-based samples reporting that ADHD symptoms caused problems in their lives did not meet these diagnostic criteria. These adults have reported disadvantage across several life domains.

Heterogeneity in ADHD

Another of the characteristic features of ADHD is the heterogeneity in imaging and genetic studies examining the inattentive, hyperactive-impulsive, and combined subtypes (Banaschewski, Becker, Scherag, Franke, & Coghill, 2010; Castellanos et al., 2005; Nikolas & Nigg, 2013). These three subtypes are our primary means of measuring ADHD and do not appear to provide a uniform construct across research methodologies. Linear statistical methods have indicated that separately, the nine inattentive and nine hyperactive-impulsive symptoms represent the most highly correlated clusters of symptoms and together account for approximately half of the variation we see in symptoms. Additional variation is evident in the expression and prevalence of symptoms across sex (Biederman et al., 2008; Rucklidge, 2010), with environmental adversity (Buschgens et al., 1996; Li & Lee, 2012) and comorbid conduct problems (Christiansen et al., 2008; Nikolas & Nigg, 2013).

[1]University of New England, Australia
[2]Queensland Institute of Medical Research, Australia
[3]King's College London, UK

Corresponding Author:
Jane L. Ebejer, Genetic Epidemiology Unit, Queensland Institute of Medical Research, Brisbane, Queensland 4029, Australia.
Email: Jane.Ebejer@qimr.edu.au

Benefits of Latent Class Analysis

Latent class analysis is a statistical method based on categories rather than linear dimensions and allocates ADHD class membership according to the probability with which people report a symptom, conditioned on their previous responses. This technique removes the need to impose a diagnostic threshold on the variation of ADHD-related behaviors within a population and allows for varied combinations of inattentive and hyperactive-impulsive symptoms. Previous studies using latent class analysis to describe variation in ADHD symptoms for children and adolescents have indicated classes are replicable across these samples (Neuman et al., 1999), with adult informants (Althoff et al., 2006), they are heritable (Neuman et al., 1999; Todd et al., 2001) and have identified groups of people reporting symptoms who do not meet diagnostic criteria for inattentive and hyperactive-impulsive subtypes.

Present Study

Previous studies have used latent class and factor analysis to characterize the dimensionality of ADHD symptoms (Ranby et al., 2012). We use these methodologies in an exploratory way to further define ADHD symptoms variation and possibly account for heterogeneity in the results of genetic, structural, and functional imaging studies of people reporting ADHD symptoms. We include ADHD symptoms and symptoms of conduct disorder also reported by these participants within sex-specific latent class analyses to identify behaviors that most often occur together and may vary with sex. Childhood risk factors are modeled as covariates in a latent class regression to measure their association with identified latent classes due to the association between ADHD symptoms and childhood adversity (Biederman, Faraone, & Monuteaux, 2002; Buschgens et al., 1996). We include health factors as an outcome measure for the disadvantage associated with latent classes. The magnitude of genetic effects on latent class membership is estimated using monozygotic (MZ) and dizygotic (DZ) twin concordance rates, and we estimate the clinical relevance of latent classes by cross-tabulating these with diagnosed cases of ADHD.

Method

Participants

Participants were recruited through the Australian Twin Registry (ATR), established to collect data from twins and their families for medical research. For this study, MZ and DZ twins born between 1972 and 1979 were approached by mail with a request for their involvement in a project examining the genetics of cannabis use and mental health. Willing twins returned their consent and agreement to possible contact with additional family members. The family participation rate was 63.7%, and the final sample included 702 female, 290 male, and 225 opposite sex twin pairs, 486 siblings of these twins, and 873 unpaired twins—in total 1,368 men and 2,425 women. The mean age was 32.6 years (SD = 3.3, range = 22-46). Ethics approval was provided by the Queensland Institute of Medical Research Human Research Ethics Committee, ATR ethics, and Washington University School of Medicine Human Research Protection Office. All participants gave informed consent to study participation.

Interview Procedures

Once a twin initiated contact with the ATR, he or she was contacted by an interviewer within approximately 10 days to arrange an interview time. A response booklet for the computer-assisted telephone interview (CATI) and guidance for completion of the online Health and Lifestyle Personality Questionnaire (HLPQ) were then sent with a request that the HLPQ be completed prior to the interview. During the interview, respondents were referred to the response booklet when providing their answer to each item. All interviews were recorded and reviewed by editors to ensure consistency across interviewers and the duration of the study.

Measures

The CATI was structured to collect self-reported sociodemographic variables: family environment during childhood, school grades, educational attainment, emotional and physical well-being, marital status, income level, employment, sexual assault prior to 18 years of age, and data relevant to psychiatric classification. The psychiatric classifications in the CATI were items from the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz, Cadoret, Cloninger, & Dinwiddie, 1994), based on diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., rev.; *DSM-III-R*; American Psychiatric Association [APA], 1987) and the *DSM-IV* (4th ed.; APA, 1994, 2000). Within this measure, 34 items addressed ADHD diagnostic criteria and 109 were specific to conduct problems. The HLPQ included 18 items addressing personal and family circumstances, 24 items adapted from the SSAGA addressing inattention and impulsivity, 74 items from the NEO Personality Inventory–Revised (Costa & McCrae, 1992), and health-related items addressing past and current physical and psychological well-being. All variables within our analyses came from the CATI.

ADHD. We used *DSM-IV* diagnostic criteria to identify inattention: (1) makes careless mistakes, (2) difficulty sustaining attention, (3) does not seem to listen, (4) does not follow through on instructions, (5) difficulty organizing,

(6) avoids sustained mental effort, (7) loses things necessary for tasks, (8) distracted by extraneous stimuli, (9) forgetful in daily tasks; hyperactivity: (1) often fidgets, (2) often leaves seat, (3) inappropriately restless, (4) difficulty remaining quiet, (5) often on the go, (6) talks excessively; and impulsivity: (1) blurts out answers, (2) difficulty awaiting turn, (3) intrudes on others. A positive symptom was recorded by interviewers if the participants reported they experienced this behavior more often than others their age and each response provided the information needed for latent class assignment. A diagnosis of ADHD required (a) six of nine possible inattentive and/or hyperactive-impulsive symptoms experienced over a 6-month period; (c) symptoms were experienced in two functional domains—home and school for childhood retrospective report and work for the report of continuing symptoms, or home and socializing, or school/work and socializing; (d) the problems reported resulted from ADHD symptoms; and (e) participants did not report a previous diagnosis of autism or Asperger's syndrome. The age of onset criterion (b) was not enforced.

