THE BROADER AUTISM PHENOTYPE IN PARENTS OF CHILDREN WITH AUTISM SPECTRUM DISORDER: IMPLICATIONS FOR THE DIAGNOSTIC PROCESS AND RELATIONSHIP TO CHILD AUTISM SPECTRUM DISORDER PHENOTYPE

Eric Rubenstein

A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology in the Gillings School of Global Public Health.

Chapel Hill
2017

Approved by:

Julie Daniels

Annie Green Howard

Andrew Olshan

Brian Pence

Rebecca Edmonson-Pretzel

ABSTRACT

Eric Rubenstein: The broader autism phenotype in parents of children with autism spectrum disorder: implications for the diagnostic process and relationship to child autism spectrum disorder phenotype
(Under the direction of Julie Daniels)

Parents of children diagnosed with autism spectrum disorder (ASD) often exhibit social tendencies similar to ASD, but functioning is not impaired nor reaches levels of clinical significance. This constellation of sub-threshold diagnostic ASD traits is referred to as the broader autism phenotype (BAP) and includes features like pragmatic and communication difficulties and poor social skills. BAP is more common in families with children who have ASD and has neurological components and genetic origins, which make it a promising area for etiologic ASD research.

The purpose of this dissertation was to explore two questions related to BAP in parents of children with ASD: 1) to assess the effect of BAP on discordance between maternal reported and clinician observed or estimated instruments reporting child ASD and 2) examine whether child ASD phenotype differs by parental BAP status. Data from the Study to Explore Early Development, a multi-site, community-based, case-control study of children aged 3-5 years with ASD, were used for all analyses.

For our first aim, we used a sample of 712 mother-child dyads referred to SEED from educational and health providers of children with developmental delays who completed BAP and child ASD evaluations. BAP was positively associated with mothers meeting thresholds for child ASD on screeners or interviews when clinician reported instruments of child ASD did not

(Risk ratios ranging from 1.45 to 2.52). Reporting discordances should be acknowledged and accounted for when diagnosing ASD.

In aim two, we used SEED data to derive latent classes for child ASD phenotype from multiple behavioral and developmental measures. BAP in at least one parent was associated with the child having increased odds of being in the class with average non-verbal functioning, mild language and motor delays, and co-occurring conditions like anxiety and depression (OR: 2.44, 95% CI: 1.16, 5.09). Exploratory analyses show similar results if the father alone had BAP. Child sex did not modify this relationship. Children of parents with BAP were more likely to have a phenotype qualitatively similar to BAP presentation; this may have implications for work exploring etiologic origins and crafting parent-mediated interventions.

ACKNOWLEDGEMENTS

This work could not be completed without the families that participated in the Study to Explore Early Development. Their time and openness made this project and others similar to it possible. I hope that the scientific findings from this study makes meaningful contribution to these families and families like that.

The SEED study staff and the Data Coordinating Committee at Michigan State University made the data analysis possible and helped troubleshoot problems that arose. Specific thanks to Chyrise Bradley, project coordinator for the North Carolina site.

This dissertation was funded through the Autism Speaks Weatherstone Pre-doctoral Fellowship and SEED.

SEED coauthors helped solidify research questions and provided meaningful comments. A special note of thanks to Dr. Lisa Wiggins for doing the legwork for the latent class analysis. Other co-authors are: Drs. Laura Schieve, Gayle Windham, Carolyn Diguiseppi, Eric Moody, Juhi Pandey, and Anne Tsai.

The dissertation committee helped to structure this dissertation and provided comments and epidemiological and biostatistical expertise. They are Drs. Andy Olshan, Brian Pence, Annie Green Howard, and Becky Edmonson-Pretzel.

Lastly, Dr. Julie Daniels served as dissertation chair, senior author, advocate, editor, boss, and mentor. Her contributions to this final work are numerous and greatly appreciated.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ASD	Autism spectrum disorder
DSM5	Diagnostic and Statistical Manual 5th edition
LCA	Latent class analysis
BAP	Broader autism phenotype
CDC	Centers for Disease Control and Prevention
RRBI	Repetitive and restrictive behaviors and interests
ADHD	Attention deficit hyperactivity disorder
PRS	Pragmatic rating scale
FHI	Family history interview
SRS-A	Social responsiveness scale- adult
BPASS	Broader phenotype autism symptom scale
BAPQ	Broader autism phenotype questionnaire
MPAS-R	Modified personality assessment schedule-revised
FHI-I	Family history interview- informant
AQ	Autism Quotient
FHI-S	Family history interview- subject
IOI	Impression of interviewer
SEED	Study to Explore Early Development
DD	Developmental disability
SCQ	Social communication questionnaire
POP	Population control
ADOS	Autism diagnostic observation schedule
ADI-R	Autism diagnostic interview- revised
OARS	Ohio State University Autism Rating Scale

CGI	Caregiver Interview
DAG	Directed acyclic graph
RR	Risk ratio
CI	Confidence interval
LCA	Latent class analysis
LMR-LRT	Lo-Mendel Rubin Likelihood Ratio Tests
BIC	Bayesian information criteria
OR	Odds ratio
PPV	Positive predictive value
NPV	Negative predictive value
RD	Risk difference
C-A	Classify-analyze
CIR	Confidence interval ratio

CHAPTER 1. INTRODUCTION

Autism spectrum disorder (ASD) is marked by impairment in social communication and social interaction as well as repetitive and restricted behaviors and interests (1). ASD is of major public health concern due to high prevalence (14.7 cases per 1000 8-year old children) (2) and high financial and emotional burden (3-5). Early intensive ASD specific interventions implemented among young children are seen to improve developmental outcomes (6-8); however, too many children are diagnosed outside the age in which these interventions are most effective (2). Early screening and accurate diagnostic evaluation are critical to reducing age at diagnosis (9).

ASD diagnosis is a complex process, often beginning with the mother (or other primary caregiver) completing a screening questionnaire, followed by trained clinicians observing the child and interviewing the mother. The clinician (or team of clinicians) synthesizes all information to give a final diagnosis based on Diagnostic and Statistical Manual-5 (DSM5) criteria (1, 10). Identifying biases and inefficiencies in this process can reduce age at diagnosis. Earlier identification of ASD allows for increased intervention during crucial developmental periods, which improves outcomes and reduces costs for families and on health systems (11). Exploring issues in diagnostic instruments is also important for public health research: ASD research often relies on population-based screening and inaccuracy in these instruments may bias results.

A source of variance in screening or evaluation may be how the informant (usually the mother) interprets and reports child characteristics. When reporting on child psychiatric conditions like depression and anxiety, parents who have those conditions often report that their child has those conditions or traits of the condition when clinicians or their child report that they do not (12-15). This may also be the case if a mother has the Broader Autism Phenotype (BAP).

BAP reflects a set of sub-clinical characteristics of ASD that are commonly seen in families of children with ASD. Traits include pragmatic and broadly defined communication difficulties, poor social skills, and aloofness (16). BAP in parents is a risk factor for ASD in offspring (17-20) and prevalence estimates of BAP in parents of children with ASD range from 10-50% (17-19, 21-24). To our knowledge, no study has assessed patterns in reporting child ASD traits during screening and evaluation instruments by maternal BAP status.

The specific objectives for the first aim of this dissertation was to examine the association between maternal BAP and discordance between maternal-reported and clinician-observed or clinician-estimated ASD evaluation instruments. For our analysis, we capitalized on the large, multi-site and community-based data in Study to Explore Early Development. These data include assessment of BAP in mothers and clinical use of multiple gold-standard ASD evaluation instruments that characterize child ASD phenotype.

To accomplish this objective, we evaluated the following sub aims:

Aim 1.1: Assess whether maternal broader autism phenotype status is associated with discordance between an ASD screening instrument completed by the mother and clinician-observation or clinician-best estimate of whether child has ASD.

Hypothesis 1.1: Mothers with BAP, compared to those without, will be more likely to report that a child reaches the threshold for ASD risk on screening instruments when a clinician does not observe or deduce that the child has ASD.

Aim 1.2: Assess whether maternal broader autism phenotype status is associated with discordance between maternal reports on interview based ASD evaluation instruments and clinician observation or clinician best estimate of whether child has ASD.

Hypothesis 1.2: Compared to mothers without BAP, mothers with BAP will be more likely to report on an ASD interview instrument that their child meets ASD thresholds when a clinician observation or best estimate does not meet ASD thresholds.

Aim 1.3: Explore whether patterns in discordance are similar for maternal self-reported past history of depression or anxiety diagnosis as compared to BAP.

Hypothesis 1.3: There will be little or no difference in discordance between maternal-reported and clinician-observed or estimated child ASD evaluation instruments with regard to maternal past history of self-reported depression or anxiety disorder diagnosis.

Aim 1 is **significant** because it is one if not the first study to assess the association between ASD screening and evaluation instruments and maternal BAP. Our approach is **innovative** in its usage of a large, well-characterized sample to evaluate this association through comparing multiple maternal and clinician instruments. These differences in reporting may delay diagnosis, which is repeatedly shown to lead to sub-optimal outcomes and increased financial burden. In addition, they may provide further insight into how BAP manifests in settings where a mother acts as an informant. **Outcomes** of this work will reinforce the importance of multi-method ASD evaluations and the need for a clinician to carefully weigh all available information when giving an appropriate diagnosis.

In our second aim we explored the association between BAP in parents and child's ASD phenotypic presentation. ASD is a phenotypically and genetically heterogeneous disorder that creates complexities when trying to deduce etiology and craft therapeutic intervention. Phenotypic traits like verbal ability, age at developmental milestones, and many other diagnostic features and associated traits vary greatly between individuals with ASD (1, 25). While genetics are known to be important, specifics regarding how chromosomal abnormalities, copy number variants, rare penetrant genes, and gene by environment interactions account for the constellation of ASD symptoms are limited (26). With such variability, it is vital to parse ASD into similar phenotypic and genotypic subgroups, to increase efficiency in etiologic research and better tailor intervention (27-29).

By evaluating the relationship between phenotypic ASD subgroups and BAP in parents, we can identify a subset of ASD that is more homogenous in phenotype and likely genotype.

Using BAP as a tool to efficiently parse genetic heterogeneity is promising because it will facilitate identification of endophenotypes. Endophenotypes are specific traits or group of traits that define a subset of people who share genetic or neurobiological origins from the full set with a specific psychological disorder (30, 31). Endophenotypes increase efficiency in etiologic studies by focusing investigations to known heritable traits rather than the whole phenotype (31). Finding groups of these traits that present together will help adapt parent-implemented intervention to account for areas that affect both parent and child.

For our second aim, we explored how child subgroups (derived from latent class analysis) were associated with parental BAP. Again, we use SEED data, which is ideal for this project due to its expansive collection of multi-modal phenotypic data, and a large more diverse sample.

Our specific aim 2 objectives were:

Aim 2.1: Determine whether parental broader autism phenotype is associated with child ASD phenotype subgroups

Hypothesis 2.1 a: Parental BAP will be associated with child phenotype subgroups that have a less severe ASD presentation.

Hypothesis 2.1.b: Parental BAP will be associated with subgroups of ASD in children that are qualitatively similar to those defining the parent BAP domain.

Aim 2.2: Evaluate whether mother, father, or both parents having BAP are differentially associated with child ASD phenotype subgroups

Hypothesis 2.2: Fathers with BAP will be more strongly associated with less severe child ASD subgroups compared to mothers with BAP.

Aim 2.3: Examine whether child sex modifies the relationship between child ASD phenotype subgroup and any parent having BAP

Hypothesis 2.3: Associations between parental BAP and child ASD will be stronger among boys than girls.

Aim 2 is **significant** because we used well-defined ASD subgroups and a good proxy measure of ASD heritability to find association that can be a source of endophenotypes. **Outcomes** of this work enable us to examine specific characteristics that are present in both parent and child as endophenotypes. This can narrow the larger ASD genotype to individual genes, consequently enhancing the efficiency of etiologic research. In addition, understanding how child phenotype relates to parent BAP can improve success of current interventions by adapting the intervention strategy to tailor a specific child phenotype with parent's with socio-communication ability.

CHAPTER 2. LITERATURE REVIEW

2A. Autism Spectrum Disorder

Improved understanding of autism spectrum disorder (ASD) is of vital public health importance because of increasing reported prevalence and the extensive financial and emotional burden that ASD places on individuals, families, and communities. The most recent Centers for Disease Control and Prevention (CDC) estimate of ASD prevalence in 8-year-old children in the United States is 14.6 per 1000, a 123% increase since 2002 (32). The National Survey of Children's Health estimated ASD prevalence among children aged 6-17 years to be 2.0% in 2011-2012, compared to 1.16% in 2007 (33).

ASD is defined by two major features: impairment in social interaction / social communication and repetitive and restricted behaviors and interests (RRBI) that present early in development and impair daily life (1). Social interaction / communication impairment is characterized by deficits in social-emotional reciprocity (lack of back and forth communication, reduced sharing of interests or emotions), deficits in nonverbal communicative behaviors (abnormal use of eye contact, lack of facial expression), and deficits in developing, maintaining and understanding relationships (adjusting behavior to suit social context, making friends) (1). RRBI include stereotyped / repetitive motor movements or speech (hand flapping, echolalia, linking up toys), insistence on sameness / routine, restricted and fixated interests, and hyper- or hypo-reactivity to sensory input (1). ASD presents before the age of three years (1) and is diagnosed three to four times more in boys compared to girls (25).

This is a broad framework for defining ASD, which results in considerable phenotypic heterogeneity among individuals with an ASD diagnosis. Associated features (which are not part

of the diagnostic criteria but are highly prevalent among those with the disorder) include intellectual disability, developmental regression, language disorder, motor deficits, and challenging behaviors (1). Specific co-occurring conditions are also highly prevalent among children with ASD. These include gastrointestinal issues, attention deficit hyperactivity disorder (ADHD), anxiety, depression, epilepsy, sleep problems, and developmental delays (1, 34).

Etiology

The etiology of ASD is not fully understood. Twin studies show the disorder to have a heritable component; monozygotic twins have between 47%-96% concordance while dizygotic twins have between 0% and 61% concordance (35-39). Overall, an estimate by Gaugler et al. (26) has genetic components (additive genetics, non-additive genetics, rare inherited genes, and de novo mutations) explaining 59% of variance in ASD liability with the other 41% belonging to unaccounted environmental factors. Genome wide association studies have found more than 100 genes and 40 gene regions related to ASD or ASD traits, but effects are weak (40) and have not been deemed causal (41). De-novo mutations may be associated with non-heritable ASD and are evident in ASD with fragile X syndrome or tuberous sclerosis (40).

Public health impact

Improved understanding of ASD is of vital public health importance because of increasing reported prevalence and the extensive financial and emotional burden that ASD places on individuals, families, and communities. The most recent estimate of age standardized disability adjusted life years has ASD accounting for 135.5 disability adjusted life years lost per 100,000 life years; this is greater than pancreatic cancer, prostate cancer, brain and nervous system cancer, and endocrine, metabolic, blood, and immune disorders (42). Additionally, although we know little about ASD in adulthood, recent studies suggest an increased rate of suicide (43), overall poorer health due to co-occurring morbidities (43, 44), and lower quality of life (45) in adults with ASD compared to typically developing peers. Lifetime cost estimates for

an individual with the disorder range from $1.4 to $2.4 million and total annual US government expenditure to support children with ASD is $61 billion (3).

Child outcomes

It is important to recognize ASD as early as possible; the younger a child is identified as having ASD and enrolled in intensive behavioral modification programs that focus on skill building and reaching developmental milestones, the better the long term outcomes (8, 11). Early intervention is defined as highly structured teaching methods where an instructor (usually a teacher or parent) works with a child one-on-one using discrete trial training techniques. Children are generally under the age of five and receive 20-40 hours a week of intervention (46). Early intervention has been shown to improve intelligence, social skill, communication, language, autism symptoms, and quality of life in children with ASD (8, 46). Additionally, by intervening at such a young age, risk of secondary symptoms (like aggression, depression, anxiety, self-injury) and parental stress can be reduced (11).

Financial outcomes

It is important to continue to research ASD etiology and intervention because ASD is extremely costly for families, health systems, and research infrastructure. A study conducted in Australia found that the median yearly expense of having a child with ASD (over and beyond having any child) on a family was ~$25,000 US dollars, mainly due to loss in income from employment (47). In the US, mothers of children with ASD earn 56% of what mothers of typically developing children earn (48). A recent estimate of total economic impact found that a child with ASD leads to an additional $17,000 per year on health, school, and other expenditures as compared to a typically developing child for a family (49). The California Department of Developmental Services spends roughly $11,000 per year per child with ASD between the ages 3-17 and roughly $27,000 per year per adult with ASD (50). The national economic impact of ASD in the US is estimated at $66 billion per year for children and $175 billion per year for adults (49). Forecasts estimate economic burden of ASD to be $461 billion by

2025 (5). Accurate diagnoses will directly lead to economic cost savings. Koegel et al. (11) estimated that lifetime savings for early identification leading to early intervention range between $187,000 and $203,000 for a child in the US. An estimate by Peters-Scheffer et al. (51) conducted in Denmark estimated savings of early intervention at €1,103,000 from age 3 to 65.

Diagnostic process

Diagnosis of ASD is a complex process. Because of the socio-communicative nature of the disorder and lack of established biomarkers (52) or genetic tests (53), the ASD diagnostic process should be multi-step with information provided from multiple sources (parents, caregivers, pediatricians, teachers, and / or psychologists) (10). Since many children are young when assessed for ASD, or when older have social impairments that may prevent accurate assessment, self-report is often unfeasible. Therefore screening and diagnosis of ASD in children is done through informant report and clinician observation (10, 25, 54). The informant is the primary caregiver for the child, usually the mother.

Screening

The first step in the ASD diagnostic process is often a brief screener (10, 25, 54, 55). This is a vital step because screening lowers the age at identification, increasing the likelihood of early intervention, which is key to better outcomes for children with ASD. Since universal screening of ASD is not mandatory for all children (56, 57), the American Academy of Pediatricians recommends developmental screening (which covers a wider range of developmental concern) at 9, 18, and 24 or 30 months and ASD specific screening at 18 and 24 months or when concerns are raised by a parent, teacher, or other child health care provider (10, 55, 58). Screeners are often short with an informant responding to questions on their child's social and communication skill and repetitive and restricted behavior (25). Common screeners include the Modified Checklist for Autism in Toddlers (59), Social Responsiveness Scale (60), and the Social Communication Questionnaire (61).

Comprehensive diagnostic evaluation

The gold standard ASD diagnosis is conducted using information from multiple sources (observations and interviews) (10, 62-64). When diagnosing children, the most common sources for information on child behavior, social skills, and other concerns are parental report and clinician observation (10, 62).

Caregiver Interview*:* When a child meets criteria on a screening instrument or a health-care professional has enough concern, the child is given a full diagnostic evaluation (10). The caregiver interview (often completed by the mother) provides information on the child's day-to-day functioning in a wide range of situations, family history and expectations, resources available to the family, and other contextual factors (10). This caregiver is often times an expert in the child's developmental and medical history and has spent the most time with the child. The interview is structured and conducted by trained professionals, usually taking between 1.5 to 4 hours (25). The caregiver is asked about past and current child traits that indicate patterns of behavior and symptoms (10). Interview tools include the Diagnostic Interview for Social and Communication Disorders (65), the Developmental Dimensional and Diagnostic interview (66), and the most frequently used Autism Diagnostic Interview- Revised (67).

Clinician Observation*:* A clinician observation allows for a child's behavior to be put in the context of typically developing children and children with ASD (10). The clinician, often a trained psychologist, observes the child's social communication behavior in a play setting or with peers (10). The observation is specific to a child's expressive language and chronologic age (25). Common observation instruments are the Childhood Autism Rating Scale (68) and the Autism Diagnostic Observation Schedule (69).

Final diagnosis*:* A final diagnosis is achieved by a clinician (or team of clinicians) synthesizing information from the caregiver interview, child observation, and any other information available to determine whether a child meets the DSM5 definition of ASD (10).

Challenges when diagnosing ASD

Challenges in diagnosis arise due to the heterogeneity of the ASD phenotype and complications of other co-occurring disorders (70, 71). A clinician needs to be cognizant of child's age and intellectual ability, since some behaviors and socio-communication abilities are greatly impacted by those two factors (10). If a clinician does not take those factors into account, a diagnosis may be incorrect due to inappropriate developmental expectations. Further, observation of the child's behaviors and social ability are limited by time and the likely unfamiliar setting in which the assessment takes place (10).

Informant reports, like the caregiver interview, are tricky. The order in which questions are asked to the informant can affect response (72). Often, a child's current behavior affects the mother's reporting of past behavior and demographics are associated with differential reporting on child characteristics (73). Informant language ability may also affect response, particularly for non-native English speakers (10, 74).

Based on other child psychiatric disorders, mother psychiatric profile may be associated with discordance between maternal-reported and clinician-observed instruments. When reporting on specific psychiatric disorders in children, a mother who has the same disorder often report that the child has more symptoms than the child reports or a clinician observes (75, 76). These results are seen for depression (12, 13, 15, 75-80) as well as anxiety (14, 15, 81, 82), ADHD (13), and stress (83). A full review of these studies is presented in Table 1. Child traits of these disorders may be reported more because mothers with psychiatric conditions could view other's behavior more negatively (84), or, children of parents with psychiatric conditions have traits of that psychiatric condition and the parent has lower tolerance or a better recognition for said traits, which influences reporting (75, 85). Learning more about reporting discordance in these other disorders has provided insight into child psychosocial adjustment (86), family dynamics (87), and intervention efficacy (88-90). Aim 1 will assess maternal autistic like traits as a potential source of this discordance.

Table 1 Literature summary of informant bias in research of psychological disorders in children

Author (year)	Child disorder/ Traits	Design (n)	Result
Noterdaeme et al. (2002) (91)	ASD	Compared maternal report measure to clinician observation in a cross sectional clinical sample (n=27 children)	Ten out of 11 children with autism were correctly classified on the maternal report and the clinician observation. One false positive on the maternal report.
De la Marche et al. (2014) (92)	ASD	Phenotypic data from families with at least one child with ASD. Parent reported on ASD traits in spouses, and children (n=24 families).	ASD score in child differs by informant type with significant interaction between informant type and past ASD diagnosis. Significant disagreement between all informants in children with ASD but not in unaffected siblings.
Rothen et al. (2009)(13)	Depression, anxiety, attention deficit hyperactivity disorder (ADHD)	Nested case-control study. Parents either had psychiatric disorder or a control. Psychiatrists interviewed parent and child, and parent was given a family history interview disorders. (n=296 pairs)	Lifetime history of depression or ADHD in parent was associated with poorer agreement (over-reporting) between child and parents.
Chapman et al. (1994)(93)	Depression, alcoholism, panic disorder, any psychiatric disorder	Case control study of probands from anxiety clinics with friend controls. Each member of the pair was given an interview on their own health history and their partner's. (n=2193)	Informants with same diagnosis as subjects had lower specificity and higher sensitivity than other informants subject pairs. There was no difference if the pair had different disorders, except for alcoholism.
Collishaw et al. (2009)(94)	Strength and difficulties questionnaire	Scottish survey of mental health in children and adolescents aged 5-15, with parent, teacher, and self report (n=4525)	Parent teacher and parent child correlations were significantly greater than teacher child correlations. Some other correlates (family functioning, child physical health) may be more associated with parent rating.

Author (year)	Child disorder/ Traits	Design (n)	Result
De los Reyes (2005)(15)	Depression, anxiety	Review of current state of knowledge of informant discrepancies on ratings of child psychopathology in clinical research.	Informant discrepancies may have a significant impact on assessment, classification and treatment of child psychopathology. Parental levels of psychopathology are related to informant discrepancies.
Verweij et al. (2011)(77)	Diabetes, psychiatric disorders	Subjects were between 18 and 50 with no psychotic disorder, and no first or second-degree relatives with psychosis and their mothers were given family history interviews (n=33 pairs)	Mothers with depression indicated significantly more depression in family members (12.4% to 5.8%). There were no reporting issues for diabetes
Vandeleur et al. (2015)(12)	Bipolar disorder, schizophrenia, major depressive disorder, drug dependence	Case control study with cases being recruited from hospital psych departments. Controls recruited from orthopedic departments. Interviewed and asked about parents siblings offspring and spouses. (n=1621 pairs)	Individuals who had a history of depression themselves were more likely to report depression in their relatives.
Mueller et al. (2011)(95)	Internalizing behavior, externalizing behavior, total problems	Cross sectional study of children selected from a psychiatric hospital and their parents. Their mothers, kindergarten teachers and therapists rated Child behavior. Maternal psychopathology was assessed by self-rating (n=124 pairs)	Overall, mothers gave higher ratings for all behaviors than teachers, who gave higher ratings than therapist. Structural equation models suggested favoring the distortion model, which obtained the best model-fit and parsimony indices. The distortion model postulates exaggerated ratings of highly distressed mothers

Author (year)	Child disorder/ Traits	Design (n)	Result
De los Reyes et al. (2011)(96)	Mood syndromes	Secondary analysis of study on bipolar disorder in youths. Parents reported on child characteristics and older children offered self-reports. (n=420 pairs)	Caregiver mood symptoms and family functioning were not significantly associated with reporting discrepancy.
Hughes et al. (2010)(76)	Internalizing behavior	Self reported internalizing symptom levels were completed by adolescents aged 13 to 18 years and a parent. Parents also completed instruments of their own depression, anxiety, and stress symptoms (n=219 families)	Mothers' depressive and stress symptoms each explained additional variance in the discrepancy between mother and son reports and in the discrepancy between mother and father reports of sons' symptoms.
Heun et al. (1998)(79)	Dementia, depression	Case control comparison of family history information for dementia and depression (n=75 pairs)	Any psychiatric disorder in a subject raises the likelihood that informants indicate a diagnosis of depression in the subjects
Randazzo et al. (2003)(97)	Internalizing / externalizing behaviors	Parents, foster parents, and teachers reported on behaviors of foster children. Depression was assessed in biological parents (n=95 groups)	Depressive symptoms are related to the difference between the biological parent report and the other two informants' report

Author (year)	Child disorder/ Traits	Design (n)	Result
Chilcoat et al. (1997)(75)	Internalizing / externalizing behaviors	Behavioral reports by mothers and teachers on six-year-old children. Mother's history of major depression, anxiety disorders, and substance use disorder was assessed (n=801 trios)	Mothers with history of any psychiatric disorder reported more externalizing problems in their children than expected.
Boyle et al. (1997)(98)	Internalizing / externalizing behaviors	Cross sectional community survey of childhood psychiatric disorders and maternal interview for her depression (n= 1151 pairs)	None of the associations between maternal depression and mother reporting errors were significant
Gartstein et al. (2009)(80)	Internalizing / externalizing behaviors	Cross sectional survey of parents on child behaviors, maternal report of her own depression (n=219 groups)	There was a modest effect of maternal depression, which leads to the inflation of reported son externalizing and daughter internalizing problems.
Zablotsky et al. (2015) (99)	ASD	Data came from the 2011 Survey of Pathways to Diagnosis and Services (n=967 parent respondents)	Children with higher family impact factor scores were more likely to have parents who rated their child's ASD as the most severe.
Ringoot et al. (2015) (78)	Internalizing / externalizing behaviors	Population-based cohort, parents reported lifetime depression and depressive symptoms. Child emotional and behavioral problems were assessed by child self-report and parent report	Depression of mothers and fathers affects young children's well-being. However, if parents had reported depression and child had behavioral problems, associations were inflated.
Pereira et al. (2014) (14)	Anxiety	Portuguese children aged 7-14 years and their mothers completed an anxiety symptoms scale. For a subsample, maternal anxiety and depression symptoms were collected (n=135 children).	Maternal anxiety was positively associated with the discrepancy between mother and child reports of anxiety symptoms.

Author (year)	Child disorder/ Traits	Design (n)	Result
Lerner et al. (2012) (88)	High functioning ASD	Community sample of children with high functioning ASD and their parents, recruited form skill training programs (n=15)	Parents who have lower self-efficacy report lower social skills in their children as compared to child self report
Daryanani et al. (2015) (83)	Stress	Mother's reported on their own depression, child stress. Child reported on own stress and depression (n=300 dyads)	Mothers with a history of depression were more likely than non-depressed mothers to report more familial, social, and youth-dependent stressors relative to their children; non-depressed mothers were more likely to report less independent stressors than their children.

Reducing heterogeneity when studying ASD

ASD research is often hampered due to the heterogeneity in phenotype and variety and uncertainty in etiological mechanisms. A current well-supported hypothesis is that ASD is really a series of 'autisms' with different presentations and etiologic origins, and by studying certain 'autisms' rather than the 'whole' ASD we could more efficiently study the disorder (28, 29, 100).

A strategy to reduce phenotypic heterogeneity when conducting ASD research is to create more similar phenotypic subgroups. Past studies have used cluster analysis and latent class analysis (LCA) to analytically create these subgroups based on phenotypic variables (Wiggins in press)(27, 28, 101-103). These subgroups have been used to assess differences in child problem behaviors and create severity gradients (28), association between child IQ and phenotype (101), associations with specific genes (27), and possible treatment trajectories (102).

Additionally, grouping children with ASD based on hereditary predisposition to ASD can improve efficiency in etiologic research (27, 29). Looking at a subset of children who likely do not have ASD through hereditary or genetic means may create a group more likely to be affected by environmental risk factors (29). Focusing on this group could lead to greater success in evaluating these environmental factors. Identifying children with likely genetic origins for ASD can help find specific genes and mechanisms that may cause ASD or ASD specific traits; past approaches have looked at families with multiple children with ASD or with ASD like traits in family members (104-107).

With this more homogenous subset of children with likely hereditary ASD, endophenotypes can be identified. An endophenotype is a measurable, more homogenous subset of a psychiatric disorder's clinical phenotype. Endophenotypes can be neurophysiological, biochemical, cognitive, or neuropsychological, but must be associated with the disorder in the population, be heritable, state independent (apparent in an individual whether they have the disorder or not), co-segregate in families, and be found in higher rates in

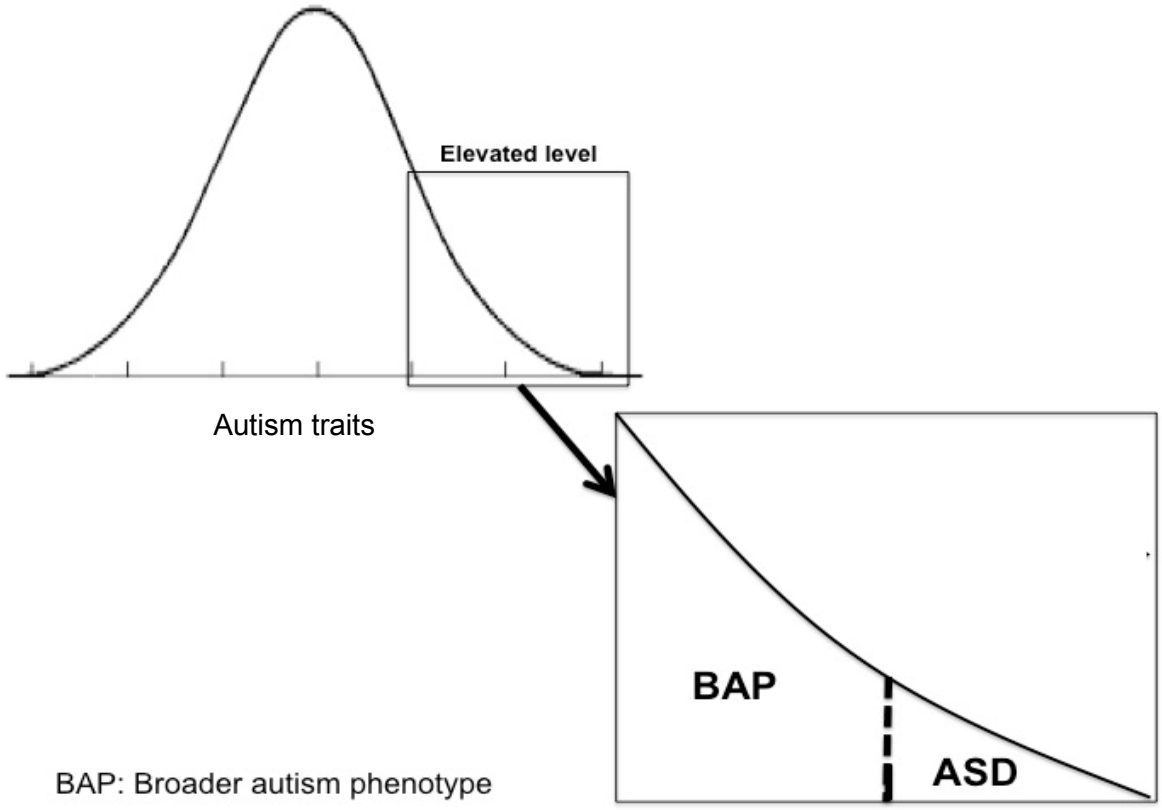
unaffected relatives of probands than in the general population (30, 31). Using these guidelines, studies have been able to trace traits associated with ASD to genetic origins (108-114).

2B. Broader autism phenotype

Since ASD was formally identified by Kanner in 1943 (115), it has consistently been observed that parents of children diagnosed with ASD often exhibit social tendencies that are similar to ASD, but do not impair functioning or otherwise reach the same level of clinical significance (116-121). The constellation of sub-threshold diagnostic ASD traits in families of people with ASD is referred to as the broader autism phenotype (BAP)(121). The range of these traits in a population is often referred to as quantitative autism traits (QAT) (107). Specific traits of BAP include pragmatic difficulties, broadly defined communication difficulties, poor social skills, rigidity, broadly defined stereotyped behaviors, impaired emotional recognition, and aloofness (10-17, 9).

A proposed distribution of BAP in the general population is presented in Figure 1. BAP is found to be continuously distributed in the general population (23, 122-126) and heritable (123, 127). Non-ASD psychiatric conditions are also highly associated with BAP; these include anxiety, depression, and obsessive-compulsive disorder (16, 24). BAP in adults is also marked by cognitive traits like weak central coherence, and diminished executive functioning and neurological processing (16, 24). BAP has neurological components and genetic origins, which makes it a promising area for etiologic ASD research.

Figure 1. Hypothesized distribution of autism traits in the general population



BAP instruments

Several tools have been developed to measure BAP (24). Table 2 presents an overview of the most commonly used tools we identified in the adult BAP literature. Many of these tools are adapted from tools that had been used in the past, specifically from the Pragmatic Rating Scale (PRS) and the Family History Interview (FHI) developed by Bolton et al. (121). Data are collected in a variety of ways. The first method used was a family history interview where one or more subjects would provide health and personality information on themselves and their relatives. Most common reports now include informant report (through questionnaire or interview) (Social Responsiveness Scale-Adult (SRS-A), Social Responsiveness Scale- 2nd edition (SRS-2), Broader Autism Phenotype Questionnaire (BAPQ), Modified Personality Assessment Schedule-Revised (MPAS-R), FHI-Informant (FHI-I)), self-report (through questionnaire or interview) (BAPQ-self report, Autism Quotient (AQ), FHI-subject (FHI-S), SRS-2) or clinician observation (Broader Phenotype Autism Symptom Scale (BPASS), FHI-Impression of Interviewer (IOI), MPAS-R). Some instruments (PRS, MPAS-R, BPASS, FHI) collect data from multiple sources (self report, informant report, clinician observation) and synthesize the results. We refer to this method as 'best estimate' because they combine various data sources and result in a more comprehensive measure of BAP. The instruments tend to be short, usually taking under an hour to complete. For more information on these instruments, specifically psychometric properties, see Gerdts et al (24).

All tools provide a continuous measure of BAP in adults. Additionally, the tools measure two (FHI), three (MPAS-R, BAPQ), four (BPASS), or five (SRS-A, SRS-2, AQ) subsets of BAP traits, called domains, factors, or scales. These subsets can better measure groups of traits like autistic mannerisms, attention, communication, rigidity, and social skills (23, 123, 126).

Many case-control studies use a continuous measure of BAP to assess BAP as a risk factor for ASD. These studies find a clear pattern of higher mean scores on BAP instruments in parents of children with ASD as compared to controls (20, 22, 92, 107, 128-146). There is value

to looking at BAP continuously, but cutoffs allow for dichotomization into BAP+ and BAP- groups that may be useful for etiologic research and creation of more homogenous familial subgroups.

Previous studies have examined correlations between these tools. The SRS-A total score and BAPQ total score were significantly inter-correlated (r=0.32) as were their subdomain scores in a study by Hurley et al. (147). Although, correlation coefficients were modest (r=0.11 to .29) in a similar analysis conducted by Davidson et al. (148). That study also found weak but significant correlation between the clinician rated FHI and the SRS-A and BAPQ (148). Ingersoll et al. (122) examined the BAPQ, SRS-A, and AQ in a non-clinical sample of college students. They found a total score correlation of 0.66 between the BAPQ and SRS-A, 0.55 between the AQ and SRS-A, and 0.65 between the AQ and BAPQ (122). Results were similar in a study conducted in Japan (149). These properties illustrate the variability in BAP measurement but the overall fact that the instruments are measuring the same concept.