Conduct problems. *DSM-IV* diagnostic criteria were used to diagnose conduct disorder. Aggression to people and animals: (1) bullies, (2) initiates fights, (3) has used a weapon, (4) been cruel to people, (5) been cruel to animals, (6) stolen while confronting, (7) forced sexual activity; destruction of property: (8) arson, (9) destroyed others' property; deceitfulness or theft: (10) broken into another's house or car, (11) cons others, (12) stolen nontrivial items; serious violations of rules: (13) stayed out at night, (14) has run away, and (15) truanted. Symptoms were recorded by interviewers if participants reported that they occurred more than once or often and prior to the age of 18. A diagnosis of conduct disorder was given if (a) three symptoms had been present within a 12-month period and (b) symptoms resulted in difficulties socially, academically, or for employment. Antisocial personality disorder was not differentiated from conduct disorder within this study because they are both clinically relevant conditions.

Childhood risk variables. Childhood risk factors were retrospectively reported for ages 6 to 13 and coded as follows: socioeconomic status 1 < average and 2 ≥ average; raised by both parents, 1 = no, 2 = yes; conflict with parents, 1 = no or rarely, 2 = sometimes or often; parental arguing and parental tension, 1 = none or rarely, 2 = sometimes or often; consistent parental rules, 1 = no, 2 = yes; parental drinking, 1 = no or rarely, 2 = sometimes or often; and experiencing a childhood sexual assault, 1 = no, 2 = once or more.

Health-related variables. For health-related factors, days ill (M = 7.3, SD = 23.0) was coded as 1 for < 30 days ill per year, and 2 for ≥ 30 days ill each year; physical and emotional health were represented as follows: 1 = poor, and 2 ≥ average; having close friends, 1 = no, 2 = yes; marital status, 1 = divorced, separated, or unmarried, and 2 = married or widowed. The experience of problem drinking was coded as 1 = no, 2 = yes.

Analyses

Principal Components Analysis

Principal components of the ADHD and conduct disorder items were calculated separately for sex using the psych package in R (Revelle, 2011) with polychoric correlations. This was to confirm that the structure of the ADHD scale corresponded with the known structure of the inattentive and hyperactive-impulsive subtypes. Principal component scores also provided linear inattentive and hyperactive-impulsive dimensions with which to compare participants' latent class membership. A correction was needed to run this analysis; the cross-tabulation of two items on the conduct disorder scale—(6) stolen while confronting and (7) forced sexual activity—resulted in a zero cell frequency so .5 was added to these contingency tables (Brown & Benedetti, 1977) representing an unbiased approximation of expected values based on the real limits of a number.

Latent Class Analysis

Latent class models were run using the R package for polytomous variables (poLCA; Linzer & Lewis, 2007) and Latent Gold 4.5 (Vermunt & Magidson, 2005). Five latent class models with consecutively increasing class number were run to find the best fit to the data separately for women and men. Model selection was guided by Akaike's information criterion (AIC) and the Bayesian information criterion (BIC), with AIC = (2 × parameters) – (2 × log [model likelihood]) representing a trade-off between model complexity and accuracy. BIC is quite similar but incorporates sample size into the estimation of model fit, −2 × log (model likelihood) + parameters × log (n), and begins to increase after the most parsimonious model has been found.

The two symptoms of conduct disorder with *zero* probabilities of being reported were removed from these analyses (forced sex and stolen during confrontation). Family membership was included as a covariate in all models to account for the relatedness of participants and manifest variables were coded as nominal. The childhood risk variables were entered as covariates into a latent class regression model and allowed to interact with latent classes to increase the accuracy of classification and to estimate the effect of the covariate on class membership. Again we entered a covariate at the group level to control for participant relatedness.

Table 1. Latent Class Model Fit Indices.

Assigned classes	AIC	BIC	Log likelihood	Parameters	*n*	*df*
Women					2,427	
3-class	16,666.54	16991.03	−8,277.27	56		2,371
4-class	16,283.48	16,718.06	−8,066.74	75		2,352
5-class	16,137.67	16,682.34[a]	−7,974.84	94		2,333
6-class	16,057.76	16,712.52	−7,915.79	113		2,314
7-class	16,001.01	16,765.87	−7,868.50	132		2,295
Men					1,369	
3-class	12,490.37	12,782.79	−6,189.18	56		1,313
4-class	12,250.81	12,642.45	−6,050.41	75		1,294
5-class	12,143.43	12,634.28[a]	−5977.71	94		1,275
6-class	12,090.12	12,680.18	−5,932.06	113		1,256
7-class	12,059.08	12,748.36	−5,897.54	132		1,237

Note. AIC = Akaike's information criterion; BIC = Bayesian information criterion.
[a]This estimate is the lowest BIC achieved and indicates the most parsimonious number of parameters suitable for the data, given the sample size.

Odds Ratio (OR) Indicating Concordance of MZ and DZ Twin Class Membership

An OR was used to represent the proportion of MZ twins in the same latent class in comparison with DZ twins within the same class (OR = $MZ_{same}/MZ_{different}/DZ_{same}/DZ_{different}$). This measure indicates the approximate effect genes have on ADHD latent class membership; MZ twins share 100% of their genes and DZ twins share approximately 50% (Neale & Maes, 1999). If MZ twins within a pair are more often in the same latent class than DZ twins within a pair, genes are influential in the expression of symptoms. The difference in the MZ and DZ within-pair class concordance rates can also indicate the relative influence of environmental experience on symptom expression. An OR of 2 indicates the theoretical OR of MZ to DZ twin concordance based on additive genetic inheritance. An OR of > 2 provides an indication of the degree of variation due to nonadditive genetic effects or rater contrast, a value of < 2 indicates the degree to which environment has an increasing influence on symptom variation.

Results

Principal Components of the ADHD and Conduct Disorder Items

Principal components analysis of the ADHD and conduct disorder items was run separately for women and men using orthogonal rotation. Within the data provided by women, five components with eigenvalues greater than 1 explained 66% of the variation. Of these five, the first three represented inattention, conduct problems, and hyperactive-impulsivity, each explaining approximately 20% of variation in symptoms. Loadings onto the additional two components explained 6% of the variance but no additional information, so analysis results of three components are presented.

A similar pattern was identified for men: six components explained 66% of the variance, and loadings onto the first three components corresponded to inattention, conduct problems, and hyperactive-impulsivity; analyses presented include these three components—each explaining approximately 20% of symptom variation. The additional three components did not explain item response to a greater degree and were excluded.

Latent Class Structure of ADHD and Conduct Disorder Symptoms by Sex

The best latent class model indicated symptoms of ADHD and conduct disorder for women (n = 2,425) and men (n = 1,368) separately was best represented within five latent classes; fit statistics for each model are presented in Table 1. Figure 1 illustrates the proportion of women and men within each latent class separately reporting each ADHD and conduct disorder item. The number of women and men within each latent class did not significantly differ, $\chi^2(4) = 8.91$, $p = .06$: (a) a *few symptoms* class for 65.3% and 65.4% of the women and men, respectively, (b) a *hyperactive-impulsive* class including 10.4% women and 7.5% of the men, (c) a *conduct problems* class for 11.6% of the women and 9.5% of the men, (d) an *inattentive* class for 9.4% women and 13.8% of the men, and (e) a *combined symptoms–CP* class representing 3.1% and 3.8% of the women and men, respectively.

Next we present the mean ADHD symptom count and then the average number of conduct problems across latent classes for women and men using Student's two-sample t test to indicate the significance of difference in these values. This parametric test was used due to the linearity and

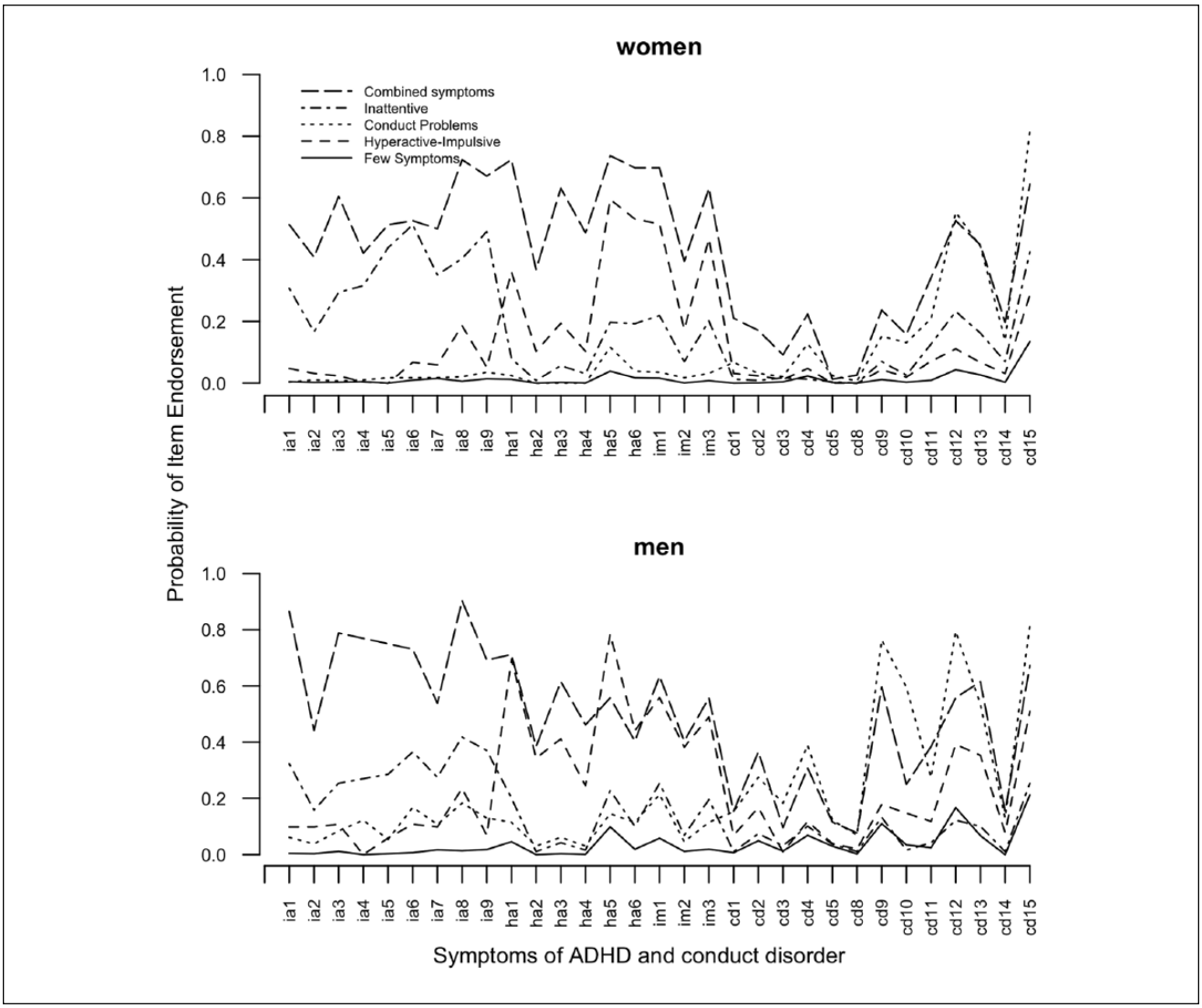

Figure 1. Proportion of participants within each latent class reporting ADHD and conduct disorder symptoms by sex.
Note. *X*-axis labels represent the 9 inattentive, 6 hyperactive, 3 impulsive, and 13 conduct disorder items included in analyses.

range of symptom count. There was variation in the pattern of item endorsement across sex. Within the few symptoms class, the mean ADHD symptom count was 0.2 (SD = 0.4) for women and 0.3 (SD = 0.6) for men, $t(2479) = -7.81$, $p < .001$; the hyperactive-impulsive class 3.5 (SD = 1.6) and 5.3 (SD = 2.1) symptoms for women and men, respectively, $t(352) = -7.39$, $p < .001$. Within the conduct problems class, average counts of ADHD symptoms were 0.4 and 1.8 for women and men, respectively (SD = 0.7 and 1.6, respectively), $t(411) = -9.37$, $p < .001$; counts with the inattentive class for women were 4.3 (SD = 2.1) and 3.8 (SD = 1.8) for men, $t(415) = 2.67$, $p = .01$. Within the combined symptoms plus CP class, these were 10.3 (SD = 2.8) and 11.2 symptoms (SD = 2.8) for women and men, respectively, $t(126) = -1.93$, $p = .06$.

The average number of conduct problems across latent classes were as follows; few symptoms class, 0.3 (SD = 0.5) for women and 1.8 (SD = 0.9) for men, $t(2479) = -15.54$, $p < .001$; within the hyperactive-impulsive class, these were 0.7 (SD = 0.9) and 3.2 (SD = 1.8) for women and men, respectively, $t(352) = -8.05$, $p < .001$; the conduct problems class had 2.7 (SD = 1.1) for women and 6.1 (SD = 1.6) for men, $t(411) = -15.21$, $p < .001$. Within the inattentive class, average counts were 2.2 (SD = 1.2) for women and 1.9 (SD = 1.0) for men, $t(415) = 2.19$, $p = .04$), and within the combined symptoms plus CP class, women had on average 3.3 (SD = 2.5) symptoms of conduct problems and men had 5.3 (SD = 2.9), $t(126) = -2.13$, $p = .04$. The average number of conduct problems was higher for men in all classes except the *inattentive.* Women in the inattentive class

Table 2. *Z* Score Indicating Probability of Class Membership, by Given Symptoms Reported by Men and Women.