All of these tools have different strengths and weakness. The BAPQ and BPASS were specifically designed to measure BAP and used samples of people with BAP to create the instrument (21, 147). The FHI-IOI and BPASS include clinician observations (150), which may remove the variance in the informant's ability but also limit the utility of the instrument in large studies. The SRS-A and AQ have both been shown to effectively measure BAP in non-clinical populations (151, 152). Informant reports may reduce biases by getting an outside opinion on a person's BAP traits. Self-report questionnaire instruments can be completed quickly, do not need the participant to find someone to report on them, and do not require a trained professional. Collecting data from more than one source can reduce some reporter related bias. The optimal tool is related to the research question; a study with a large non-clinic based sample may select a instrument that is self-report and easy to complete, while a study that wants to maximize precision would use a clinician observation and a best estimate approach.

Table 2 Overview of adult BAP instruments

Instrument	Author, year	Reporter	Description	Scoring
Autism Spectrum Quotient (AQ)	Baron-Cohen, 2001(126)	Self	-50 question self-administered instrument -Answers range from strongly agree to strongly disagree -Five domains: attention switching, social skill, attention to detail, communication, and imagination -Intended for individuals with normal / high IQ (126)	-1 point for definitely or slightly agree / disagree depending on question -1 to 2 standard deviations above mean (145)
Social Responsiveness Scale- Adult (SRS-A), SRS-2	Constantino, 2005 (123, 153)	Informant/ Self (SRS-2)	-65-item likert scale questionnaire -The questionnaire takes 15-20 minutes to complete -Measures five domains: social awareness, social cognition, social communication, social motivation, and autistic mannerisms -SRS-2 has informant and self-report versions	-Items scored 0-3 BAP cutoffs: - A T-score ≥ 60 (60) -A T-score >70 (154) -Top 20% of scores in a population based sample has been used to indicate BAP (17) -Top 25% of a sample of Hispanic parents (154)
Broader Autism Phenotype Questionnaire (BAPQ)	Hurley, 2007 (147)	Self / Informant	-36 Items derived from previous direct assessments of autistic traits (MPAS-R) -Scales corresponding to three components: aloofness, rigid personality, pragmatic language problems	- Item scoring range: 1-6(147) -'Best estimate' is the mean of a self- and informant report score -Sex specific BAP cutoffs defined Males: 3.55 self 3.65 informant Females: 3.17 self 3.46 informant(23)

Instrument	Author, year	Reporter	Description	Scoring
Broader Phenotype Autism Symptom Scale (BPASS)	Dawson, 2007 (21)	Interview / direct observation	-Interview with trained clinician who rates subjects socio-communication ability -Four domains: social motivation, social expressiveness, communication, and flexibility	- 1 to 4 or 5 point scales ranging from highly atypical to above average -Mean score above 2 indicates BAP (21)
Family History Interview	Bolton, 1994 (121), Piven, 1997(140), IMGSAC, 2000(150, 155, 156)	Interview, self, informant, direct observation	-Older version (121, 140) is a structured interview where a responder answers questions on their own and family's health history and personality traits. -77 Items, 30 to 60 minutes in length --Factor analysis suggests two factor solution: social communication and rigidity, reading and spelling impairments (150)	-Rating from 0-not reaching scoring threshold to 2-associatedi impairment -Clinical significance determined by summing results with scoring algorithm, if score ≥ 1 than evidence of BAP (150, 155, 156)
Modified Personality Assessment Schedule	Piven, 1994, 1997 (119, 140)	Interview, informant	-Trained professional conducted semi-structured interview of ASD traits -Focuses on six traits (aloof, anxious, hypersensitive, overly conscientious, rigid, and untactful)(136)	-Characteristics rated 2=present, 1=unknown, 0=absent (157) -Results synthesized to a 'best estimate' -Algorithm of sum of traits ≥ 2 = BAP (158)

Instrument	Author, year	Reporter	Description	Scoring
Pragmatic Rating Scale	Landa, 1992 (118)	Interview, direct observation	-Subscales: disinhibited social communication, awkward / inadequate expression, odd verbal interaction(24)	-25 behaviors rated by clinician on three point scale: 0- normal, 1-moderately abnormal, 2-strikingly abnormal -Summed and averaged by subscale (158)
Communication Checklist-Adult	Whitehouse, 2010 (159)	Informant	-Questionnaire -70 behavioral statements that the informant judges on frequency: less than once a week or never (0), at least once a week but not every day (1), once or twice a day (2), or several times a day or always (3). -Three subscales: language structure, pragmatic skills, social engagement (160)	-All questions summed -BAP is identified as 2 SD below the mean (by sex)(160)

Percentage of parents with BAP

We conducted a systematic review and identified 40 studies that assessed percentage of parents of children with ASD who have BAP; these studies are presented in Table 3. All studies present crude percentages as no studies estimated BAP prevalence by means of statistical analyses. The earliest identified used data collected in 1994 (161) with the most recent study being published in 2016 (162).

Specific samples

We also present BAP percentage if a control group was used; 16 studies provided percentage for controls (either parents of typical developing children, parents of children with Down Syndrome or non-biological relatives of children with ASD)(17, 19, 23, 128, 129, 139, 141, 144, 145, 154, 156, 159, 163-166). Uniformly, parents in the control group had lower percentage of BAP. Some studies looked at specific subgroups of ASD parents, including multiplex or simplex families (106, 156, 166), high functioning autism or Asperger's syndrome (167), specifically Hispanic samples (154), samples with and without regression (22), and by parents usage of anti-depressants (168). By subgroup, the percentage of parents with BAP was higher in multiplex families as compared to simplex families (106, 136, 166). Other subgroups were not assessed in more than one study.

By sample size

Our range was from 4 (168) to 3299 (148). Figure 2 presents sample size after stratification by instrument. There is some indication that there are a larger percentage of parents with BAP when sample size was smaller. This may be a result of sample type (population sample or clinical) or desire to have statistical power by lowering cut-offs.

By parent type

Of 40 studies identified, 25 reported percentages in all parents who completed the assessment (i.e. not stratified by sex). Twenty-two reported percentage in fathers of children with ASD and 23 reported percentage in mothers of children with ASD (see Table 3). These

results are visually presented in Figure 2 after stratification by instrument. Overall, fathers had a slightly higher percentage of BAP, which is in concordance with the male: female sex ratio in ASD and may signify a male predisposition to the disorder (169). However father BAP was not consistently higher in all studies that measured both mother and father. Mother results were similar to results for any parent.

By informant type / instrument

Figure 2 presents results by instruments. The FHI had the highest estimates, but also had a large range. This may be a result of the different informant styles for the FHI (FHI-S, FHI-I, IOI), change in the tool over time, and differences in sample type. AQ, BAPQ, and SRS-A had similar distributions to one another. Informant type did not vary greatly between methods.

Relationship between BAP and child ASD characteristics

Fourteen studies assessed the association between parental BAP and child ASD phenotype and they are presented in Table 4. These studies used a variety of the BAP measures and most were conducted in the US. The majority of studies assessed children aged 3-18 years, but some restricted to younger children or expanded to adult children. Most studies were conducted in clinical settings. Samples ranged in size from 50 (170) to 711 probands (165). Most common analytic approaches were analysis of variance tests (20, 162, 163, 165, 171, 172). Other analytic approaches included predictive modeling (132, 173), controlling for covariates like parent age and sex in models (168, 170), and mixed models (92, 171).

Positive associations were found between child scores on ASD screeners and parent scores on BAP measures (19, 20, 132, 165). Additional significant associations were found between child intense preoccupation and father rigidity domain (170), autistic like social functioning in parents and child daily functioning level (174), and parent and child RRBI score (162). Levin-Decanini et al. (168) stratified their results by anti-depressant status and found that there was a relationship between parent BAP and child RRBI among parents not taking anti-depressants (23). Father's BAP tended to have a stronger association with child phenotype as

compared to maternal BAP (19, 20, 170). Two studies found no associations between maternal BAP and child phenotype (20, 157), whereas Hasegawa et al. (132) found associations between maternal BAP and four of five child SRS domains with no associations between father BAP and child phenotype. Two studies had null results. Bishop et al. (129) found no association between BAP and child IQ and no difference between children having ‘autism’ or ‘pervasive developmental disorder’ by parental BAP status. Taylor et al (172) found no association between parental BAP and child ADOS severity.

Table 3 Studies that present percentage with BAP in parents of children with ASD

Author	Year[a]	Instrument	Informant	Parent	N	Parent group assessed / domain	Percent of parents
Fombonne et al. (161)	1994	FHI	Interview	F/M	160	ASD	10.0
Szatmari et al. (166)	1998	FHI	Interview	F	681	ASD / ≥1 domain	28.3
						ASD / ≥2 domain	9.5
				M	681	ASD / ≥1 domain	16.7
						ASD / ≥2 domain	4.0
				F/M	1362	ASD / ≥1 domain	22.5
						ASD / ≥2 domain	10.4
						ASD simplex / ≥1 domain	19.0
						ASD simplex / ≥2 domain	5.3
						ASD multiplex / ≥1 domain	26.4
						ASD multiplex / ≥2 domain	8.3
			Informant		337	Non bio relative / ≥1 domain	6.8
						Non bio relative /≥2 domains	2.4
Pickles et al. (139)	1994	FHI	Interview	F/M	92	ASD	12.1
					72	DS	9.8
Starr et al. (143)	2001	FHI	Interview	F/M	86	ASD	15.0
Lainhart et al. (22)	2002	MPAS-R, PRS	Best estimate	F/M	18	ASD w regression	27.8
					70	ASD w no regression	32.9
Bishop et al. (129)	2004	AQ	Self	F	52	ASD	36.9

Author	Year[a]	Instrument	Informant	Parent	N	Parent group assessed / domain	Percent of parents
					37	TD	13.5
				M	69	ASD	15.4
					52	TD	3.5
Bishop et al. (163)	2004	AQ	Self	F/M	114	ASD	21.3
					87	TD	3.4
Klin et al. (175)*	2005	FHI	Interview	F	-	ASD	21.0
				M	-	ASD	3.0
				F/M	220	ASD	12.0
Ghaziuddin et al. (167)	2005	FHI	Interview	F/M	58	Asperger's	29.0
					39	HFA	20.5
Dawson et al. (21)	2007	BPASS	Best estimate	F	172	ASD / expressiveness	16.0
						ASD/ communication	13.5
				M	151	ASD / expressiveness	6.0
						ASD / communication	5.0
		FHI	Interview	F/M	299	ASD / ≥1 BAP domain	50.3
						ASD /≥ 2 domain	11.4
Hurley et al. (147)	2007	BAPQ	Best estimate	F	35	ASD	40.0
				M	43	ASD	9.3
				F/M	86	ASD	31.4
			Self			ASD	25.0
			Informant			ASD	25.0
Losh et al. (109)	2007	MPAS-R, PRS,	Best estimate	F/M	48	ASD / ≥1 domain	50.0
Ruser et al. (176)	2007	PRS	Best estimate	F/M	47	ASD	15.0
Whitehouse et al. (177	2007	AQ	Self	F	10	ASD	10.0
				M	20	ASD	25.0

Author	Year[a]	Instrument	Informant	Parent	N	Parent group assessed / domain	Percent of parents
Losh et al. (136)	2008	MPAS-R, PRS,	Best estimate	F/M	78	SX ASD / ≥2 domains	33.0
					48	MX ASD / ≥2 domains	56.0
					60	DS control/ ≥2 domains	10.0
Losh et al. (109)	2009	MPAS-R	Best estimate	F/M	83	ASD / social domain	26.5
Whitehouse et al. (159	2010	CC-A	Informant	F/M	238	ASD	25.6
					187	TD	16.0
Wheelwright et al. (14	2010	AQ	Self	F	571	ASD	33.0
					349	TD	22.0
				M	1429	ASD	23.0
					658	TD	9.0
Coon et al. [b](178)	2010	SRS-A	Informant	F/M	518	ASD pedigrees[b]	12.1
Ingersoll et al. (179)	2011	AQ	Self	F/M	149	ASD	10.0
Ruta et al. (141)	2012	AQ	Self	F	115	ASD	43.5
					150	TD	20
				M	130	ASD	26.2
					150	TD	11.3
Seidman et al. (18)	2012	BAPQ	Best estimate	F	38	ASD	2.6
			Self			ASD	10.5
			Informant			ASD	7.9
			Best estimate	M	38	ASD	13.1
			Self			ASD	21.0
			Informant			ASD	15.8
Mohammadi et al. (138)	2012	AQ	Self	F	96	ASD	50.0
						TD	11.0
				M		ASD	37.0
						TD	11.8

Author	Year[a]	Instrument	Informant	Parent	N	Parent group assessed / domain	Percent of parents
Levin-Decanini et al.(168)	2013	BAPQ	Self	F	115	ASD w no SSRI use	17.4
					4	ASD w SSRI use	20.0
				M	136	ASD w no SSRI use	11.8
					19	ASD w SSRI use	36.8
Taylor et al. (172)	2013	AQ	Self	F	82	ASD	26.8
				M	82	ASD	25.6
Berthoz et al. (128)	2013	AQ	Self	F/M	87	ASD	13.8
					47	TD	8.2
Maxwell et al. (19)	2013	BAPQ	Best estimate	F	245	ASD	21.0
					129	TD	7.0
				M	245	ASD	10.0
					129	TD	1.0
				F/M	490	ASD	26.0
					258	TD	8.0
Sasson et al. (23)	2013	BAPQ	Best estimate	F	359	ASD	19.0
					490	TD	8.9
				M	352	ASD	23.2
					491	TD	8.1
Sasson et al. (165)	2013	BAPQ	Best estimate	F/M	711	ASD	36.0
					981	TD	14.1
Gerdts et al. (106)	1998-2011	BPASS	Best estimate	F	71	Mx ASD / social	66.0
					40	Sx ASD / social	33.0
				M	84	Mx ASD / social	44.0
					41	Sx ASD / social	32.0
Sasson et al. (180)	2014	BAPQ	Informant	F	222	ASD	17.6
			Self			ASD	9.5

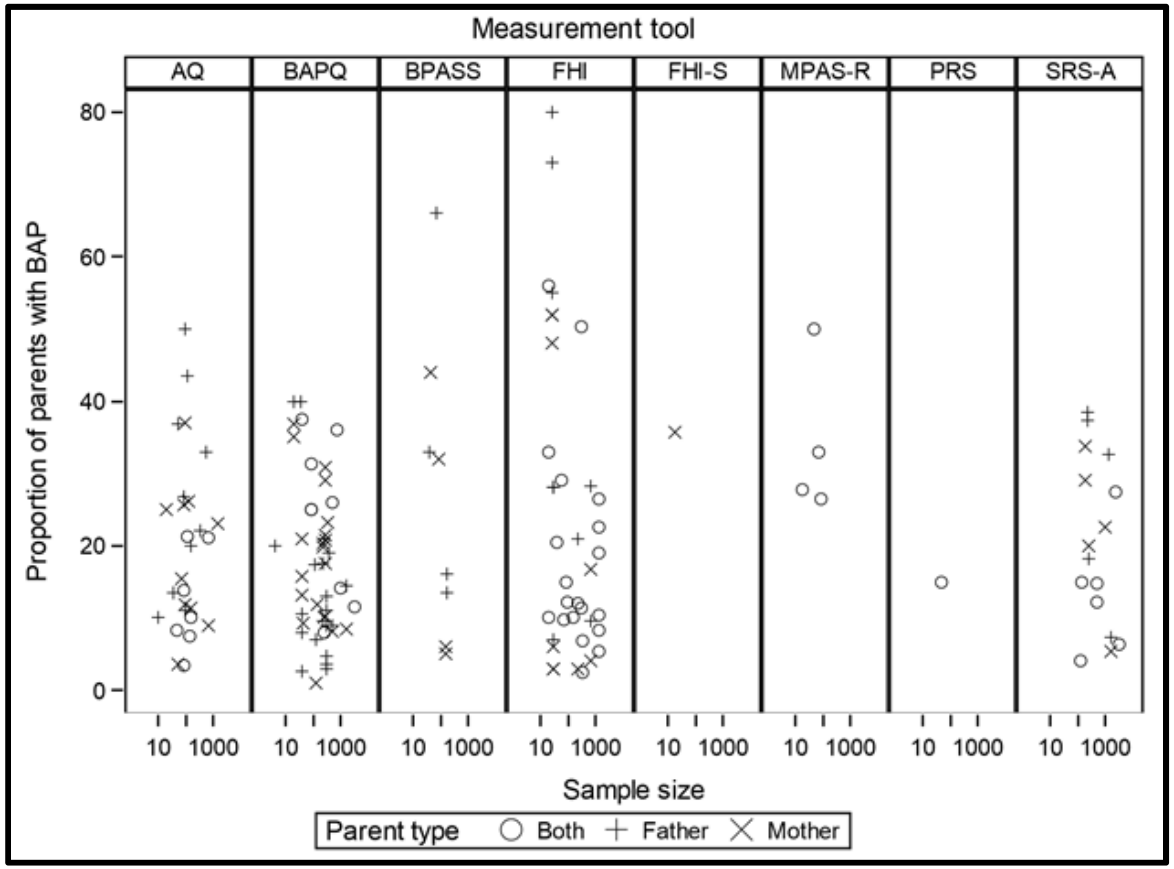
Author	Year[a]	Instrument	Informant	Parent	N	Parent group assessed / domain	Percent of parents
			Informant	M	222	ASD	19.8
			Self			ASD	20.3
Davidson et al. (148)	2014	BAPQ	Best estimate	F	1582	ASD	14.5
				M	1596	ASD	8.5
				F/M	3178	ASD	11.5
		SRS-A	Informant	F	1647	ASD	7.3
				M	1652	ASD	5.3
				F/M	3299	ASD	6.3
Lyall et al. (17)	2014	SRS-A	Informant	F/M	2365	ASD	27.5
					482	TD	14.7
				F	1372	ASD	32.6
					242	TD	18.1
				M	993	ASD	22.5
					240	TD	20.0
Shi et al. (144)	2012-2015	BAPQ	Best estimate	F	299	ASD	13.0
			Self			ASD	9.0
			Informant			ASD	11.0
			Best estimate			TD	2.9
			Self			TD	3.6
			Informant			TD	4.7
			Best estimate	M	274	ASD	30.8
			Self			ASD	29.1
			Informant			ASD	21.4
			Best estimate			TD	20.8
			Self			TD	17.5
			Informant			TD	10.2