	Few symptoms		Hyperactive-impulsive		CP		Inattention		Combined symptoms	
Scale item	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men
ia1	−3.99***	−5.67***	0.13	−0.69	−1.68	−1.95	4.39***	3.67***	6.22***	8.06***
ia2	−5.63***	−4.86***	−0.39	0.89	−2.37*	−1.06	5.88***	2.86**	9.77***	7.71***
ia3	−5.46***	−7.69***	−1.43	−0.65	−2.37*	−1.66	7.42***	2.47*	11.00***	9.30***
ia4	−3.59***	−1.45	−1.66	−0.79	−1.68	0.86	5.95***	1.39	7.17***	2.64*
ia5	−0.85	−4.69***	−0.62	−1.17	−0.06	−1.42	2.04*	4.34***	2.25*	9.37***
ia6	−7.41***	−6.79***	−1.39	−1.12	−2.84**	0.05	10.07***	4.39***	9.13***	8.70***
ia7	−6.82***	−7.14***	−1.29	−1.09	−2.58*	−1.13	7.03***	3.91***	8.97***	7.41***
ia8	−8.25***	−9.03***	1.99*	−0.25	−3.50***	−1.91	7.41***	3.22***	11.10***	6.88***
ia9	−8.72***	−7.38***	−2.77*	−2.19*	−2.76*	−0.94	8.99***	4.73***	10.47***	8.42***
ha1	−8.78***	−10.74***	7.10***	6.34***	−3.48***	−2.71*	−1.03	−1.69	9.71***	6.62***
ha2	−0.51	−0.80	0.95	1.49	−0.39	0.22	0.38	−0.19	1.31	1.66
ha3	−0.96	−5.39***	1.16	6.35***	−0.68	−1.02	0.51	−1.52	2.03*	8.78***
ha4	−0.90	−3.14**	0.88	4.77***	−0.49	−0.89	0.40	−1.01	1.67	7.36***
ha5	−13.33***	−9.16***	8.68***	7.31***	−4.09***	−3.65***	−1.63	−1.87	8.44***	3.72***
ha6	−11.08***	−7.88***	8.95***	6.17***	−4.28***	−1.06	0.48	−1.54	9.83***	5.51***
im1	−10.30***	−11.04***	8.79***	4.81***	−4.27***	−2.16*	1.41	−0.80	9.84***	5.44***
im2	−3.25***	−6.83***	4.65***	6.40***	−1.51	−1.97*	1.56	−0.90	7.47***	6.66***
im3	−9.02***	−8.81***	9.07***	5.69***	−4.18***	−2.06*	1.94	0.37	9.78***	6.71***
cd1	−0.45	−4.41***	0.25	1.47	0.51	4.45***	0.10	−2.14*	0.94	3.85***
cd2	−2.70*	−6.77***	0.65	0.56	1.64	3.38***	−0.64	−2.49*	5.67***	4.44***
cd3	−3.14**	−3.47***	−0.78	−1.40	0.92	5.17***	−0.25	−0.43	4.06***	2.35*
cd4	−4.36***	5.93***	−0.43	−0.92	3.15**	5.01***	−1.92	−2.78*	5.09***	3.22***
cd5	0.01	−2.77*	−0.19	−0.79	0.36	2.73*	0.13	−1.04	0.27	1.51
cd8	−0.11	−3.33***	−0.07	−0.10	0.26	2.12*	−0.07	−0.85	0.33	2.87**
cd9	−6.87***	−8.36***	−1.88	−2.60*	3.84***	7.94***	0.45	−3.93***	5.13***	4.53***
cd10	−4.58***	−5.37***	−1.35	0.58	4.71***	8.81***	−0.49	−3.43***	4.89***	2.72*
cd11	−7.37***	−7.03***	−1.28	0.44	3.31***	3.65***	1.43	−2.15*	6.57***	5.89***
cd12	−11.06***	−8.20***	−3.48***	0.16	6.97***	7.15***	0.47	−5.33***	5.45***	2.83*
cd13	−8.93***	−10.39***	−3.49***	1.85	6.87***	4.57***	0.34	−4.32***	6.30***	5.48***
cd14	−5.20***	−0.63	−1.18	0.67	3.97***	0.92	1.66	−0.06	4.85***	0.97
cd15	−13.74***	−9.87***	−3.90***	0.27	7.30***	5.78***	0.01	−5.35***	3.25***	3.11**

Note. CP = conduct problems. Negative values indicate reduced probability and positive values indicate increased probability, with the symptoms reported by participants within the indicated class.
*$p \leq .05$. **$p \leq .01$. ***$p \leq .001$.

had a marginally higher symptom count than men, and sex difference of mean conduct problems within the combined symptoms class was also marginal—possibly due to the greater variation in male scores. *Z* scores listed in Table 2 indicate the probability with which members of a latent class reported each ADHD and conduct disorder item. To further illustrate variation in ADHD symptoms across sex, latent classes are plotted against participants' scores for each of the three principal components and presented in Figure 2.

Clinical Relevance of Latent Classes

Within our sample, there were 52 (1.4%) participants with a lifetime diagnosis of inattentive ADHD (27 women [1.1%] and 25 men [1.8%]), 31 (0.8%) with the primarily hyperactive-impulsive subtype (18 women [0.7%] and 13 men [0.9%]), and 24 (0.7%) with the combined type (12 women [0.5%] and 12 men [0.9%]). Table 3 indicates the distribution of these diagnoses across the five latent classes. The average age at which participants first experienced either inattentive or hyperactive-impulsive symptoms is displayed at the end of the column (or row) in which latent classes and *DSM* diagnostic categories are presented. Males in the CP latent class ($p = .004$) and males meeting criteria for ADHD plus conduct problems in adolescence and adulthood ($p < .001$) reported a significantly lower age of ADHD symptom onset than females in the corresponding categories.

OR Indicating Twin Concordance for Latent Classes and DSM-IV *Diagnoses of ADHD*

There were significantly more MZ than DZ twin-pairs within the none/few symptoms, hyperactive-impulsive, and conduct problems latent classes. The concordance of class membership for MZ twins was not significantly greater than that of DZ twins within the two most clinically relevant classes (inattention and combined symptoms with conduct problems). ORs and the significant variation across zygosity for class membership are presented in Table 4. There were no concordant twin pairs within any *DSM-IV* diagnosed subtypes of ADHD or age-specific cases of conduct disorder.

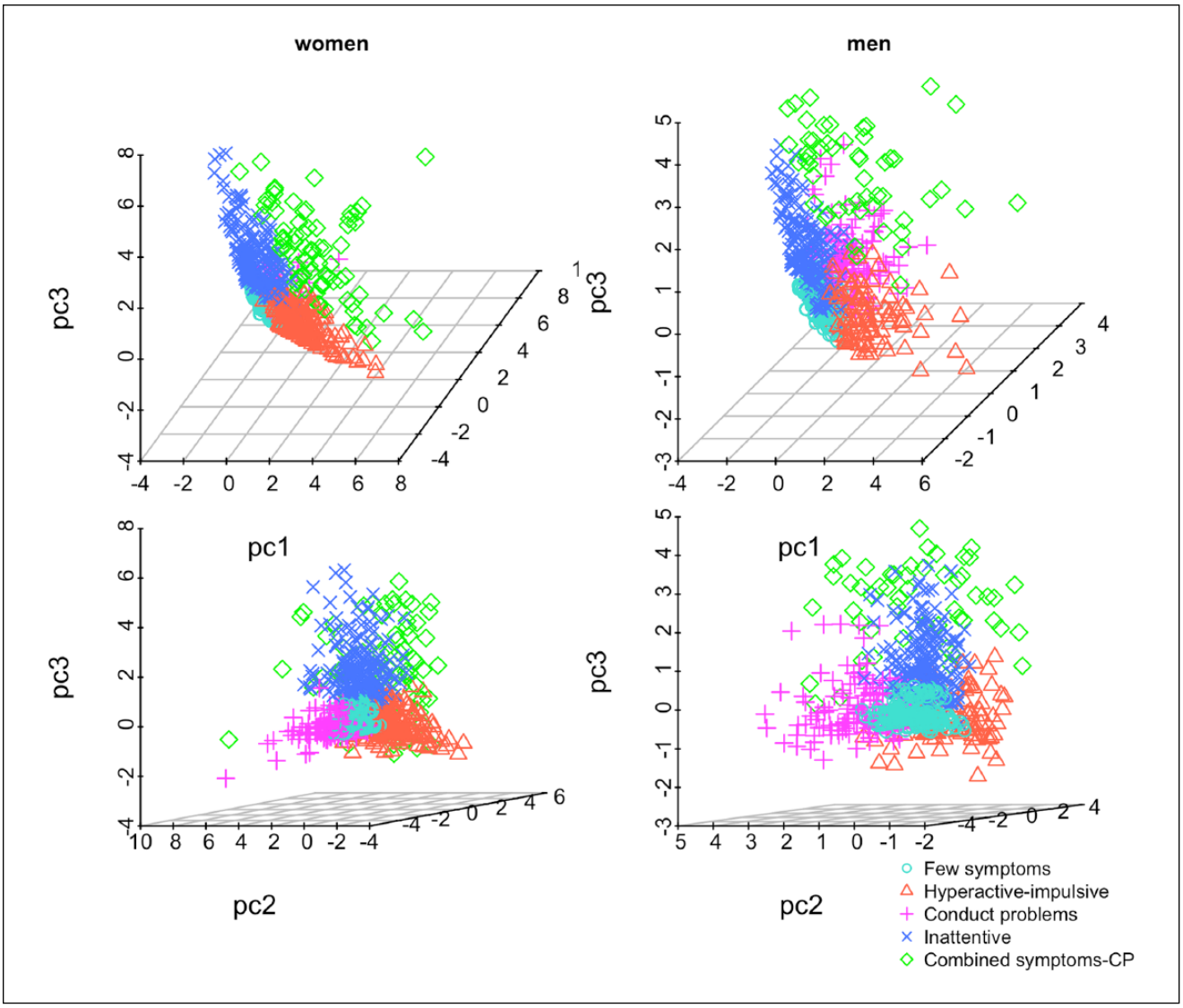

Figure 2. Dispersion of ADHD latent classes across the three principal components of ADHD plus conduct disorder scale items.
Note. pc1 = hyperactive-impulsivity; pc2 = conduct problems; pc3 = inattention.

Latent Class Regression Onto Childhood Risk Factors

The regression of latent classes onto childhood risk variables indicated that participants reporting fewer symptoms experienced more consistent rules during childhood and less conflict with their parents, and were less likely to have been sexually assaulted (see Table 5). Both men and women with inattentive symptoms were more likely to have been raised by both parents and to have experienced tension between their parents within their family homes. Women and men with combined symptoms more often reported experiencing a sexual assault and women in this class also indicated more often that they were less likely to have been raised by both parents.

Latent Class Regression Onto Health Variables

Participants reporting good health outcomes more often fell into the few symptoms latent class relative to participants falling into the symptomatic classes—they were less likely to report an alcohol problem and more likely to be married. Women within the few symptoms class more often reported having close friends and fewer days ill each year. Men reporting an alcohol problem more often fell into the conduct problems class, and women reporting an alcohol problem were more likely to be in the inattentive or combined symptoms latent classes. Again the inattentive class for women appeared to be associated with poorer outcomes than it was for men; these results are presented in Table 6.

Table 3. Proportion (%) of Participants Meeting *DSM-IV* Criteria for ADHD and/or CD Within Each Latent Class.

		Latent ADHD classes					
ADHD category	Frequency (*n*)	No or few symptoms	Hyperactive-impulsive	CP	Inattention	Combined symptoms	Mean age of ADHD symptom onset
Women		1,585	253	282	229	76	
ADHD full criteria							
Subthreshold	2,369	67.0	11.9	10.6	9.0	1.5	—
Inattention	27	—	—	—	55.6	44.4	10.0 (5.1)
Hyp-Imp	18	—	11.11	—	—	88.9	12.1 (8.3)
Combined	12	—	—	—	—	100.0	9.8 (8.4)
CD							
Childhood	4	—	—	25.0	—	75.0	6.0 (1.0)
Adolescence	112	1.8	7.1	50.9	15.2	25.0	10.7 (5.0)
Adulthood	43	2.3	—	41.9	9.3	46.5	9.5 (5.5)
CD and ADHD							
Childhood	1	—	—	—	—	100.0	11.4 (6.3)
Adolescence	18	—	—	—	5.6	94.4	11.5 (6.4)
Adulthood	12	—	—	—	—	100.0	11.5 (6.4)
Mean age of ADHD symptom onset (years)		11.0 (6.3)	10.7 (6.4)	13.3 (5.7)	11.9 (6.1)	10.9 (6.8)	
Men	(*n*)	894	103	130	189	52	
ADHD full criteria							
Subthreshold	1,319	67.8	7.1	9.9	14.0	1.1	—
Inattention	25	—	—	—	16.0	84.0	8.7 (3.8)
Hyp-Imp	13	—	69.2	—	—	30.8	6.7 (3.5)
Combined	12	—	—	—	—	100.0	6.1 (4.0)
CD							
Childhood	13	—	—	53.8	7.7	38.5	6.2 (2.1)
Adolescence	158	15.2	13.9	48.1	4.4	18.4	9.3 (4.4)
Adulthood	82	7.3	14.6	50.0	7.3	20.7	8.1 (4.8)
CD and ADHD							
Childhood	5	—	—	—	—	100.0	7.2 (2.0)
Adolescence	23	—	8.7	—	—	91.3	7.9 (3.8)
Adulthood	17	—	11.8	—	—	88.2	6.4 (2.6)
Mean age of ADHD symptom onset (years)		11.0 (4.7)	12.6 (6.4)	11.3 (5.0)	7.8 (3.5)	8.5 (3.7)	

Note. DSM-IV = Diagnostic and Statistical Manual of Mental Disorders (4th ed.); CD = conduct disorder; CP = conduct problems; Hyp-Imp = hyperactive-impulsivity. The ADHD categorizations are not mutually exclusive but include all individuals who meet the criteria listed irrespective of whether they have been included in a previous category, and diagnoses represent lifetime prevalence. The subthreshold category includes people with no or few symptoms.