Author	Year[a]	Instrument	Informant	Parent	N	Parent group assessed / domain	Percent of parents
de Jonge et al. (156)	2015	FHI-I	Informant	F	26	Mx ASD	80.0
		FHI-S	Interview			Mx ASD	73.0
		IOI	Best estimate			Mx ASD	55.0
		FHI-I	Informant		29	DS	7.0
		FHI-S	Self			DS	28.0
		IOI	Best estimate			DS	28.0
		FHI-I	Informant	M	27	Mx ASD	48.0
		FHI-S	Self			Mx ASD	52.0
		IOI	Best estimate			Mx ASD	52.0
		FHI-I	Informant		30	DS	6.0
		FHI-S	Self			DS	3.0
		IOI	Best estimate			DS	3.0
Duvekot et al. (181)	2016	SRS-2	Self	F	224	ASD	37.4
			Informant			ASD	38.4
			Self	M	182	ASD	33.7
			Informant			ASD	29.0
Yucel et al. (182)	2015	BAPQ	Best estimate	F	20	ASD	40.0
				M	20	ASD	35.0
				F/M	40	ASD	37.5
Parr et al. (183)	2015	FHI-S	Interview	M	18	ASD	35.7
Bora et al. (164)	2016	AQ	Self	F/M	673	ASD	21.1
					146	TD	7.5
Page et al. (154)	2016	SRS-2	Informant/ Self	F/M	140	ASD	15.0
					125	TD	4.0

[a] Year is year data collected if indicated, otherwise year of publication
[b] Includes pedigrees
DS Down Syndrome
Mx Multiplex

Sx Simplex
TD typically developing
F Father
M Mother
F/M Either parent

Figure 2. Scatter plot of percentage of parents with BAP, by instrument, sample size, and parent type



Control percentages excluded from graph

AQ= Autism Quotient, BAPQ= Broader Autism Phenotype Questionnaire, BPASS= Broader Phenotype Autism Screening Scale, FHI-Family History Interview, MPAS-R= Modified Personality Assessment-Revised, PRS= Pragmatic Rating Scale, SRS-A= Social Responsiveness Scale Adult

Table 4 Studies that assess traits in children with ASD that are associated with parent BAP and their results

Author, year	Instrument	Probands	Parent	Country	Child age (years)	Results
Bishop et al., 2004 (129)	AQ	65	M (65) F (42)	Australia	-	-Neither Mother nor father BAP was associated with proband IQ or whether proband had ASD or pervasive developmental disorder diagnosis
Mazefsky et al., 2008 (184)	FHI	77	F/M (77)	US	8-39	-Parental BAP did not predict Vineland adaptive behavior score in socialization, communication, and daily living skills. -Autistic like social function in relatives did predict whether a child would be in a high functioning or lower functioning cluster
Smith et al., 2009 (170)	MPAS	50	M (50) F (50)	US	5-22	-Child intense preoccupation was associated with fathers aloof and rigid BAP domains -No association between parental BAP domains and insistence on sameness factor
Schwichtenberg et al., 2010 (20)	SRS-A	115 Sx 10 Mx	Sx F/M (124) Mx F/M (11)	US	-	-Father SRS-A but not mother SRS-A predicted proband SRS score
Losh et al, 2012 (185)	MPAS	89	M (89)	US	-	-No association between mother BAP and child SRS score

Author, year	Instrument	Probands	Parent	Country	Child age (years)	Results
Levin-Decanini et al., 2013 (168)	BAPQ	197	M (196) F (161)	US	3-50	-Fathers not on anti-depressants total and aloof domain scores significantly correlated with child RRBI subscales and childhood routines and inventory score and father aloof domain score was associated with child compulsive score -If mother took antidepressants, a significant partial correlation was found between maternal aloof scores and proband ADOS RRBI total.
Taylor et al., 2013 (172)	AQ	82	F/M (82)	Australia	4-17	-No association between parental BAP status and child ASD severity.
Maxwell et al., 2013 (19)	BAPQ	245	F/M (245)	US	6-18	-When at least one parent met criteria for total BAPQ or exceeded threshold in any subdomain, child SRS scores were higher. -Stronger association between father BAP and child SRS score than mothers-child association
Sasson et al., 2013 (165)	BAPQ	711	F/M (711)	US	-	-Total BAPQ and aloof BAPQ in parent associated with child total and social scores on ASD screener -Parent pragmatic language domain score were associated with child social score -No association between parental BAPQ rigidity domain and child score

Author, year	Instrument	Probands	Parent	Country	Child age (years)	Results
Hasegawa et al, 2014 (132)	AQ	44	F/M (44)	Japan	37-95 months	-Maternal AQ total associated with all child SRS domains excluding awareness and mannerism. -Maternal attention switching and communication scores associated with child SRS total score -No association between father AQ score and child SRS total score
Rocnoni et al., 2014 (186)	AQ	26	F/M (26)	Italy	8 months	-Higher AQ attention to detail score was associated with a longer time for child to look away from a previous cue and worse alerting skills of the child -Negative correlation between parental AQ communication score and child rapid orienting index - Results were not significant between mother and child

Author, year	Instrument	Probands	Parent	Country	Child age (years)	Results
Klusek et al., 2014 (171)	MPAS	52	M (50) F (42)	US	7-36	-No association between mother BAP and child ASD traits when child was 4-5 years -Untactful personality in fathers was associated with child's total severity, degree of social impairment, and deficits in communication at 4-5 years -Father aloof traits were positively associated with child severity of RRBI at 4-5 years -Father overly conscientious trait was negatively associated with child severity of RRBI at 4-5 years -Parent pragmatic language total score and dominating subscale associated with child's current communication impairment -Aloof trait in fathers was positively associated with child current overall symptom and RRBI severity. -Overly conscientious in fathers was negatively associated with a current overall severity and degree of social impairment

Author, year	Instrument	Probands	Parent	Country	Child age (years)	Results
Duvekot et al., 2015 (181)	SRS-2	231	M (224) F (182)	US	2.5-18	-Paternal BAP significantly predicted child's ASD symptoms - Maternal BAP was associated with child anxiety symptoms. -No cross-symptom associations between paternal BAP and children's anxiety symptoms when correcting for paternal anxiety symptoms.
De la Marche et al., 2015 (92)	SRS-A	310	M (296) F (256)	Belgium	4-17	-Paternal BAP had a significant effect on child SRS while maternal BAP had no effect on child SRS -No difference by child gender or whether family was simplex or multiplex
Uljarevic et al., 2016 (162)	AQ RRBI	169	F/M (169)	Australia	2-18	-Having both parents within the top 20% of RRBI scores was associated with an increase of RRBI scores in their children -No parent of origin effect for RRBI effect

F Female
M Male
RRBI Repetitive and restricted behaviors and interests
SRS Social Responsiveness Scale
SRS-A Social Responsiveness Scale- Adult
AQ Autism Quotient
BAPQ Broader Autism Phenotype Questionnaire
MPAS Modified Personality Assessment Schedule

BAP as a source of reporting discrepancy during diagnosis

To date, autism-like traits in a mother have not been reported as a factor in discordance between ASD screening, interview, and observation instruments. The presence of BAP among mothers may be a source of differential reporting, similar to what has been reported in the depression literature. Studies have shown that individuals with BAP may have more impairment in communication, emotional understanding, ability to understand non-verbal cues, narrative ability, and have decreased empathy, higher attachment anxiety, and increased avoidance compared to people without BAP (16, 117, 128, 187). Inhibition in these socio-communicative traits may impact informant ability (188, 189). Additionally, maternal BAP may affect how a mother reports on her child's characteristics; maternal BAP is a predictor of increased parental stress (179, 190) and anxiety (191), which both may impact informant ability (95). We have identified no published work has assessed how BAP in mothers' may affect reporting of child ASD during the ASD evaluation process.

BAP as a tool to improve efficiency in ASD research

As discussed earlier, subgrouping approaches may be an efficient way to better research ASD. Efficiently finding children with genetic predisposition can be difficult. Genetic testing is not yet universal among children with ASD, let alone family members, and families are concerned about costs and relevance (192). Comparing multiplex and simplex families is biased by reproductive stoppage (defined as changes in reproductive behavior after the birth of a child with serious health needs) among families with children with ASD (193-195). Using parental BAP may be an ideal way to subset child ASD by hereditary origin since BAP is a risk factor for ASD and heritable.

CHAPTER 3. METHODS

3A. Study to Explore Early Development

Our study is a secondary analysis using data from the Study to Explore Early Development. SEED is a multi-site, community based, case-control study. The purpose of this study was to 1) characterize the autism behavioral phenotype and associated behavioral, medical, and developmental conditions and 2) investigate genetic and environmental risk factors for ASD (196).

SEED includes six sites (California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania) with a target population of between 33,000 and 52,000 births for each site in each study year. Data on children born between 2003 and 2006 were collected between 2007 and 2012. Eligible children were between 30 and 68 months at time of developmental assessment, were born and resided in the study catchment area at the time of first study contact, and lived with a knowledgeable caregiver who was able to communicate the child's developmental history in English (or Spanish in Colorado and California) (196).

Children that were likely to have ASD or DD were identified through health clinics, early intervention programs, special education programs, or self-referral. Population controls were randomly selected from birth certificates. Sixty-four percent of participants identified from ASD or DD service providers and 68% from the population sample did not respond (196). After study entry, case status was confirmed (see section 3B) which created four groups: children with SEED confirmed ASD, population controls without ASD (POP), children referred to the study from DD service providers without SEED determined ASD (DD), and children who were unable to be accurately classified due to refusal or inability to receive the full ASD evaluation (PC). The

final SEED sample included 3899 children of whom 722 were in the ASD group, 1304 in the DD group, 1289 in the POP group, and 584 in the PC group.

Upon agreeing to participate, a telephone interview was conducted in which the Social Communication Questionnaire (SCQ) (61) was administered as an instrument to screen for ASD. All families were invited to a clinic to complete a standard developmental evaluation and bio-specimen collection. If the child had a past history of ASD, screened positive, or a clinician suspected ASD at the standard developmental evaluation, the child received a full ASD evaluation. ASD evaluations were done for research purposes and children were not formally diagnosed. All caregivers completed a series of questionnaires and provided medical records on pregnancy history and child development. A full list of data collection tools and SEED data collection procedure are presented in appendix 1 and 2.

3B. Final classification

Study ASD classification was determined using a diagnostic algorithm which incorporated ASD specific instruments (197).

Autism Diagnostic Observation Schedule (ADOS) (198)

The ADOS (version 2) was used in SEED as the clinician observation instrument. SEED clinicians had advanced degrees in developmental pediatrics, developmental psychology, clinical psychology, and related fields. All had extensive experience with the assessment and diagnosis of children with ASD (197). Clinicians observed children for over 40 minutes while creating settings that measured social affect and RRBI. The ADOS has specific modules based on age and verbal ability (69); our sample used modules 1 for children with no or limited verbal ability, module 2 for children with some verbal ability but no phrase speech, and module 3 for verbally fluent children (197). To meet SEED ASD criteria, the child had to score > 11 if they received module one and had no words, a score ≥ 8 if they received module one and had some words, a score ≥ 7 on if they were younger than 59 months and received module two, score ≥ 8

they were older than 59 months and received module two, and a score ≥ 7 if they received module three (197). Inter-site reliability was 99% and intra-site reliability was 99% (197).

Autism Diagnostic Interview- Revised (ADI-R) (199)

Along with the ADOS, the ADI-R was administered at the comprehensive evaluation. The ADI-R is a 93-item, 150 minute structured interview with the child's caregiver that is administered by the clinician. The ADI-R measures the child's social communication, RRBI, and developmental delays or deficits (67, 199). ADI-R cutoff scores for ASD were a social score ≥ 10, communication score ≥ 8 for children with some words or ≥ 7 for non-verbal children, and a RRBI score ≥ 3 (197). In SEED, inter-site reliability was 99% and intra-site reliability was 87% (197).

The Ohio State University Autism Rating Scale (OARS) (200)

The OARS is a tool filled out by a clinician and was used to measure symptom severity, degree of impairment, and clinician certainty in child's ASD diagnosis. SEED investigators specifically modified this tool. The OARS was calibrated to a five-point Likert rating of clinician degree of certainty that the child had ASD dichotomized into ‘‘uncertain’’ (scores of 1–3 or note that ASD symptoms better accounted for by another disorder) and ‘‘certain’’ (scores of 4–5).

3C. Broader autism phenotype

BAP was assessed using the Social Responsiveness Scale-Adult (SRS-A). Although designed to measure autistic traits in the general population, the SRS-A has shown good consistency with other BAP and qualitative autism trait instruments (122, 149). The SRS-A is 65-item likert scale questionnaire that a friend, spouse, or relative completes was asked to complete on the parent. The questionnaire takes 15-20 minutes to complete and is filled out before the clinic evaluation. The full questionnaire is presented in appendix 3. Examples of question's asked are “[Parent] seems too dependent on others for help with meeting basic needs” and “[Parent] does extremely well at a few intellectual or computational tasks, but does

not do as well at most other tasks." Another strength of the SRS-A is its ability to measure five distinct domains to define ASD and ASD-like traits; domains are social awareness, social cognition, social communication, social motivation, and autistic mannerisms (60). These domains are derived through sub-setting specific questions of the SRS-A that relates to these topics. The SRS-A has strong internal validity, exhibiting a Cronbach's alpha internal consistency coefficient of 0.95 (122, 123). SRS-A scores have been shown to be independent of IQ and age (60, 201). The child version of the SRS has been seen to be independent of race (123) and the SRS-2 (which incorporates a self-report version of the SRS-A) shows minimal effect of race and ethnicity in adults (153). Informant type showed strong inter-rater agreement ($r > .84$ comparing two different informers). However, using the self-report version (added in the SRS-2) had lower inter-rater agreement (r was between 0.61 and 0.66)(153). This is similar to scoring discrepancies between self- and informant-report from other instruments (147, 202-204). Ultimately, the SRS-2 standardized both the self- and informant version on the same scale, which suggests minimal informant effects (153).

Raw SRS-A scores were adjusted to create T-scores, which have a mean of 50 and a standard deviation of 10. The cutoff point for BAP on these instruments is often variable. Past studies have used various cut points to indicate BAP: a score greater than or equal to an adjusted T-score of 60 on the SRS-A (60), participants in the top 20% of scores for the SRS-A (17), participants with scores in the top half on the Family History Interview (183), or one to two standard deviations above the population mean in the Autism Spectrum Quotient (145). We made BAP a binary variable using a score of greater than or equal to 60 as our cutoff based on past work using the SRS-A (60), but will also conducted analyses using a score ≥58 which represents 20% of our sample). The same scoring procedure was used for the five domains.

3D. Human subjects protection / Data security

All sites that participated in SEED received Institutional Review Board approval, as did this dissertation as a secondary data analysis. Personal identifying information was not included in any analyses. The SEED data coordinating committee located at Michigan State University oversaw the data, which could only be accessed through a secure remote data access connection.

3E. Aim 1 specific methods

Sample

For this study, we included all children in SEED identified from educational or medical providers that serve children with DDs, excluding siblings (which would violate independence), children without a completed SCQ, ASD evaluation, or maternal SRS-A; and children whose mother did not act as the sole informant on the ADI-R or SCQ. Although some children with history of DD did not receive the full evaluation, we elected to include those who did in our sample. DD is a broad category and many children who did not receive the full evaluation had no ASD symptoms (205). Additionally, children with DD who did not meet SCQ thresholds were still eligible to receive a full ASD evaluation if a clinician suspected ASD during the clinic visit

Approximately 20% of mothers did not have completed SRS-As. Based on a logistic regression of collected maternal demographics, mothers without SRS-As were more likely to have some college, less likely to have a college degree or higher, and were more likely to be from the Georgia site compared to mothers with SRS-As. We explored this missingness, by running sensitivity analyses that weighted mothers to approximate the demographics of the total sample. We chose not to impute values because the SRS-A is designed to be independent with race, age, or IQ or other variables that could be used in an imputation model (123). We also have no reason to believe that the SRS-A was differentially completed based on BAP status. Further, we explored this missingness as a sensitivity analysis (rather than main analysis) since

the SEED sample (which is overly white, educated, and non-Hispanic (206)) is not a very generalizable sample even without missingness. To apriori choose to weight our results to this sample was not vital.

Exposure

We used the SRS-A as described in section 3C. Unfortunately, the informant (who filled out the SRS-A on the mother) is missing for approximately 75% of mothers. This prevents us from accounting for potential informant effects. We address this as a limitation in our discussion.

Outcome

We created variables to indicate discordance between a maternal screener (SCQ) or maternal interview (ADI-R) and clinician observation (ADOS) or clinician best estimate (OARS) using the cut-off scores used in SEED. We compared difference in whether the child did or did not meet thresholds for being at high risk for ASD (SCQ) or for having ASD (ADOS, ADI-R, and OARS) between the maternal and clinician instruments. Our four comparisons were the SCQ versus the ADOS, the SCQ versus the OARS, the ADI-R versus the ADOS, and the ADI-R versus the OARS. If the two instruments were in agreement about whether the child met ASD criteria (whether both positive or both negative), they were considered 'not discordant'. Since the ASD evaluation is a complex process that takes place over a limited amount of time, we do not want to imply that a mother's report or clinician observation on child ASD is 'right'; however, since we are more concerned about influence of maternal characteristics on reporting, we used the clinician completed instruments as our 'gold-standard' when presenting our results. Therefore, we define 'over-reporting' as the maternal report instrument meeting ASD thresholds when the clinician instrument does not and 'under-reporting' when the maternal report instrument does not meet ASD thresholds while the clinician instrument does. Outcomes are listed in **Table 5**.

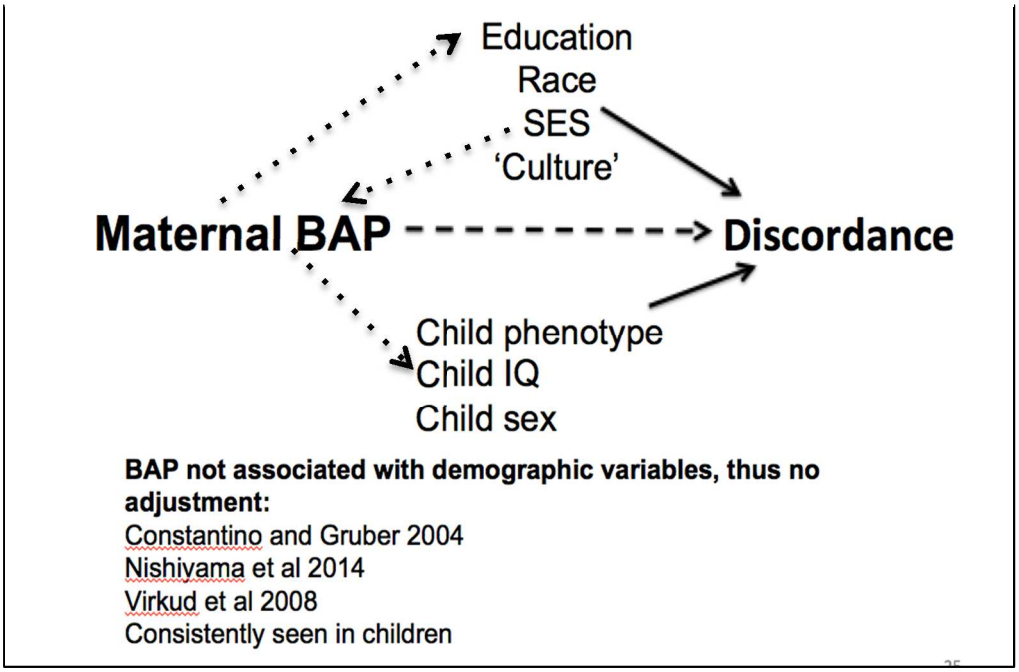
Covariates / confounding

For aim 1.3, we assessed maternal self-reported history of depression or anxiety disorder diagnosis. Those data were taken from the maternal health history interview, where the mother reported on her past diagnosed health conditions.