Table 4. Odds Ratio Indicating Within-Pair MZ and DZ Twin Latent Class Membership.

Class	MZ (*n*)	DZ (*n*)	Odds ratio	CI	*Z* score
1. No/mild symptoms	750	873	1.45	[1.16, 1.82]	3.23***
2. Hyp-Imp	111	116	8.57	[3.30, 22.24]	4.42***
3. Conduct problems	120	131	2.07	[1.08, 3.96]	2.19*
4. Inattention	117	136	1.14	[0.53, 2.46]	0.35
5. Combined symptoms	32	44	2.99	[0.50, 17.97]	1.20

Note. MZ = monozygotic; DZ = dizygotic; Hyp-Imp = hyperactive-impulsivity. Only complete pairs of MZ and DZ, same and opposite sex twins were included in analyses. There was no MZ or DZ concordance for *DSM-IV* inattention hyperactive-impulsivity or combined symptoms.
*$p \leq .05$. **$p \leq .01$. ***$p \leq .001$.

Table 5. Z Scores (*SE*) Indicating Associations Between Latent Class Membership and Childhood Risk Factors Between Ages 6 and 13 by Sex.

Childhood risk variables	Frequency (*n*)	Few symptoms	Hyperactive-impulsive	CP	Inattentive	Combined symptoms + CP
Women						
5-class model	2,426					
Consistent rules		5.21*** (0.06)	0.91 (0.08)	−0.75 (0.07)	−1.43 (0.08)	−1.85 (0.10)
Parental tension		−1.90 (0.07)	−1.14 (0.10)	0.80 (0.10)	2.34* (0.10)	−0.53 (0.14)
Parental arguing		0.08 (0.07)	1.02 (0.10)	−1.31 (0.10)	−0.60 (0.10)	0.59 (0.14)
Conflict with parents		−7.45*** (0.05)	−2.23 (0.07)	1.93 (0.08)	1.08 (0.08)	2.57* (0.12)
Raised by both parents		5.54 (0.06)	1.32 (0.08)	−2.00 (0.07)	2.07* (0.09)	−4.71*** (0.11)
Parental drinking		−2.85** (0.07)	−0.63 (0.10)	1.50 (0.08)	0.04 (0.09)	1.01 (0.12)
Socioeconomic status		2.44** (0.06)	−1.78 (0.08)	0.18 (0.09)	0.77 (0.09)	−0.74 (0.13)
Childhood sexual assault		−10.11*** (0.08)	−1.72 (0.10)	3.50 (0.08)	1.16 (0.09)	5.74*** (0.10)
Men						
5-class model	1,369					
Consistent rules		2.99** (0.07)	−0.67 (0.11)	−0.84 (0.11)	1.68 (0.11)	−1.56 (0.14)
Parental tension		−1.49 (0.09)	−0.51 (0.15)	−0.17 (0.14)	2.95** (0.13)	−0.77 (0.19)
Parental arguing		0.39 (0.08)	1.19 (0.13)	0.09 (0.13)	−2.04* (0.12)	0.43 (0.16)
Conflict with parents		−5.74*** (0.06)	−1.17 (0.11)	2.20* (0.11)	−1.32 (0.09)	2.37* (0.14)
Raised by both parents		1.74 (0.07)	−0.82 (0.13)	−2.25 (0.11)	2.83* (0.13)	−0.90 (0.15)
Parental drinking		0.87 (0.10)	−1.07 (0.19)	1.50 (0.15)	0.60 (0.13)	−0.06 (022)
Socioeconomic status		0.55 (0.07)	−0.03 (0.12)	0.76 (0.13)	0.67 (0.11)	−1.41 (0.14)
Childhood sexual assault		−2.72* (0.15)	−0.66 (0.28)	−0.46 (0.25)	1.22 (0.18)	2.36* (0.20)

Note. CP = conduct problems.
*$p \leq .05$. **$p \leq .01$. ***$p \leq .001$.

Table 6. *Z* Score (*SE*) Indicating Associations Between Latent Class Membership and Health Variables by Sex.

Health-related variables	Frequency (*n*)	Few symptoms	Hyperactive-impulsive	CP	Inattentive	Combined symptoms & CP
Women						
5-class model	2,425					
Physical health		3.06*** (0.06)	0.64 (0.09)	−0.26 (0.09)	−1.43 (0.08)	−0.76 (0.11)
Emotional health		5.80*** (0.06)	0.94 (0.09)	4.50*** (0.12)	−4.26*** (0.08)	−5.92*** (0.11)
Close friends		3.26*** (0.14)	0.43 (0.20)	0.65 (0.19)	−1.08 (0.17)	−2.29* (0.20)
Marital status		3.82*** (0.04)	−1.37 (0.07)	0.67 (0.07)	−0.22 (0.07)	−1.01 (0.10)
Alcohol problem		−3.40*** (0.32)	−1.19 (0.30)	0.64 (0.24)	3.73*** (0.17)	3.27*** (0.20)
Days ill per year		−3.45*** (0.10)	−0.89 (0.17)	−0.56 (0.15)	2.03* (0.12)	2.41* (0.15)
Men						
4-class model	1,368					
Physical health		3.48*** (0.07)	—	0.31 (0.09)	−1.45 (0.11)	−1.05 (0.12)
Emotional health		5.21*** (0.08)	—	−2.52 (0.09)	1.27 (0.13)	−2.85** (0.12)
Close friends		1.71 (0.13)	—	−0.81 (0.15)	−0.48 (0.18)	−0.11 (0.21)
Marital status		2.85** (0.06)	—	0.92 (0.08)	−0.56 (0.10)	−1.57 (0.12)
Alcohol problem		−4.13*** (0.17)	—	−1.67 (0.17)	4.99*** (0.14)	1.71 (0.17)
Days ill per year		−0.19 (0.19)	—	−0.50 (0.18)	0.47 (0.22)	−0.62 (0.25)

Note. CP = conduct problems.
*$p \leq .05$. **$p \leq .01$. ***$p \leq .001$.

Discussion

We use latent class analysis, regression, and principal components analysis to characterize ADHD symptoms across sex, with environmental exposure, in relation to specific outcomes and diagnosed cases of ADHD. We were also able to estimate the relative influence of genetic effects on variation across latent class membership. In addition to a low-symptom endorsement class, we found four symptomatic classes: hyperactive-impulsivity, conduct problems, inattentive, and combined symptoms plus conduct problems. There were significant sex interactions evident in the relationship between ADHD and conduct problems, and childhood sexual assault, exposure to parental arguing, and being raised by one parent only, suggesting etiological variation in ADHD. Women within the inattentive class experienced greater disadvantage and more conduct problems than men in the same class; both women and men reporting a childhood sexual assault or being raised by one parent were more often found within the combined ADHD plus conduct problems latent class. The combined symptoms class represented approximately the same level of symptom expression for women and men in contrast to the other three symptomatic classes.