Based on BAP being a well validated construct (24) and the SRS-A being designed to be independent of age and IQ (123) and minimal association with race (153), we do not believe there is any confounding to adjust for in our primary analysis (Figure 3).

Race, ethnicity, age, and education variables for mothers, children, and families were collected using child's birth records and a SEED specific Caregiver Interview (CGI). The CGI is a 60 minute telephone interview administered by SEED staff to the child's caregiver to assess family demographics, maternal reproductive and pregnancy history, diagnosed developmental outcomes in all children in the household, and medical, therapeutic, obstetric, and lifestyle complications of pregnancy with index child (196). We were able to use multiple sources collected by SEED to first use the caregiver interview for demographic variables, and then fill in missing values with the child's birth record. Exploratory analyses show that these variables are sufficiently concordant.

Figure 3. Directed acyclic graph for aim 1 analyses



SES: Socioeconomic status

Table 5. Outcome instrument for aim 1.

Maternal report instrument	Instrument type	Clinician Instrument	Instrument type	Direction of discordance
SCQ	Screener	ADOS	Observation	None, ‘over’, ‘under’
SCQ	Screener	OARS	Best estimate	None, ‘over’, ‘under’
ADI-R	Interview	ADOS	Observation	None, ‘over’, ‘under’
ADI-R	Interview	OARS	Best estimate	None, ‘over’, ‘under’

Table 5.B Outcomes for aim 1.

Maternal report (SCQ or ADI-R) **Clinician (ADOS or OARS)**

	+	-
+	None	‘Over-reporting'
-	‘Under-reporting’	None

SCQ Social Communication Questionnaire
ADOS Autism Diagnostic Observation Schedule
ADI-R Autism Diagnostic Interview Revised
OARS The Ohio State Autism Rating Scale

Primary analysis

We ran log-binomial regression models to estimate risk ratios (RR) and 95% confidence intervals for the relationship between a binary maternal BAP variable and discordance outcome variables. Based on our approach outlined in the confounding / covariate section, we had no covariates or other type of adjustment in this primary analysis. All analyses describe below were run for all out outcomes in **Table 5**.

Next, we assessed correlation between maternal BAP and BAP domains (aim 1.2). Since our desire was to assess whether a BAP domain was associated with discordance independent of other domains, we reran our models with five binary indicators for each BAP domain (the intercept being no BAP in any domain). Since there was some correlation between domains, not adjusting for the other domains would muddy the interpretation of our results.

For aim 1.3, we addressed maternal self-reported past history of depression or anxiety disorder diagnosis to better understand whether discordance is particular to BAP or more general to other psychiatric conditions. First, we assessed correlation between BAP, reported past history of diagnosed depression, and reported past history of a diagnosed anxiety disorder. We did not control for maternal BAP in these analyses because correlation in our data were low between maternal BAP, self-reported depression, and self-reported anxiety diagnosis. Additionally, since the literature is limited on whether BAP confounds the relationship between depression or anxiety and reporting on ASD instruments and this analysis is more exploratory in nature, we do not condition our estimates on maternal BAP status. We qualitatively examined whether effect estimates differed from the BAP estimates.

Additional analysis

We ran a series of additional analyses to better understand our data and to explore the relationship between maternal BAP and discordance in ASD instruments. First, we evaluated psychometric properties comparing both maternal report instruments (SCQ, ADI-R) to clinician reported instruments (ADOS, OARS)(used as gold standard). We calculated sensitivity

(probability of maternal report reaching ASD criteria | clinician report reaching ASD criteria), specificity (probability of maternal report not reaching ASD criteria | clinician report not reaching ASD criteria), positive predictive value (PPV) (probability of clinician report reaching ASD criteria | maternal report reaching ASD criteria), negative predictive probability (NPV) (probability of clinician report not reaching ASD criteria | maternal report not reaching ASD criteria) four our overall sample and by maternal BAP status.

Additionally, we reran all aim 1.1 and 1.2 analyses using linear-risk regression to calculate risk differences. We chose this to be additional analyses rather than primary because using risk ratios is the standard measure of effect in the ASD literature.

To evaluate the effect of language preference we also reran primary analyses restricting to mothers whose preferred language was English. Similar to exploring language preference, we examined differences by site by running models that weighed for differences in site using inverse probability weighting. We did this because two sites administered evaluations in Spanish and site may be considered a design variable in the SEED study; however, because of SEED's strong internal and external validity and lack of difference in site between discordant and non-discordant mothers, consider it a sensitivity analysis. Other sensitivity analyses included using the standard SCQ score of ≥ 15 as our ASD threshold and weighting for missing SRS-As.

Lastly, we examined race/ethnicity as a potential effect measure modifier. We reran analyses stratified by race (white, black, other) and ethnicity (non-Hispanic or Hispanic). Our goal was to determine if there were differences by these demographic variables. All analyses were conducted in SAS 9.3 (SAS Institute, Cary NC)

3F. Aim 2 specific methods

Sample

For aim 2, we include all children with SEED determined ASD and an SRS-A completed for both parents. If a family had multiple children in the study who had ASD (n=7), we excluded the second child (who was brought into the study after their sibling) to be in line with past latent class analysis (LCA) work done in SEED, and to ensure statistical independence. In the future, it may be worthwhile to include multiplex families.

There was missing data in our sample due to incomplete SRS-A data. We explored this using inverse probability weights to make our restricted sample look more like our total sample. We ran a logistic model predicting SRS-A completion for both parents by site, maternal race, maternal ethnicity, and maternal age at childbirth. Probabilities were calculated and if both parents had a completed SRS-A then the weight was 1/(probability of not missing). If one or both parent were missing an SRS-A, then the weight was 1/(1-probability of not missing). These weights were used in sensitivity analyses.

Exposure

We used BAP cutoffs as described in section 3c. We included paternal BAP scores and created variables to signify whether father only, mother only, or both meet BAP cutoffs.

Creating latent classes

Our outcome was latent classes derived using an analytical approach first used by Wiggins et al (under review). They identified 27 variables that would characterize the ASD phenotype and differentiate between those with ASD, rather than those with and without. Variables come from multiple measures that use multiple modes of data collection. This is an improvement on other LCA approaches that derived classes from only one measure. Three sources of indicators, the ADOS, ADI-R, and SCQ are described in section 3E. Four other data sources were used:

The Child Behavior Checklist (CBCL): The CBCL is a fifteen-minute questionnaire filled out by a parent to assess the child's behavior problems and social competencies (207).

Mullen Scale of Early Learning (MSEL): The MSEL is a 45 minute clinician administered measure to assess cognitive ability and motor development in children from birth to 68 months (208).

Gastrointestinal Questionnaire (GIQ*):* SEED constructed the GIQ, a ten-minute parent-completed questionnaire to assess the child's past and current gastrointestinal distress (196). Indicator variables to create these classes are listed in Table 6.

Early Developmental Questionnaire (EDQ): Brief questionnaire filled out by a parent to assess child's regression of language and social skills and functional behavior (209.)

Covariates

Covariates were used to describe our sample, weight for possible selection bias, and were used as an effect measure modifier (child sex). These variables were collected in maternal interviews, the child's birth certificate, and other medical records.

Confounding

Since our exposure in aim 2 is the same as in aim 1, our confounding model is similar. We know that BAP is theorized and BAP measures are designed to be independent of IQ, age, and race (123). Since we consider BAP to be an underlying genetic trait, there are not characteristics that can precede BAP. Factors like SES, parental education, parental age, child age at diagnosis, and child service usage are potential mediators. In aim 1 we ran sensitivity analyses to examine the effect of ethnicity, but for this aim there were no associations between child ethnicity and ASD phenotypic classes (Wiggins under review). Our decision making process is presented as a DAG (Figure 4). Further, all but two studies presented in Table 4 (review of studies that assessed associations between parent autism-traits and child ASD phenotype) did not adjusted for any demographic covariates or proposed confounders. One study controlled for sex (which we explored by categorizing BAP by parent type) (170) and the

other controlled for age and sex, but their research question was specific to interactions with anti-depressant use (168).

Table 6 Latent class variables for children with autism spectrum disorder enrolled in the Study to Explore Early Development (SEED)

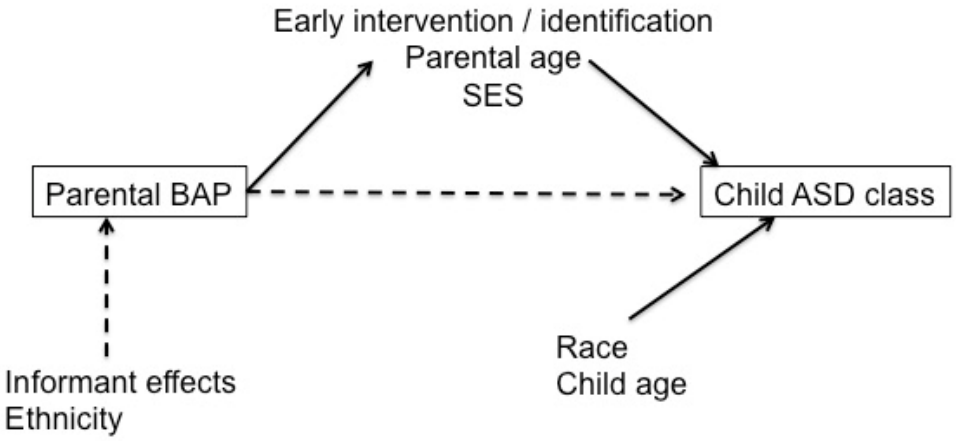
SEED data source	Latent class variables	Scores used in latent class analysis	Scores indicating impairment
Autism Diagnostic Observation Schedule	Autism symptom severity	Total severity scores from 1-10	Higher
Autism Diagnostic Interview – Revised	Age at verbal language development	Item scores from 4-62 months	Higher
	Age at walking	Item scores from 7-43 months	
	History of regression	Item score dichotomized into yes (regression in either language or social domains reported) or no (regression in language or social domains not reported)	
	Insistence on sameness	Item scores representing compulsions/rituals, difficulties with minor changes in routines, and resistance to trivial changes in the environment dichotomized into yes (any reported) and no (not reported)	
	Repetitive behavior with objects	Item score dichotomized into yes (reported) and no (not reported)	
	Repetitive motor mannerisms	Item scores representing hand and finger mannerisms and other complex mannerisms dichotomized into yes (any reported) and no (not reported)	
	Restricted interests	Item scores representing unusual preoccupations, circumscribed interests, and unusual attachment to objects dichotomized into yes (any reported) and no (not reported)	

SEED data source	Latent class variables	Scores used in latent class analysis	Scores indicating impairment
	Self-injurious behaviors	Item score dichotomized into yes (self-injurious behavior reported) and no (no self-injurious behavior reported)	
	Unusual sensory response	Item scores representing unusual sensory interests, undue sensitivity to noise, and negative response to specific sensory stimuli dichotomized into yes (any reported) and no (not reported)	
Caregiver Interview	Early recognition of epilepsy/seizure disorder	Item score dichotomized into yes (parent report of epilepsy/seizure disorder) or no (no parent report of epilepsy/seizure disorder)	Higher
Child Behavior Checklist	Aggressive behaviors, anxiety/depression, attention problems, emotional reactivity, somatic complaints, withdrawn behaviors	Domain t-scores from 50-100	Higher
Child Sleep Habits Questionnaire	Sleep problems	Total problems scores from 0-91	Higher
Early Development Questionnaire	Problems with age at first social smile	Item scores dichotomized into yes (delayed social smile) and no (typical social smile)	Higher
Gastrointestinal Questionnaire	Current diet restrictions	Item score dichotomized into yes (diet restrictions) or no (no diet restrictions)	Higher

SEED data source	Latent class variables	Scores used in latent class analysis	Scores indicating impairment
Mullen Scales of Early Learning	Expressive language skills	Age equivalent scores from 2-70	Lower
	Fine motor skills	Age equivalent scores from 4-68	
	Receptive language skills	Age equivalent from 1-69	
	Visual reception skills	Age equivalent scores from 5-69	
Social Communication Questionnaire	Social communication abilities	Total scores from 1-35	Higher

**Table adapted from Wiggins et al (under review)*

Figure 4. Directed acyclic graph for aim 2 analyses



Analysis

For our analysis, we created latent classes by replicating the approach used by Wiggins et al. (under review). We used an LCA approach because we believe that there is an underlying latent variable that explains the observed ASD phenotype. An extended LCA allows for use of continuous, dichotomous, and categorical variables. Response probabilities and patterns of observed data are used to create subgroups. Each individual has a probability of being in each class based on response patterns seen in the larger sample. In the past classes were assigned by highest probability, pseudo random draws, or maximum likelihood; but, the current consensus is that that approach leads to biased estimates because it does not account for classification error (210, 211).

We evaluated number of classes by running models up to 5 classes. Fit was evaluated using Bayesian Information Criterion (BIC) and Lo-Mendel-Rubin Likelihood Ratio Tests (LMR-LRT). Lower BIC values indicate better fit. A LMR-LRT p-value <0.05 improved fit over the model with one less class. Entropy ranges from 0 to 1 and higher entropy indicates greater classification precision. Low quality items (response probabilities close to 0.5) were dropped. These were gestational age and gastrointestinal issues. Tables from the Wiggins paper detailing model selection and response probabilities are presented in the appendix.

When adding covariates to assess associations with latent classes, there are multiple methods, each with strengths and weaknesses. Table 7 presents these three methods. Based on the literature and our research question, we used the inclusive LCA for our primary analyses. A three-step approach was used as additional analyses and is further expanded on below.

Table 7 Approaches for latent class analysis with covariates for aim 2 analysis

Approach	Citation	Overview	Positives	Negatives
Inclusive LCA	(211)	An LCA is run with just the indicators to determine class numbers and profiles. Then classes are re-ran with a covariate(s) and posterior probabilities are calculated (either through pseudo random sampling of maximum likelihood) and used in multinomial regression	Does not attenuate effect estimates due to omission of classification error, does not attenuate effect estimates due to not incorporating covariate into the LCA model, accounts for the fact that latent classes are a case of missing data	May be impractical with large number of covariates, may slightly affect class makeup
Three-step	(212)	LCA is run to create classes and classification errors are saved in a matrix, observations are assigned to classes based on posterior probabilities (either through pseudo random sampling of maximum likelihood). Then, in a separate multinomial model covariates are regressed on the classes while using the covariance matrix to weight for classification error	Classes remain the same independent of the covariates, easier model to fit, effects are not attenuated due to lack of classification error, more in line with how models are built	Effects are still attenuated due to missing data theory that a variable in the imputation model should be in the analytic model
Classify-analyze	(213)	An LCA is run and observations are assigned to classes (whether through highest probability, pseudo-random sampling, maximum likelihood). This classification is deterministic and does not allow for classification error. Analyses are run outside of the LCA framework and classes are treated like any other categorical variable	Can be run outside of the LCA framework (do not need Mplus or other software), classes will always be the same, if LCA has high enough entropy, classification error will be minimal	Attenuates effect estimates due to lack of classification error. Does not account for any differences in class if covariate variables are missing.

As mentioned earlier, we had missing data on parental BAP for 183 children. In order to use data on all cases and ensure that our classes were appropriate, we included an indicator for missing SRS-As. Past work has shown that using an indicator is less biased than restricting the sample (214). Using an indicator for missingness allows us to model both our observed data and missing data mechanism within the latent class framework (214). Further, if we believe that the classes represent an underlying structure in our data, the classes derived from the total SEED case sample would be the 'right' answer. In the absence of confounding, a complete case analysis that restricts to those with BAP measured makes the same assumption that an indicator for missingness does; those who are missing look like those who are not. It is well known that a missing indicator is biased in epidemiological analyses because it removes the effects covariates have on one another, which prevents adequate control of confounding (215, 216). However, in our analysis, we have no confounders and our exposure variables (whether dichotomous BAP or BAP by parent type) are independent. We believe that the cost of the extra missing parameter is made up for the ability to use data on all cases and used this approach in our primary analysis. For our third aim, we found no association between child sex and missingness, holding our assumption of no association between covariates and missingness. As sensitivity analyses, we used the complete case and weighting approaches. Strengths and weaknesses of these methods are described in Table 8.

We additionally explored inverse probability weights for missingness. These weights are calculated by using a logistic regression model to calculate probability of having complete BAP data. We used maternal race, age, ethnicity, and education as our covariates. If a child was not missing BAP data on parents, then their weight was 1/(probability of not missing) and 1/(1-probaiblity of not missing) if the data were missing. Analyses were weighted using these values and correct standard errors were calculated using a sandwich estimator.

After accounting for this missingness, we calculated odds ratios using multinomial logistic regression using an inclusive LCA where the additional covariates help improve the

posterior probability of class membership (211). Our aim 2.1 analysis ran the LCA with BAP dichotomized as any one parent having BAP or neither parent having BAP as an added covariate with a missing indicator. For aim 2.2, we split our BAP classification by parent type (neither parent has BAP, father has BAP only, mother has BAP only, both have BAP) with an indicator for missingness. Lastly, we added child sex and a child sex by BAP interaction term to our aim 2.1 model to assess differences by child sex. Data cleaning and weight calculations were conducted in SAS 9.3 (217). Latent class creation and multinomial logistic regression were done in Mplus 7 (218).

Table 8 Approaches for missing covariate data in latent class analysis for Aim 2

Approach	Description	Positive	Negatives
Indicator for missing SRS-As	When using an inclusive LCA approach, a covariate with missing data will cause creation of classes that do not mirror the underlying structure in the total data. This approach adds a missing indicator for the covariate (basically creating a categorical variable) and then is used in the model (214)	Allows use of all data, unbiased if there are no other covariates in the model: same assumptions as a complete case approach if no other confounders, can observe class pattern by missingness, easy to model	Biased if multiple covariates because it does not adequately account for correlation between covariates. Assumes missing completely at random
Complete case	Restrict our sample to just those with complete data on the covariate, then create classes and run multinomial analysis on this sample	Can handle multiple confounders without bias. Unbiased if missing completely at random	Biased if not MCAR, does not use all available data and classes may not represent true underlying latent class
Inverse probability of missingness weights	Run logistic model to predict missingness, and then create inverse probability weights. Run the LCA model weighted for missingness. Past work has looked at survey sampling weights and LCA: we believe that using those techniques for missing data is a natural extension (219, 220).	Adequately controls for selection bias, can use multiple covariates in the model	Does not use available data from those missing data to create classes

Additional analyses

As additionally analyses, we used the three-step approach and compared our estimates to the inclusive approach. We did this using two approaches for missing covariate data (missing indicator, inverse probability of missing weights).