To compare our results, one previous study has examined the latent structure of ADHD and conduct problems in adults within a sample selected for an ADHD proband (Acosta et al., 2008). The classes Acosta and colleagues found appeared to represent clusters of combined symptoms that varied only in severity in contrast to the apparent qualitative variation we found. An earlier study of ADHD latent classes without conduct problems and within a community-based sample of adolescents and young adults found that hyperactive-impulsivity formed a distinct subclass while combined symptoms and inattentive symptoms clustered together (Todd et al., 2001). We found that for women, this seemed to be the case, but not for men. The variation of ascertainment across these studies is likely to account for variation in latent classes.

Studies of ADHD often include a high proportion of cases with combined symptoms but within our community-based sample, there were more participants with diagnosable inattention and hyperactive-impulsivity than combined symptoms, and the combined symptoms latent class appeared categorically distinct from the other classes. So what is sometimes described as characteristic of ADHD in relation to combined symptoms may represent an etiologically distinct subtype as has previously been suggested for combined ADHD with and without conduct problems (Anney et al., 2008; Hinney et al., 2011; Mick et al., 2011). The age of ADHD symptom onset for males was significantly lower than for females reporting similar symptoms when conduct symptoms were also present. This does not provide direct support for an etiological variation with comorbid conduct problems, but it does indicate interesting sex differences that may need to be accounted for in ADHD research.

The primacy of either ADHD symptoms or conduct problems and the environmental conditions to which a person has been exposed could implicate the pathways involved in symptom expression. In a previous latent class analysis of ADHD in children including candidate genes as covariates, girls with the 10/10 DAT1 allele who had been exposed to environmental adversity were more often found in a severe combined symptoms latent class (Li & Lee, 2012). This effect may extend into adulthood for women and deserves further study. Symptom variation could also be related to the number of stressors perceived in the environment (Biederman et al., 2002), and an environmental effect is suggested by the relative similarity of twin concordance within the inattentive and combined latent classes.

Our comparison of ADHD latent classes with the principal components clarified greater variance in male scores. It also indicated that men within the conduct problems latent class reported relatively higher levels of inattention than women. Within our sample, we also found that the experience of a childhood sexual assault was associated with more symptoms of ADHD and conduct problems as previously been found (Biederman et al., 2012). We found men in general were more likely to report deficits in motor inhibition but women within the inattentive class reported this more often than men. In addition, the women who reported that they were raised by both parents were considerable less likely to be in the severe combined symptoms latent classes, but this was not the case for men. However, there has been little work done to characterize ADHD symptoms in women due to the relatively low number of met criteria; this work provides important information about how and why symptoms might vary by sex.

One limitation of this study was the retrospective report of childhood risk variables, possibly introducing a memory bias into our analysis, and needs to be considered when interpreting the significance of our findings. In addition, latent class analyses were exploratory in this study, and class membership may vary to a degree with the order in which participant scale responses are entered into the analysis and with sample size. An additional limitation is suggested by the lack of concordance within MZ twin pairs for *DSM-IV* diagnoses of ADHD. ADHD is highly heritable and this result was surprising. The number of symptoms reported into adulthood appears to decline with age (Barkley & Murphy, 2006) but the disadvantage associated with symptoms does not (Das et al., 2012). This developmental change in symptoms could account for the lack of twin concordance for the *DSM-IV*-defined subtypes. This result also highlights the need to reconceptualize the way we measure these symptoms across development.

There is similarity in the basic pattern of symptom expression for women and men evident in Figure 1, but there also appear to be several pathways involved in the manifestation of symptoms given the variation in their expression across latent classes, with environmental covariates and sex, and evident in the variation of twin concordance across specific latent classes. The primacy of symptoms and the circumstances to which a person has been exposed could be diagnostic for the pathways involved. Therefore, focusing on how genetic vulnerability interacts with environments and manifests into adulthood is fundamental for an understanding of ADHD symptoms and their appropriate treatment. Twin studies indicating the relative contribution of genes and environments to latent class membership will provide information that can guide treatment development. Genetic association studies and methylation patterns associated with ADHD latent classes will provide important biological information about genetic and epigenetic effects underlying these symptoms.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: J.L.E. was supported by an Australian Postgraduate Award and a Strategic Doctoral Scholarship from the University of New England. The data collection was supported by the National Institutes of Health (USA; Grant DA018267 9 to principal investigator M.L.) and Australian National Health and Medical Research Council (Grant 1009839); S.E.M. received an Australian Research Council Future Fellowship (Grant 110100548).

References

Acosta, M. T., Castellanos, F. X., Bolton, K. L., Balog, J. Z., Eagen, P., Nee, L., . . . Muenke, M. (2008). Latent class subtyping of attention-deficit/hyperactivity disorder and comorbid conditions. *Journal of the American Academy of Child & Adolescent Psychiatry*, *47*, 797-807.

Althoff, R. R., Copeland, W. E., Stanger, C., Derks, E. M., Todd, R. D., Neuman, R. J., . . . Hudziak, J. J. (2006). The latent class structure of ADHD is stable across informants. *Twin Research and Human Genetics*, *9*, 507-522.

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed., rev.). Washington, DC: Author.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.

Anney, R. J. L., Lasky-Su, J., Ó'Dúshláine, C., Kenny, E., Neale, B. M., Mulligan, A., . . . Gill, M. (2008). Conduct disorder and ADHD: Evaluation of conduct problems as a categorical and quantitative trait in the International Multicentre ADHD Genetics Study. *American Journal of Medical Genetics: Part B. Neuropsychiatric Genetics*, *147*, 1369-1378.

Banaschewski, T., Becker, K., Scherag, S., Franke, B., & Coghill, D. (2010). Molecular genetics of attention-deficit/hyperactivity disorder: An overview. *European Child & Adolescent Psychiatry*, *19*, 237-257. doi:10.1007/s00787-010-0090-z

Barkley, R. A., & Murphy, K. R. (2006). Identifying new symptoms for diagnosing ADHD in adulthood. *ADHD Report*, *14*, 7-11.

Biederman, J., Faraone, S. V., & Monuteaux, M. C. (2002). Differential effect of environmental adversity by gender: Rutter's Index of adversity in a group of boys and girls with and without ADHD. *American Journal of Psychiatry*, *159*, 1556-1562.

Biederman, J., Kim, J. W., Doyle, A. E., Mick, E., Fagerness, J., Smoller, J. W., & Faraone, S. V. (2008). Sexually dimorphic effects of four genes (COMT, SLC6A2, MAOA, SLC6A4) in genetic associations of ADHD:A preliminary study. *American Journal of Medical Genetics: Part B. Neuropsychiatric Genetics*, *147B*, 1511-1518.