The three-step approach starts with running the LCA as described by Wiggins et al. (under review). We then assigned classes based on posterior probabilities and ran our multinomial regressions weighting for classification error. Missingness was accounted for using our approaches detailed above (Table 8).

CHAPTER 4. RESULTS

4A. Mothers with the broader autism phenotype may be more likely to be discordant with clinician observation when reporting on child autism spectrum disorder

Overview

Diagnosis of autism spectrum disorder (ASD) relies on parent-reported and clinician-observed instruments. At times results between these instruments are discordant. The broader autism phenotype (BAP) in a parent-reporter may be associated with discordance. We used data from the Study to Explore Early Development (N=712) to address whether BAP+ mothers of children with ASD or DD were more likely than BAP- mothers to 'over-' or 'under-report' child ASD on ASD screeners or interviews compared with clinician observation or overall impression. Maternal BAP was associated with a child meeting thresholds on a maternal-reported screener or maternal-interview when clinician ASD instruments or impressions did not (risk ratios from 1.30 to 2.85). Reporting discordances should be acknowledged and accounted for when diagnosing ASD.

Introduction

The diagnostic criteria for autism spectrum disorder (ASD) are impairment in social communication and interaction and restricted and repetitive behaviors and interests (RRBI) (1). When diagnosing young children, the ASD diagnostic evaluation process relies on a caregiver (usually a parent) reporting on child behavioral and developmental traits as well as on a clinician observing the child's social abilities and behavior. Generally, one or more clinicians synthesize

all available information to reach a diagnosis based on the Diagnostic and Statistical Manual 5th edition criteria for ASD (1, 10).

ASD evaluation instruments, whether clinician observation or parent-report, have strengths and limitations. Clinicians are often experts in ASD evaluation and can compare a child to typically developing children or children with ASD. However, there is only a brief time to observe a child during an evaluation, they can only assess current behaviors at a single point in time, and they may be constrained by a clinical setting (e.g. cannot observe daily living skills, interacting with peers) (69, 91, 221). Parents (or other caregivers) are usually the most aware of the child's development, health status, and current behaviors. Parents are often advocates and experienced reporters on the child's health conditions (222, 223). But, ASD interview instruments based on parent report also have potential shortcomings. The order in which questions are asked can affect response (72) and responses about the child's developmental history might be influenced by current child behavior, developmental level, and demographic characteristics (73). Informant language ability may also affect response, particularly for non-native English speakers (10, 74). Using parent interviews in combination with clinician observation enables collection of a wider range of information while minimizing potential error of relying on only one clinical observation of child ASD or only on parental report (63, 64, 197, 224, 225). Sometimes these two approaches produce discordant information. Past studies found discordance to be associated with a child's age (224, 226) and RRBI (63, 197, 226).

Reporting discordance between parents and clinicians or parent and child self-report in other psychiatric disorders may provide background into potential reasons for discordance between interview and observation instruments when evaluating ASD. Mothers with a psychiatric condition like depression (12, 13, 15, 75-80), anxiety (14, 15, 81, 82), ADHD (13) or high stress (83) were more likely to report traits of that condition in their child as compared to a clinician observation or child interview (75, 76). These traits may be reported more frequently because mothers with psychiatric conditions could view other's behavior more negatively (84),

or, children of parents with psychiatric conditions have traits of that psychiatric condition and the parent is more finely attuned when reporting (75, 85). Learning more about reporting discordance in these other disorders has provided insight into child psychosocial adjustment (86), family dynamics (87), and intervention efficacy (88-90).

Similarly, the presence of broader autism phenotype (BAP) among mothers may be a source of differential reporting. BAP is a sub-clinical collection of quantitative autism traits seen in families of children with ASD (17, 23, 24, 128, 138, 141, 144, 156, 163-166, 227). Traits of BAP most often include difficulties with pragmatic language, reciprocal social interaction, and social cognition, as well as behavioral and cognitive rigidity (16). Studies have shown that individuals with BAP may also have more problems with anxiety, articulation, empathy, language development, and social initiation and response, compared to people without BAP (16, 117, 128, 187). These socio-communicative traits may impact informant ability (188, 189). Additionally, maternal BAP is a predictor of increased parental stress (179, 190) and anxiety (191), which both may have an effect on an informant's ability (95). Research is needed to examine if autism-like traits in a mother are a factor in discordance between child ASD evaluation instruments.

Our objective was to evaluate whether maternal BAP is associated with discordance between a child being at risk for ASD on a maternal-reported screening instrument or meeting ASD criteria on an interview instrument as compared to a clinician observation instrument or a measure of clinician overall certainty that the child has ASD ('best estimate'). We evaluated this discordance by examining whether the maternal report was more or less likely to meet these criteria than clinician observation or 'best estimate'. Additionally, we evaluated each of five BAP-related domains (social awareness, social motivation, social communication, social cognition, and autistic mannerisms) to see whether a particular area of BAP traits influence discordance. Lastly, we explored whether discordance is associated with maternal self-reported history of a

diagnosis of depression or anxiety disorders to better understand whether discordance is specific to BAP or to overall maternal psychiatric conditions more generally.

Methods

Study to Explore Early Development

We used data collected in the first phase of the Study to Explore Early Development (SEED). SEED is a multi-site, community sampled, case-control study with the purpose of characterizing the autism behavioral phenotype and associated behavioral, medical, and developmental conditions and investigating genetic and environmental risk factors for ASD (196). SEED included six sites: California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania. Data on children born between 2003 and 2006 were collected between 2007 and 2012. Eligible children were between 30 and 68 months at the time of developmental assessment, were born and resided in the study catchment area at the time of first study contact, and lived with a knowledgeable caregiver who was able to communicate the child's developmental history in English (or in Spanish in California and Colorado) (196).

Three groups of children were sampled in SEED. The first two groups were children with a past diagnosis or other indication of ASD or a non-ASD developmental disability or delay (DD). These children were identified from multiple education and health providers in the study areas that diagnose and serve children with a broad range of DDs including health clinics, early intervention programs, and special education programs. The third group of children was from the general population. They were randomly sampled from birth records at each study site. Identified families were sent a written invitation to participate and a follow-up invitation telephone call was conducted.

ASD evaluation

During the preliminary phone call with SEED staff, children's caregivers (99.0% biological mothers) completed the Social Communication Questionnaire (SCQ) (61), an autism screening instrument. The SCQ is comprised of 40 yes or no questions aimed at assessing a

child's socio-communication ability. The recommended cut-off score that indicates ASD risk is 15 points. Previous research suggests that a cut-off score of 11 points maximizes sensitivity and specificity in young children. Because of the young age of included children (3 to 5 years of age), a cut-off of ≥11 was used to define a positive autism screen in order to maximize case finding (228).

After completing the SCQ, all children had a developmental assessment that included the Mullen Scales of Early Learning (MSEL). Children with a past diagnosis of ASD or a positive score on the SCQ received a full diagnostic evaluation. DD and POP children who scored negative on the SCQ were given a full evaluation if a clinician suspected ASD during the developmental assessment. Primary diagnostic instruments used were the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R) (10).

Clinicians conducted the ADI-R (67) with the child's caregiver during an in person visit. The ADI-R is a 93-item, 150-minute semi-structured interview that obtains comprehensive information from the caregiver in three domains of child development: social skills, communication skills, and RRBI. The ADI-R also obtains information on whether developmental delays or deficits were noted in the first three years of life (67, 199). SEED used the standard ADI-R algorithm to determine whether the child met ADI-R criteria for ASD. Inter-site reliability was 99% and intra-site reliability was 87% for the ADI-R (197).

SEED used the ADOS (198) as the clinician observation instrument. During the ADOS, clinicians interact with and observe a child for over 40 minutes while creating social opportunities that elicit social communication and social interaction that allows the clinician to record RRBI. The ADOS has specific modules based on age and verbal ability (69); SEED used module 1 for children with no or few words and no phrase speech, module 2 for children with phrase speech who were not verbally fluent, and module 3 for verbally fluent children (197). Standard ADOS algorithms were used for each module to determine ASD classification. Inter-site reliability was 99% and intra-site reliability was 99% (197).

The Ohio State University Autism Rating Scale (OARS) served as the global clinical judgment instrument. The OARS is a tool filled out by the clinician that uses all available information to measure symptom severity, degree of impairment, and clinician certainty in child's ASD diagnosis (200). This tool was specifically modified to a five point Likert scale for SEED. We dichotomized this scale into ‘‘uncertain’’ (scores of 1–3 or note that ASD symptoms better accounted for by another disorder) and ‘‘certain’’ (scores of 4 or 5) (196, 197). For this study, a score of 4 or 5 indicated a case and the OARS served as our 'best estimate' of clinician certainty of ASD. Additionally, since it incorporates all available information and is similar to how diagnosis is derived in a clinical setting, the OARS acted as a diagnostic 'gold standard' in our analyses. Details of these instruments are presented in Table 9. Further information on SEED procedure can be found in Schendel et al. (196) and Wiggins et al. (197).

BAP instrument

BAP was assessed using the Social Responsiveness Scale-Adult (SRS-A) (60). Although not originally designed to measure BAP, the SRS-A has shown good consistency with other BAP and qualitative autism trait instruments (122, 149). The SRS-A is a 65-item Likert scale questionnaire that takes 15-20 minutes to complete and assesses the caregiver's social and communication traits. In SEED, the caregiver was asked to have a spouse (or friend or relative if no spouse) to complete the SRS-A on them, as recommended for this instrument. A strength of the SRS-A is its ability to measure five distinct domains of social responsiveness: social awareness, social cognition, social communication, social motivation, and autistic mannerisms (60). The SRS-A has strong internal validity, exhibiting a Cronbach's alpha internal consistency coefficient of 0.95 (122, 123). SRS scores in children have been shown to be independent of IQ and age (60, 201) and psychometric properties are assumed to be the same in adults (122). Raw overall and domain SRS-A scores were standardized to T-scores, which have a mean of 50 and a standard deviation of 10. For this study we used the standard 'mild range' recommendation of ≥60 (59) to indicate BAP. We will refer to scores that meet or exceed

this threshold as BAP positive (BAP+) and those that do not as BAP negative (BAP-). The domain scores use the same T score standardization but include only specific questions that fit the domain.

Discordance

We created variables to indicate discordance between the maternal screener (SCQ) or maternal interview (ADI-R) and the clinician observation (ADOS) or clinician 'best estimate' (OARS) using the SEED cut-off scores. Our four comparisons were the SCQ versus ADOS, SCQ versus OARS, ADI-R versus ADOS, and ADI-R versus OARS. If the two instruments were in agreement (both indicated ASD or ASD risk or both indicated no ASD or ASD risk) then they were considered 'not discordant'. Since the ASD evaluation is a complex process that takes place over a limited amount of time, we do not want to imply that a mother's report or clinician observation on child ASD is the 'correct one'; however, since we are more concerned about influence of maternal characteristics on reporting, we use the clinician completed instruments as our reference group when presenting our results. Therefore, we define 'over-reporting' as the maternal report meeting the instrument's threshold when the clinician did not and 'under-reporting' when the maternal report did not meet the threshold while the clinician did.

Study Sample

For this study, we included all children in SEED identified from educational or medical providers that serve children with DDs (N=2,541), then excluded siblings (which would violate independence) (N=61); children without a completed Social Communication Questionnaire (SCQ) (N=26), ASD evaluation (N=1424) or maternal SRS-A (N=167); and children whose mother did not act as the sole informant on the ADI-R or SCQ (N=151). Our final analytic sample was 712 mother-child dyads.

Although some children with history of DD did not receive the full evaluation, we elected to include those who did in our sample. We chose to include these children because if a child screened negative on the SCQ and a clinician had suspicion of ASD at the clinic visit, the child

still received the full ASD evaluation (N=51). Additionally, DD is a broad category and many children with DD did not present any ASD symptoms (205). Our study is not designed to assess discordance among children without ASD symptoms.

Analytic approach

Demographic information and maternal-reported psychiatric history were collected in SEED using a maternal interview, self-completed questionnaires, and data abstraction from child's birth and medical records. Maternal psychiatric history was collected using the maternal medical history form where a mother checked whether she had past physician diagnosis of certain conditions. We calculated means and percentages for these demographic characteristics by BAP status and by ADOS vs. ADI-R discordance as a representative outcome.

We used log-binomial models to estimate percent discordance and evaluated whether discordance ('over-reporting' or 'under-reporting' compared to not discordant) differed by maternal BAP status (BAP+ or BAP-) using $\alpha=0.05$ to indicate statistically significant differences. A model was run for 'over-reporting' which excluded those who 'under-reported' and a model was run for 'under-reporting' which excluded those who 'over-reported'.

Since 163 mothers were missing SRS-A (18.6% of mothers who met other eligibility criteria), we ran a sensitivity analysis to examine potential selection bias. We predicted missing SRS-A based on demographic variables then used individual probabilities to calculate inverse probability weights. We reran our analysis using these inverse probability weights to evaluate the impact of this missingness.

Based on BAP being a well-validated construct that is not affected by demographics like age or education (24) and the SRS-A being designed to be independent of age and IQ (123), we do not believe that there are confounders for which to adjust in our main analyses. However, It is possible that language difficulties affected both completion of the SRS-A and the SCQ or ADI-R. We ran sensitivity analyses to evaluate how our estimates would change if we excluded those who indicated that their preferred language was Spanish (n=47).

For our secondary objectives, we ran models with all five SRS-A domains in one model rather than total BAP score to evaluate associations in each domain. Domains were dichotomized using a T score ≥60 as our cut-point. We include all domains in the same model to evaluate a single domain controlling for the others. To explore whether maternal self-reported history of a diagnosis of depression or an anxiety disorder (referred to as depression diagnosis or anxiety diagnosis) has an association with discordance, we ran models with these measures of depression diagnosis or anxiety diagnosis as an independent variable instead of BAP status. Being that this analysis is more exploratory in nature and the literature is limited on whether BAP confounds the relationship between depression or anxiety and reporting on ASD measures, we elected to calculate effect estimates that were not conditional on maternal BAP status. Further, there was negligible correlation in our data between maternal BAP and depression diagnosis (Φ=0.07), or with anxiety disorder diagnosis (Φ=0.03), supporting our decision not to control for maternal BAP. We qualitatively examined whether effect estimates differed from the BAP estimates.

Results

In our analytic sample of 712 mother-child dyads that met all entry criteria, 67 mothers (9.4%) were BAP+ and 645 were BAP- (91.6%). Table 10presents demographic variables by overall BAP status and discordance status (using ADI-R vs. ADOS as a representative discordancy outcome). BAP+ mothers were 40.3% black, 23.9% Hispanic, and 19.4% had ≥16 years of education. BAP- mothers were 19.8% black, 14.8% Hispanic, and 51.0% had ≥ 16 years of education. Mothers who ‘over-reported’ were 68.6% white and 22.9% had <12 years of education. Mothers with no discordance were 60.9% white and 7.1% had <12 years education.

In our total sample, 624 children met the threshold for ASD risk on the SCQ (87.7%), 456 met ADI-R criteria for ASD (64.0%), 544 met ADOS criteria (76.4%), and 466 had a clinician best estimate of ASD based on the OARS (65.4%). Table 11 presents counts and estimated discordances percentages between maternal report instruments and clinician

instruments stratified by BAP status. Discordance was common in our sample, as our comparison with the least discordance (ADI-R vs. ADOS in BAP- mothers) was 78.1% concordant. Most common discordance was 'over-reporting' between the SCQ and ADOS or SCQ and OARS in BAP+ mothers (32.8% and 40.3% respectively). Qualitatively, 'over-reporting' was less common when the ADI-R was the maternal measure compared to the SCQ. Phi coefficients for correlation between discordance outcomes were moderate to low (ranging from φ =0.60 to φ =0.09).

Figure 1 graphically presents risk ratios for discordance comparing BAP+ mothers to BAP– mothers. Being BAP+ was significantly associated with 'over-reporting' compared to no discordance when comparing the SCQ to the ADOS (RR: 1.63, 95% CI: 1.12, 2.37), and the ADI-R to the ADOS (RR: 2.85, 95% CI: 1.35, 6.03) [Figure 1]. The effect estimate for the SCQ versus the OARS (RR 1.26, 95%CI: 0.95, 1.77) and ADI-R compared to the OARS (RR: 1.65, 95% CI: 0.97, 2.81) were similarly elevated, but did not reach statistical significance. There were no significant differences when assessing 'under-reporting', but the effect estimates suggest less 'under-reporting' by BAP+ mothers when reporting on the SCQ (ADOS RR: 0.57, 95% CI: 0.21, 1.50; OARS RR: 0.51, 95% CI: 0.16, 1.57).

We ran a series of sensitivity analyses for our overall estimates. Weighting to control for potential bias due to missing SRS-As showed minimal differences compared to un-weighted estimates (Table 12); therefore, we present un-weighted estimates. Excluding mothers whose preferred language was Spanish attenuated effect estimates for 'over-reporting' and slightly increased our effects for 'under-reporting.' Although there were some differences, restricting to English speakers did not change our interpretation of overall results so we present our full sample estimates (Table 13). Using a SCQ cut-off of 15 (instead of 11) increased our effect estimates for 'over-reporting' for comparisons between the SCQ and the ADOS and the SCQ and the ADI-R by approximately 10% (results not presented). Lastly, we restricted to just those

with a prior diagnosis of ASD. Effects were not meaningfully different, except confidence intervals were wider due to the restricted sample (results not presented).

We also evaluated the association between the five SRS-A domains and discordance. Of all mothers in our sample, 7.0% of mothers had a T score ≥60 in the social awareness domain, 13.8% in the social cognition domain, 9.3% in the social communication domain, 13.9% in the autistic mannerism domain, and 10.5% in the social motivation domain. Table 14 presents results for 'over-reporting' by SRS-A domain. Social cognition (RR: 1.94, 95% CI: 1.06, 3.55) and social awareness (RR: 2.1, 95% CI: 1.15, 3.82) were significantly associated with 'over-reporting' on the ADI-R compared to the OARS. No other comparisons, including for 'under-reporting' (not shown) met statistical significance.

In our sample, 36.5% of BAP+ mothers reported ever having a past diagnosis of depression whereas BAP- mothers reported 24.8%. Nevertheless, depression diagnosis was not associated with either 'over-reporting' or 'under-reporting' (Table 15). For anxiety disorders, 17.7% of BAP+ mothers and 13.2% of BAP- mothers reported past diagnosis. Risk of 'over-reporting' between the ADOS and the ADI-R by anxiety disorder diagnosis was elevated, but did not meet statistical significance (RR: 1,97, 95% CI: 0.92, 4.20). Compared to those without anxiety disorder diagnosis, those that did also had non-significant elevated risk of 'over-reporting' on the SCQ compared to the ADOS (RR: 1.35, 95% CI: 0.95, 1.92) and to the OARS (RR: 1.27, 95% CI: 0.96, 1.77).

Discussion

In a sample of children with past diagnosis of ASD or other non-ASD DDs, We found that discordance between maternal report instruments (a screening questionnaire or diagnostic interview) and clinician observation or clinician 'best estimate' of ASD was prevalent in our sample. For our purposes, we used clinician observation as our referent category and used 'over-reporting' or 'under-reporting' as a way to characterize how maternal reporting relates to observations and opinions of clinicians.

Mothers with BAP were significantly more likely than mothers without to 'over-report' on the SCQ versus both the ADOS and the OARS, and on the ADI-R versus the ADOS. These results are in agreement with literature for other psychiatric disorders that show that a mother with a psychiatric condition may report more characteristics of the condition in her child than child self-report or clinician observation (13, 75, 76, 80, 96). Qualitatively, effect estimates for 'over-reporting' were slightly higher when using the ADI-R compared to the SCQ. This may be a result of the instruments delivery in SEED (in-person vs. telephone), length (150 minutes vs. 15-20 minutes), or purpose (diagnostic interview vs. screening instrument).

We found that BAP+ mothers were less likely than BAP- mothers to 'under-report' when reporting on the SCQ (compared to ADOS or OARS), but effect estimates were not statistically significant. 'Under-reporting' could be less likely because of the nature of the SCQ as a screening instrument, which we chose to have high sensitivity at the expense of specificity, and our exclusion of children with DD who scored negative and did not have ASD characteristics. Ultimately, we do not believe this sampling is differential by BAP status. When comparing the ADI-R to the ADOS or OARS, effect estimates for 'under-reporting' were near 1.0. This difference in point estimate for 'under-reporting' effects may be a function of the instruments purpose and administration in conjunction with BAP status. Based on BAP traits like aloofness, it could be postulated that a person with BAP would be more likely to 'under-report' another's ASD symptoms because of differences in social understanding; however, our results did not support this belief.

Although we found significant 'over-reporting' on the SCQ compared to both the ADOS and the OARS in BAP+ vs. BAP- mothers, none of the specific SRS-A domains were significantly associated with such 'over-reporting' after controlling for the other domains. It is possible that the overall construct identified by total SRS-A score is more important than any individual domain (which is made up from specific questions of the larger SRS-A) when assessing discordance on the SCQ. Our sample size may have limited our ability to precisely

estimate effects by domain. The autistic mannerisms domain was significantly associated with 'over-reporting' on the ADI-R versus the ADOS and the social cognition domain was associated with 'over-reporting' on the ADI-R versus the OARS. It is possible that effects of traits that comprise those two domains are more pronounced in the longer, more intensive ADI-R interview process, but confidence intervals were wide. Further work should examine whether specific BAP traits in those domains, or domains from other BAP instruments, are associated with discordance.

Even though mothers with depression may 'over-report' child depression symptomatology (13, 15, 85) and maternal depression is associated with BAP (133), we found no effect of maternal depression diagnosis on discordance between the instruments we evaluated. Our findings are restricted to those who reported a past diagnosis of depression, which may not capture the full extent of maternal depression; it may be of future interest to examine associations with dysphoria or trait based depression since depressive traits could mediate the relationship between BAP and discordance. As for maternal anxiety disorder diagnosis, we saw patterns suggesting 'over-reporting' when using the ADI-R compared to the ADOS or the OARS. It is possible that the ADI-R facilitates state anxiety in those with a reported history of an anxiety disorder diagnosis due to the in-depth nature of questioning and time required to complete the interview. It is also possible that trait anxiety (which we do not have measured) is exacerbated during the ADI-R and this effects reporting of ASD symptoms in the child. Future research should evaluate this question and associations with BAP using trait based anxiety measures.

In the context of our results it should be noted that our sample was comprised primarily of children with past history of DD or ASD. Once concern is raised about a child's development, a mother may be more likely to push for a diagnosis and report in such a way to receive maximum services, running counter to 'under-reporting' child traits (229, 230). It may be of future interest to evaluate discordance among mothers of children with ASD symptoms who

have never been through the ASD evaluation process to evaluate these patterns without the mother's past experience.

Potential causes of these BAP-related discordances in reporting ASD characteristics should also be examined in future work. We can hypothesize that the 'over-reporting' we see could be due to social desirability (231, 232), where mothers with BAP who know that their child has a history of DD may be more susceptible to giving answers that they think the clinician wants. Certain social traits like agreeableness and self-esteem are associated with more socially desirable responding (233). As yet, no empirical studies have evaluated the association between BAP and social desirability bias. We examined self-reported past history of diagnosis of psychiatric conditions, but state based emotional traits that are associated with BAP may play a role in how a mother completes an instrument. Further, mothers may notice or be less tolerant of traits they themselves have and this could lead to 'over-reporting' as has been seen when studying depression (84). Alternatively, this 'over-reporting' may be due to mothers with BAP having children who have a different ASD presentation that is more difficult to assess in the limited clinical observation setting. It is possible that mothers with BAP within SEED have children with different ASD profiles compared to children of mothers without BAP, which may be difficult to identify in the limited clinical observation setting. This question will be evaluated in future work. Along with different phenotypes, it is also possible that a mother with BAP is more finely attuned to the child's presentation, being that they may have experienced similar socio-communication difficulties, and are able to report on the finer details that a clinician does not have the time or opportunity to see or recognize.

This study has some limitations. Our sample is restricted to children who were identified through ASD and DD education and health providers, which prevents us from making inferences about the larger SEED sample or the general population. Additionally, the SEED sample is more educated and less Hispanic than the general population, which limits our generalizability. In our study, mothers who are BAP+ versus BAP- differ in demographic

variables like education and age. However, based on our causal framework, which posits that BAP is independent of demographics like education and maternal age, we do not suspect confounding. Covariate differences may be because our effects are mediated through education, past child ASD diagnosis, or maternal age. When examining effects of culture, specifically language difference, our sensitivity analysis showed slight attenuation of effects when restricting to mothers whose preferred language was English. Next steps may be to examine cultural difference, measured as ethnicity or race, as an effect measure modifier of the BAP discordance relationship. Further, it is likely that the same clinician completed all instruments and this may lead to excessive correlation. Nevertheless, SEED's thorough evaluation procedure and strong inter- and intra-rater reliability minimize this potential bias. We were missing data on the identity of the informant for the SRS-A for 18.8% of mothers. Mothers were asked to have a spouse or friend complete the SRS-A on her, but the relationship to the mother was often left blank on the form. If the SRS-A were completed through self-report, it could create misclassification. A past study has shown differential BAP scores between a self- and informant report using another BAP instrument (180). We ran sensitivity analyses defining BAP using various SRS-A T-score cutoffs and results did not show meaningful differences in risk of discordance between T scores of 58 and 62 (data not shown). We believe that are results are robust to minor misclassification in the SRS-A, but it would have been informative to know the effect of informant type on the SRS-A scores.

This study also has major strengths and can inform future research and the ASD diagnostic processes. Our study sample was derived from multiple sites and from various types of education and health providers, not solely clinic-derived. Having a broader population sampling scheme allows for more diversity in included ASD phenotype and family demographics. Additionally, we have data on full diagnostic evaluations with data reported by informants and clinicians, regardless of screener score. This allows us to assess properties of the screener without risk of bias from evaluating only those who score positive. Moreover, data

were used on four separate instruments with different uses (screeners, interviews, observation, best estimate), allowing for us to assess discordance between instruments with different goals and methods. We believe that this is one of the first studies to assess BAP as a source of discordance between ASD evaluation instruments.

Our study found that mothers with BAP were more likely to 'over-report' and indicate that a child meets an instruments criteria for ASD when a clinician does not meet those conclusions. This result was not seen when assessing maternal depression diagnosis and was evident only when comparing the ADI-R and the ADOS for maternal anxiety disorder diagnosis. Future work should address whether the phenotypic profile of children with ASD whose parents have BAP differs from that of children with ASD whose parents do not have BAP, which may explain some of this observed discordance. Additionally, much is still unknown on how people with BAP report on others, regardless of whether they are reporting on ASD; more work can be done to explore how people with BAP act as informants. Based on our results, clinicians may need to be cognizant of maternal socio-communicative ability when synthesizing available information and accounting for instrument discordance when deciding on a final diagnosis for child ASD.

.

Table 9 Description of measures used to evaluate child autism spectrum disorder in the Study to Explore Early Development

Instrument	Instrument Type	Respondent	Length	Description
Social Communication Questionnaire (SCQ)	Screening questionnaire	Mother	40 yes or no questions that take approximately 15 minutes to complete	SEED staff administered the questionnaire about a child's behavior and development over the phone during study enrollment call
Autism Diagnostic Interview-Revised (ADI-R)	Interview	Mother	93 items that take approximately 150 minutes to complete	Structured interview about child's past and current behavior and development that is led by a SEED clinician either at the mother's home, SEED clinic, or over the phone
Autism Diagnostic Observation Schedule	Observation	Clinician	40 minute observation and interaction period	SEED clinician interacts and observes the child at the child's home or SEED clinic. Different modules are administered based on child's age and verbal language ability
The Ohio State University Autism Rating Scale (OARS)	Synthesis of available data	Clinician	Clinician completed Likert scale of certainty that the child has ASD, completed after all other data are collected	SEED clinician or team of clinicians used all available data, specifically from the ADI-R and ADOS to give best clinical impression of whether the child has ASD

Table 10. Distribution of socio-demographic characteristics for families referred into the Study to Explore Early Development, by maternal broader autism phenotype status and ADI-R-ADOS discordance

	BAP+ N=67		BAP- N=645		Not discordant N=553		'Over-reporting' N=35		'Under-reporting' N=124	
	N	%	N	%	N	%	N	%	N	%
Child Case status										
ASD	40	59.7	439	68.1	410	74.1	0	0.0	69	55.7
DD	25	37.3	174	27.0	122	22.1	29	83.9	48	38.7
Possible Case	2	3.0	32	5.0	21	3.8	6	17.1	7	5.7
Child Sex										
Male	51	76.1	514	79.7	442	79.9	28	80.0	95	76.6
Female	16	23.9	131	20.3	111	20.1	7	20.0	29	23.4
Maternal race										
White	33	49.3	462	62.3	385	60.9	24	68.6	75	60.5
Black	27	40.3	147	19.8	139	22.0	5	14.3	25	20.2
Asian	3	4.5	51	6.9	43	6.8	1	2.9	9	7.3
Other	3	4.5	46	6.2	39	6.2	3	8.6	8	6.5
Multi-racial	1	1.5	35	4.7	26	4.1	2	5.7	7	5.6
Maternal ethnicity										
Hispanic	16	23.9	95	14.8	86	17.4	8	22.9	17	13.7
Not-Hispanic	51	76.1	549	85.3	466	84.4	27	77.1	107	86.3
Missing			1		1					
Maternal education (years)										
<12	13	19.4	42	6.5	39	7.1	8	22.9	8	6.5
12 to <16	41	61.2	274	42.5	252	45.6	16	45.7	47	37.9

>=16	13	19.4	329	51.0	262	47.4	12	34.3	69	55.6
Maternal self-reported history of depression diagnosis										
Yes	23	36.5	158	24.8	147	27.1	8	23.5	26	21.8
No	40	63.5	479	75.2	400	73.7	26	76.5	93	78.2
Missing	4		8		6		1		5	
Maternal self-reported history of an anxiety disorder diagnosis										
Yes	11	17.7	84	13.2	70	12.9	8	21.6	17	14.2
No	51	82.3	551	86.8	473	87.1	26	70.3	103	85.8
Missing	5		10		10		1		4	
Site										
California	15	22.4	95	14.7	80	14.5	11	31.4	19	15.3
Colorado	9	13.4	132	20.5	116	21.0	5	14.3	20	16.1
Georgia	10	14.9	130	20.2	115	20.8	4	11.4	21	16.9
Maryland	11	16.4	81	12.6	80	14.5	5	14.3	7	5.6
North Carolina	8	11.9	135	20.9	97	17.5	8	22.9	38	30.6
Pennsylvania	14	20.9	72	11.2	65	11.8	2	5.7	19	15.3
Child age										
Mean, SD	60.3	6.0	59.5	6.6	59.7	6.4	61.6	5	58.4	7.4
Missing			3		2		1			
Maternal age										
Mean, SD	34.1	6.4	36.1	5.7	35.9	5.8	33.8	6.1	36.3	5.7
Missing			1		1					
Number of children in household										
Mean, SD	2.5	1.3	2.2	1.0	2.3	1	2.4	1.37	2.3	1.0
Missing	2		8		8		1		1	
Past child ASD diagnosis										
Yes	37	55.2	458	71.2	407	73.9	16	45.7	72	58.1
No	30	44.8	185	28.8	144	26.1	19	54.3	52	41.9
Missing			2		2					

ASD: autism spectrum disorder;
DD: developmental disability;
SRS-A: social responsiveness scale adult;
SD standard deviation
Sample: referred into SEED, had completed SRS-A, SCQ, and full evaluation
Excludes siblings

[a] Not discordant is when SCQ or ADI-R has the same result as the ADOS or OARS
[b] 'Over reporting' is when the SCQ or ADI-R meets ASD criteria while ADOS or OARS does not
[c] 'Under reporting' is when the SCQ or ADI-R does not meet ASD criteria while ADOS or OARS does
[d] Possible Cases are children whose final case status could not be determined

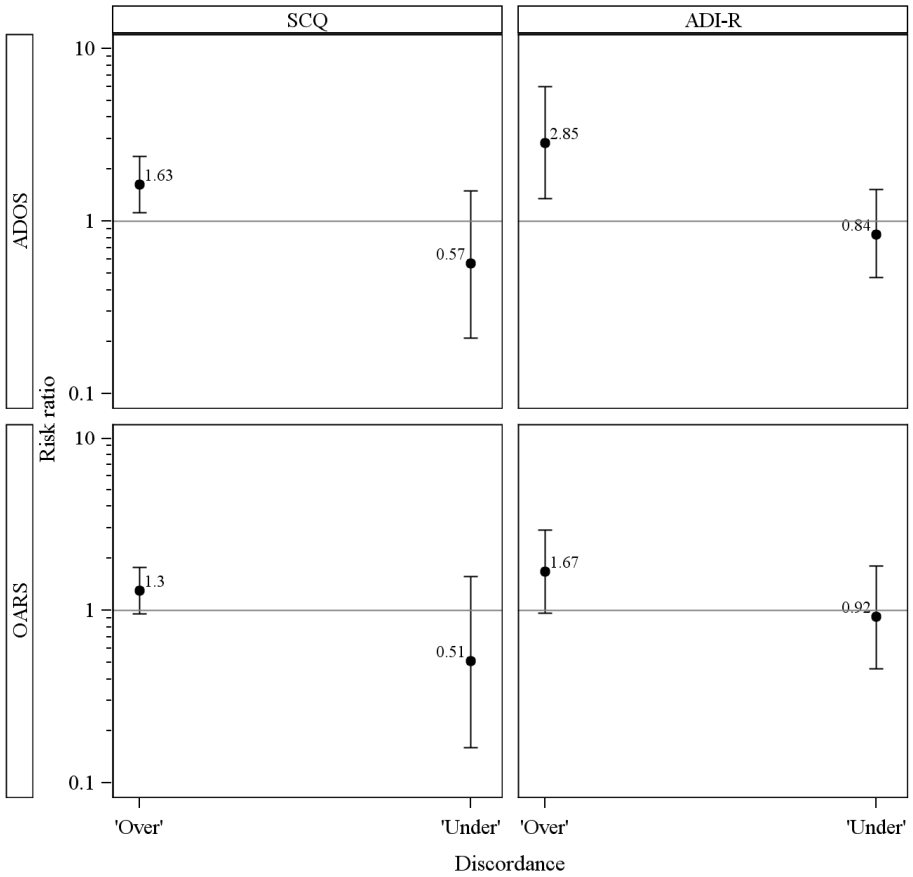
Table 11. Discordance between maternal and clinician ratings on child autism spectrum disorder screening and evaluation in children referred into the Study to Explore Early Development, by maternal broader autism phenotype status

	BAP+ N=67			BAP- N=645		
Discordance	N	Percent	95% CI	N	Percent	95% CI
SCQ ADOS						
'Over'	22	32.8	23.3, 46.3	130	20.2	17.3, 46.3
'Under'	4	6.0	2.3, 15.4	68	10.5	8.4, 13.2
None	41	61.2	50.6, 74.1	447	69.3	65.8, 73.0
SCQ OARS						
'Over'	27	40.3	26.3, 33.4	191	29.6	30.1, 53.9
'Under'	3	4.5	1.5, 13.5	57	8.8	6.9, 11.3
None	37	55.2	44.5, 68.5	397	61.6	57.9, 65.4
ADI-R ADOS						
'Over'	8	11.9	6.2, 22.9	27	4.2	6.2, 22.9
'Under'	10	14.9	8.4, 26.4	114	17.7	15.0, 20.9
None	49	73.1	63.2, 84.6	504	78.1	75.0, 81.4
ADI-R OARS						
'Over'	12	17.9	10.7, 29.9	69	10.7	8.6, 13.4
'Under'	8	11.9	6.2, 22.9	84	13.0	10.7, 15.9
None	47	70.2	60.0, 82.0	492	76.3	73.1, 79.6

CI: confidence interval;
BAP: broader autism phenotype
SCQ: Social Communication Questionnaire;
ADI-R: Autism Diagnostic Interview Revised;
ADOS: Autism Diagnostic Observation Schedule;
OARS: The Ohio State University Autism Rating Scale;

[a] Not discordant is when SCQ or ADI-R has the same result on meeting SEED thresholds for ASD or ASD risk as the ADOS or OARS
[b] 'Over-reporting' is when the SCQ or ADI-R meets SEED ASD risk or ASD criteria while ADOS or OARS does not
[c] 'Under-reporting' is when the SCQ or ADI-R does not meet SEED criteria for ASD risk or ASD criteria while ADOS or OARS doe

Figure 5. Risk ratios comparing discordance between maternal and clinician ratings on child autism spectrum disorder screening and evaluation instruments in children referred into the Study to Explore Early Development, by maternal broader autism phenotype status



No BAP and Clinician observations / estimates are the referent category
SCQ: Social Communication Questionnaire;
ADI-R: Autism Diagnostic Interview-Revised;

ADOS: Autism Diagnostic Observation Schedule;
OARS: The Ohio State University Autism Rating Scale;