Biederman, J., Petty, C. R., Spencer, T. J., Woodworth, K. Y., Bhide, P., Zhu, J., & Faraone, S. V. (2012). Examining the nature of the comorbidity between pediatric attention deficit/hyperactivity disorder and post-traumatic stress disorder. *Acta Psychiatrica Scandinavica*. doi:10.1111/acps.12011

Brown, M. B., & Benedetti, J. K. (1977). On the mean and variance of the tetrachoric correlation coefficient. *Psychometrika*, *42*, 347-355.

Bucholz, K. K., Cadoret, R., Cloninger, C. R., Dinwiddie, S. H., Hesselbrock, V. M., Nurnberger, J. I. Jr., . . . Schuckit, M. A. (1994). A new, semi-structured psychiatric interview for use in genetic linkage studies: A report on the reliability of the SSAGA. *Journal of Studies on Alcohol*, *55*, 149-158.

Buschgens, C. J. M., van Aken, M. A. G., Swinkels, S. H. N., Altink, M. E., Fliers, E. A., Rommelse, N. N. J., . . . Buitelaar, J. K. (1996). Differential family and peer environmental factors are related to severity and comorbidity in children with ADHD. *Journal of Neural Transmission*, *115*, 177-186.

Castellanos, F., Sonuga-Barke, E., Scheres, A., Di Martino, A., Hyde, C., & Walters, J. (2005). Varieties of attention-deficit/hyperactivity disorder-related intra-individual variability. *Biological Psychiatry*, *57*, 1416-1423.

Christiansen, H., Chen, W., Oades, R. D., Asherson, P., Taylor, E. A., Lasky-Su, J., . . . Faraone, S. V. (2008). Co-transmission of conduct problems with attention-deficit/hyperactivity disorder: Familial evidence for a distinct disorder. *Journal of Neural Transmission*, *115*, 163-175.

Costa, P. T. Jr., & McCrae, R. R. (1992). *NEO Personality Inventory–Revised (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI) professional manual*. Odessa, FL: Psychological Assessment Resources.

Das, D., Cherbuin, N., Butterworth, P., Anstey, K. J., & Easteal, S. (2012). A population-based study of attention deficit/hyperactivity disorder symptoms and associated impairment in middle-aged adults. *PLoS ONE*, *7*, e31500.

Ebejer, J. L., Medland, S. E., van der Werf, J., Gondro, C., Henders, A. K., Lynskey, M., . . . Duffy, D. L. (2012). Attention deficit

hyperactivity disorder in Australian adults: Prevalence, persistence, conduct problems and disadvantage. *PLoS ONE*.

Hinney, A., Scherag, A., Jarick, I., Albayrak, O., Putter, C., Pechlivanis, S., . . . Psychiatric, G.C.A. Subgroup. (2011). Genome-wide association study in German patients with attention deficit/hyperactivity disorder. *American Journal of Medical Genetics: Part B. Neuropsychiatric Genetics, 156B*, 888-897. doi:10.1002/ajmg.b.31246

Li, J. J., & Lee, S. S. (2012). Interaction of dopamine transporter (DAT1) genotype and maltreatment for ADHD: A latent class analysis. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *53*, 997-1005. doi:10.1111/j.1469-7610.2012.02563.x

Linzer, D. A., & Lewis, J. (2007). poLCA: Polytomous variable latent class analysis (R package version). Retrieved from http://userwww.service.emory.edu/~dlinzer/poLCA/

Mannuzza, S., Klein, R. G., & Moulton, J. L. (2003). Persistence of attention-deficit/hyperactivity disorder into adulthood: What have we learned from the prospective follow-up studies? *Journal of Attention Disorders*, *7*, 93-100.

Mick, E., McGough, J., Loo, S., Doyle, A. E., Wozniak, J., Wilens, T. E., . . . Faraone, S. V. (2011). Genome-wide association study of the child behavior checklist dysregulation profile. *Journal of the American Academy of Child & Adolescent Psychiatry*, *50*, 807-817.e8. doi:10.1016/j.jaac.2011.05.001

Neale, M. C., & Maes, H. H. M. (1999). *Methodology for genetic studies of twins and families*. Unpublished manuscript.

Neuman, R. J., Todd, R. D., Heath, A. C., Reich, W., Hudziak, J. J., Bucholz, K. K., . . . Kuperman, S. (1999). Evaluation of ADHD typology in three contrasting samples: A latent class approach. *Journal of the American Academy of Child & Adolescent Psychiatry*, *38*, 25-33.

Nikolas, M. A., & Nigg, J. T. (2013). Neuropsychological performance and attention-deficit hyperactivity disorder subtypes and symptom dimensions. *Neuropsychology*, *27*, 107-120. doi:10.1037/a0030685

Ranby, K. W., Boynton, M. H., Kollins, S. H., McClernon, F. J., Yang, C., & Fuemmeler, B. F. (2012). Understanding the phenotypic structure of adult retrospective ADHD symptoms during childhood in the United States. *Journal of Clinical Child & Adolescent Psychology*, *41*, 261-274. doi:10.1080/15374416.2012.654465

Revelle, W. (2011). Psych: Procedures for psychological, psychometric, and personality research .

Rucklidge, J. J. (2010). Gender differences in attention-deficit/hyperactivity disorder. *Psychiatric Clinics of North America*, *33*, 357-373.

Todd, R. D., Rasmussen, E. R., Neuman, R. J., Reich, W., Hudziak, J. J., Bucholz, K. K., . . . Heath, A. (2001). Familiality and heritability of subtypes of attention deficit hyperactivity disorder in a population sample of adolescent female twins. *American Journal of Psychiatry*, *158*, 1891-1898.

Vermunt, J. K., & Magidson, J. (2005). Technical guide for Latent GOLD 4.0: Basic and advanced. Belmont, MA: Statistical Innovations.

Author Biographies

Jane L. Ebejer is a PhD candidate with social work experience, a psychology degree and is receiving training in behavior genetic methodology at QIMR.

Sarah E. Medland is an assistant professor and team leader of the quantitative genetics group at QIMR. Associate professor Medland has multiple publications on genetics and ADHD.

Julius van der Werf is a professor within the Animal genetics department at UNE, in Armidale. Professor van der Werf has expertise in quantitative genetics and its application in animal breeding programs.

Michael Lynskey is a professor within the Addictions Department of King's College, London and has published widely on the genetic and environmental factors associated with cannabis use.

Nicholas G. Martin is a professor and team leader of the genetic epidemiology lab at QIMR. Professor Martin is renowned internationally for his contribution to behavior genetics.

David L. Duffy is a senior scientist at QIMR. Dr Duffy has published extensively in the areas of asthma, genetics and statistical genetics.