‘Over reporting’ is when the SCQ or ADI-R meets SEED ASD risk or ASD criteria while ADOS or OARS does not
‘Under reporting’ is when the SCQ or ADI-R does not meet SEED ASD risk or ASD criteria while ADOS or OARS does

Table 12 Overall estimates comparing discordance between maternal and clinician ratings on child autism spectrum disorder screening and evaluation instruments in the Study to Explore Early Development, by maternal broader autism phenotype status, weighted to account for missing Social Responsiveness Scale-adult

	SCQ				ADI-R			
	'Over-reporting'		'Under-reporting'		'Over-reporting'		'Under-reporting'	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
				Weighted				
ADOS	**1.49**	1.02, 2.17	0.72	0.27, 1.91	**2.58**	1.20, 5.54	0.94	0.51, 1.72
OARS	1.28	0.94, 1.75	0.63	0.20, 1.97	1.61	0.91, 2.82	1.00	0.50, 1.98
				Unweighted				
ADOS	**1.55**	1.07, 2.25	0.67	0.26, 1.76	**2.85**	1.35, 6.03	0.84	0.47, 1.53
OARS	1.30	0.95, 1.77	0.6	0.20, 1.82	1.67	0.96, 2.92	0.92	0.46, 1.81
				Difference				
ADOS	-4.0		6.9		-10.5		10.6	
OARS	-1.6		4.8		-3.7		8.0	

RR Risk ratio
CI Confidence interval
ADI-R: Autism Diagnostic Interview-Revised
ADOS: Autism Diagnostic Observation Schedule
OARS: The Ohio State University Autism Rating Scale;
[a] 'Over reporting' is when the SCQ or ADI-R meets SEED ASD risk or ASD criteria while ADOS or OARS does not
[b] 'Under reporting' is when the SCQ or ADI-R does not meet SEED ASD risk or ASD criteria while ADOS or OARS does

Table 13. Overall estimates comparing discordance between maternal and clinician ratings on child autism spectrum disorder screening and evaluation instruments in the Study to Explore Early Development, by maternal broader autism phenotype status, evaluating excluding mothers with Spanish as a preferred language

	SCQ				ADI-R			
	'Over-reporting'		'Under-reporting'		'Over-reporting'		'Under-reporting'	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
				English speakers only (n=665)				
ADOS	1.40	0.90, 2.18	0.70	0.27, 1.83	**2.66**	1.13, 6.22	0.94	0.51, 1.75
OARS	1.14	0.79, 1.66	0.60	0.20, 1.82	1.39	0.74, 2.61	0.96	0.47, 1.97
				Full sample (N=712)				
ADOS	**1.63**	1.12, 2.37	0.57	0.21, 1.50	**2.85**	1.35, 6.03	0.84	0.47, 1.53
OARS	1.3	0.95, 1.77	0.51	0.16, 1.57	1.67	0.96, 2.92	0.92	0.46, 1.81
				Percent difference				
ADOS	-16.4		18.6		-7.1		10.6	
OARS	-14.0		15.0		-20.1		4.2	

CI: Confidence interval;
RR: Risk ratio;
SCQ: Social Communication Questionnaire;
ADI-R: Autism Diagnostic Interview-Revised
ADOS: Autism Diagnostic Observation Schedule;
OARS: The Ohio State University Autism Rating Scale

[a] 'Over-reporting' is when the SCQ or ADI-R meets SEED ASD risk or ASD criteria while ADOS or OARS does not
[b] 'Under-reporting' is when the SCQ or ADI-R does not meet SEED ASD risk or ASD criteria while ADOS or OARS does

Table 14. Over-reporting' discordance between maternal and clinician ratings on child autism spectrum disorder screening and evaluation instruments in the Study to Explore Early Development, by Social Responsiveness Scale-Adult domains

	RR	95% CI
SCQ ADOS		
Overall	**1.63**	1.12, 2.37
Social awareness	0.65	0.36, 1.17
Social cognition	1.09	0.67, 1.78
Social communication	1.55	0.88, 2.73
Autistic mannerisms	1.17	0.75, 1.82
Social motivation	0.94	0.57, 1.54
SCQ OARS		
Overall	1.30	0.95, 1.77
Social awareness	1.23	0.80, 1.89
Social cognition	1.28	0.88, 1.86
Social communication	1.13	0.68, 1.88
Autistic mannerisms	0.97	0.68, 1.40
Social motivation	0.67	0.42, 1.07
ADI-R ADOS		
Overall	**2.85**	1.35, 6.03
Social awareness	1.33	0.40, 4.39
Social cognition	0.50	0.13, 1.92
Social communication	3.03	0.65, 14.14
Autistic mannerisms	1.73	0.63, 4.77
Social motivation	0.50	0.13, 1.68
ADI-R OARS		
Overall	1.67	0.96, 2.92
Social awareness	**2.10**	1.15, 3.82
Social cognition	**1.94**	1.06, 3.55
Social communication	0.64	0.26, 1.60
Autistic mannerisms	1.29	0.70, 2.37
Social motivation	0.51	0.20, 1.30

RR: Risk ratio;
CI: Confidence interval;
BAP: Broader Autism Phenotype;
SCQ: Social Communication Questionnaire;
ADI-R: Autism Diagnostic Interview-Revised;
ADOS: Autism Diagnostic Observation Schedule
OARS; The Ohio State University Autism Rating Scale:

[a] RR for ‘over-reporting’ compares domain positive mothers to domain negative mothers
Bold indicates statistical significance at an alpha=0.05 level

Table 15. Risk ratios and 95% confidence intervals for discordance between maternal and clinician ratings on child autism spectrum disorder screening and evaluation instruments in the Study to Explore Early Development by maternal self-reported history of depression or anxiety, or maternal broader autism phenotype

	SCQ				ADI-R			
	'Over-reporting'		'Under-reporting'		'Over-reporting'		'Under-reporting'	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
				Depression				
ADOS	0.93	0.68, 1.28	1.02	0.95, 1.10	0.85	0.39, 1.83	0.8	0.53. 1.19
OARS	01.99	0.72, 1.36	0.93	0.53, 1.64	1.14	0.73, 1.78	0.90	0.57, 1.42
				Anxiety				
ADOS	1.35	0.95, 1.92	0.66	0.30, 1.47	1.97	0.92, 4.20	1.09	0.69, 1.73
OARS	1.27	0.96, 1.68	0.99	0.47, 2.08	1.13	0.64. 2.0	1.10	0.64, 1.89
				Maternal BAP				
ADOS	**1.63**	1.12, 2.37	0.57	0.21, 1.50	**2.85**	1.35, 6.03	0.84	0.47, 1.53
OARS	**1.30**	0.95, 1.77	0.51	0.16, 1.57	1.67	0.96, 2.92	0.92	0.46, 1.81

CI: confidence interval;
RR: Risk ratio;
SCQ: Social Communication Questionnaire;
ADI-R: Autism Diagnostic Interview-Revised
ADOS: Autism Diagnostic Observation Schedule
OARS: The Ohio State University Autism Rating Scale

[a] 'Over-reporting' is when the SCQ or ADI-R meets SEED ASD risk or ASD criteria while ADOS or OARS does not
[b] 'Under-reporting' is when the SCQ or ADI-R does not meet SEED ASD risk or ASD criteria while ADOS or OARS does

4A.2 Additional analyses for Aim 1

Our goal for aim 1 was to determine whether maternal BAP was associated with higher risk of discordance with a clinician on instruments that measured child ASD. This analysis required a series of assumptions and decisions that impacted our results. We ran a series of supplemental and sensitivity analyses to better understand the effects of these choices. Our results for these analyses are presented here and provide a larger context and illustrate the robustness of our results. These analyses also highlight intriguing avenues for future work.

Correlation analyses

In this study, we used two ways to parameterize BAP (SRS-A total score and domain scores), four instruments to measure ASD (SCQ, ADI-R, ADOS, and OARS), and discordance outcomes comparing those instruments. Because we had so many different aspects to our analyses, it was important to make sure that these factors were not overly correlated so we were not presenting redundant results. Correlational analyses for our study sample are presented in Tables 16-18. There was moderate correlation when comparing BAP domains (Table 16) with a range from 0.31 (social cognition vs. social motivation) to 0.84 (overall BAP vs. social communication). This moderate level of correlation was not surprising since if a mother was BAP+ she would have some of the traits that comprise the subdomains. When assessing correlation between 'over-reporting' outcomes (Table 17), we found very weak to moderate correlations. This indicates that different mothers 'over-reported' on different instruments; our results are not the representation of a group of mothers that had 'over-reported' for all four comparisons. In regards to meeting instrument thresholds, correlations were higher between evaluation instruments (ADI-R, ADOS, OARS) than with the screener (SCQ), but still lower than expected. Correlation with the SCQ was low likely due to the choice to maximize case finding, which lowered the SCQ threshold. We expected instruments to not be overly correlated based on results from Wiggins et al. (197) work using the full SEED sample; however, we expected

higher correlation between the ADI-R and the OARS, since the OARS was the clinician's overall opinion after completing the ADI-R and ADOS. Overall, these results do not change our interpretations of results in chapter 4a.

Psychometric properties of instruments

This work is similar in approach to an assessment of psychometric properties of ASD evaluation instruments by BAP status. **Table 19** presents these results. As suspected, specificity for the SCQ (which used an altered lower cutoff score of 11) was low to maximize case finding. Qualitatively, sensitivities were higher and specificities were lower for all instruments for BAP+ mothers compared to BAP- mothers. This reiterates our findings of elevated RRs for 'over-reporting'.

Weighting to control for differences by study site

Reporting differences may be due to differences in preferred language. Our sensitivity in chapter 4a restricted our sample to mothers whose preferred language was English. We also examined this effect by weighting to control for study site. Study site acts as a variable that can account for language, since two sites conducted the evaluations in Spanish. Additionally, site can be considered a design variable in SEED that may need to be included in analyses regardless of DAG theory. Our assessment of study site was a sensitivity analysis because intra- and inter-site reliability was so strong in SEED and we did not consider site to be a confounder because it did not precede BAP. There are qualitative differences when comparing the SCQ to the ADOS or the OARS (Table 20). We found a 41% reduction of effect when weighting for site when looking at the ADI-R vs. OARS. Neither RR was significant and the other ADI-R or OARS comparisons did not have that large of an effect. We saw a smaller attenuation when addressing preferred language. This larger change might be due partially to the difference in language between sites, differences in clinicians, or statistical chance.

Table 16 Correlation between overall broader autism phenotype status and broader autism phenotype domains measured by the Social Responsiveness Scale-adult in mothers in the Study to Explore Early Development

Domain	Percent	BAP total	Awareness	Cognition	Communication	Mannerisms	Motivation
BAP Total	9.4	1	0.57	0.64	0.84	0.68	0.56
Social awareness	7.0		1	0.46	0.48	0.43	0.37
Social cognition	13.8			1	0.62	0.55	0.31
Social communication	9.3				1	0.59	0.57
Autistic mannerisms	13.9					1	0.40
Social motivation	10.5						1

Percent is percent of all mothers who had a T score ≥ 60
BAP Broader Autism Phenotype

Table 17 Correlation between whether a child met discordance criteria comparing two instruments from the Study to Explore Early Development

'Over' correlation	SCQ v OARS	SCQ v ADOS	ADI-R v ADOS	ADI-R v OARS
SCQ v OARS	1	0.58	0.22	0.42
SCQ v ADOS			0.42	0.09
ADI-R v ADOS				0.42
ADI-R V OARS				1

Table 18 Correlation between whether a child meets ASD thresholds on an instrument used in the Study to Explore Early Development

Meeting criteria	SCQ	ADOS	ADI-R	OARS
SCQ	1	0.14	0.05	-0.02
ADOS			0.49	0.47
ADI-R				0.57
OARS				1

Key for strength of correlation

0.8-1	Very strong
0.6-0.79	Strong
0.4-0.59	Moderate
0.2-0.39	Weak
0-0.19	Very weak

SCQ Social Communication Questionnaire
ADOS Autism Diagnostic Observation Schedule
ADI-R Autism Diagnostic Interview-Revised
OARS Ohio State University Autism Rating Scale
'Over-reporting' is when the mother's reporting meets ASD thresholds when the clinician's reported / observed score des not

Table 19. Psychometric properties for measures used in chapter 1 analysis, overall and by BAP status

	ADOS				OARS			
				Full sample				
	Sn	**Sp**	**PPV**	**NPV**	**Sn**	**Sp**	**PPV**	**NPV**
SCQ	0.87	0.10	0.76	0.18	0.74	0.10	0.65	0.27
ADI-R	0.77	0.79	0.92	0.52	0.80	0.67	0.82	0.64
				BAP+				
	Sn	**Sp**	**PPV**	**NPV**	**Sn**	**Sp**	**PPV**	**NPV**
SCQ	0.91	0.04	0.65	0.20	0.81	0.06	0.56	0.40
ADI-R	0.77	0.68	0.81	0.60	0.79	0.59	0.71	0.68
				BAP-				
	Sn	**Sp**	**PPV**	**NPV**	**Sn**	**Sp**	**PPV**	**NPV**
SCQ	0.86	0.10	0.77	0.20	0.76	0.11	0.59	0.26
ADI-R	0.77	0.81	0.93	0.50	0.80	0.68	0.83	0.64

SCQ Social Communication Questionnaire
ADOS Autism Diagnostic Observation Schedule
ADI-R Autism Diagnostic Interview-Revised
OARS Ohio State University Autism Rating Scale
BAP Broader autism phenotype
Sp Specificity
Sn Sensitivity
PPV Positive Predictive Value
NPV Negative Predictive Value

Using the standard SCQ cutoff

Our study relied on instrument cutoffs used in SEED. As mentioned previously, SEED used a SCQ cutoff of ≥11 to maximize case finding, which differed from the standard ≥15 (196). It was important to also assess associations using the more widely used cutoff, as that may be what is used in clinical practice (**Table 21**). Estimates were less precise and the 'under-reporting' model between the SCQ and OARS when using the ≥15 cut-off was not estimable. There was no change >15% for models that converged and inferences remained the same.

Analyses on the additive scale

Our main results are presented on the multiplicative scale. We chose to use risk ratios for two reasons: 1) the multiplicative scale is generally used in ASD research and 2) our outcome (discordance) was common, which means that a large RR does not hide a small absolute effect. However, we also ran our analyses on the additive scale for comparison (**Table 22**). BAP was associated with a 12-percentage point difference in risk of 'over-reporting' between the SCQ and the ADOS (95% CI: 0.00, 25.0) and 10-point difference between the SCQ and the OARS, although not reaching statistical significance (95%CI: -3.0, 22.0). The difference in risk of 'over-reporting' between mothers with and without BAP on the ADI-R vs. ADOS and the ADI-R vs. OARS were nine and eight percentage points respectively and did not reach statistical significance. These results differed in terms of statistical significance, but not in effect size or in our inferences.

We also assessed associations between 'over-reporting' and BAP domains on the additive scale. These are presented in Table 23. No domains were significantly associated with 'over-reporting'. On the multiplicative scale we found significant elevated risk for 'over-reporting' between the ADI-R and the OARS on social awareness and social cognition domains. These risks were elevated on the additive scale (12 and 11 percentage point increase respectively) but did not meet statistical significance. The difference in significance may be a result of model approaches. Inferences did not largely differ between the measurement scales.

Table 20 Risk ratios and 95% confidence intervals for discordance between maternal and clinician ratings on child autism spectrum disorder screening and evaluation instruments in the Study to Explore Early Development; change by weighting for site

	SCQ				ADIR			
	'Over-reporting'		'Under-reporting'		'Over-reporting'		'Under-reporting'	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95%CI
				Weighted for site				
ADOS	**1.74**	1.20, 2.53	0.54	0.20, 1.41	**2.54**	1.14, 5.67	0.82	0.43, 1.60
OARS	**1.31**	0.94, 1.82	0.72	0.26, 1.99	1.18	0.64, 2.17	0.85	0.40, 1.82
				Not weighted for site				
ADOS	**1.63**	1.12, 2.37	0.57	0.21, 1.50	**2.85**	1.35, 6.03	0.84	0.47, 1.53
OARS	1.30	0.95, 1.77	0.51	0.16, 1.57	1.67	0.96, 2.92	0.92	0.46, 1.81
				Percent change				
ADOS	6.3		-5.6		-12.2		-2.4	
OARS	0.8		29.2		-41.5		-8.2	

CI confidence interval
SCQ social communication questionnaire
ADI-R autism diagnostic interview revised
ADOS autism diagnostic observation schedule
OARS Ohio State University Autism Rating scale
RR Risk ratio

'Over reporting' is when the SCQ or ADI-R meets ASD criteria while ADOS or OARS does not
'Under reporting' is when the SCQ or ADI-R does not meet ASD criteria while ADOS or OARS

Table 21 Risk ratios and 95% confidence intervals for discordance between maternal and clinician ratings on child autism spectrum disorder screening and evaluation instruments in the Study to Explore Early Development by cutoffs on the social communication questionnaire

	'Over'		'Under'	
	RR	95% CI	RR	95% CI
		SCQ 15		
ADOS	1.64	0.95, 2.86	0.66	0.40, 1.11
OARS	**1.52**	0.97, 2.40	-	-
		SCQ 11		
ADOS	**1.63**	1.12, 2.37	0.57	0.21, 1.50
OARS	**1.3**	0.95, 1.77	0.51	0.16, 1.57
		Percent change		
ADOS	0.6		13.6	
OARS	14.5		-	

CI Confidence interval
RR Risk ratio
SCQ Social Communication Questionnaire
ADOS Autism Diagnostic Observation Schedule
OARS Ohio State University Autism Rating Scale
'Over reporting' is when the SCQ or ADI-R meets ASD criteria while ADOS or OARS does not
'Under reporting' is when the SCQ or ADI-R does not meet ASD criteria while ADOS or OARS does

Table 22 Risk differences and 95% confidence intervals for discordance between maternal and clinician ratings on child autism spectrum disorder screening and evaluation instruments in the Study to Explore Early Development

	SCQ				ADIR			
	'Over-reporting'		'Under-reporting'		'Over-reporting'		'Under-reporting'	
	RD	**95% CI**	**RD**	**95% CI**	**RD**	**95% CI**	**RD**	**95% CI**
ADOS	**0.12**	0.00, 0.25	-0.04	-0.13, 0.05	0.09	-0.03, 0.18	-0.02	-0.12, 0.09
OARS	0.10	-0.03, 0.22	-0.05	-0.14, 0.04	0.08	-0.03, 0.19	0.00	-0.10, 0.10

CI Confidence interval
RD Risk difference
SCQ Social Communication Questionnaire
ADOS Autism Diagnostic Observation Schedule
ADI-R Autism Diagnostic Interview-Revised
OARS Ohio State University Autism Rating Scale
'Over reporting' is when the SCQ or ADI-R meets ASD criteria while ADOS or OARS does not
'Under reporting' is when the SCQ or ADI-R does not meet ASD criteria while ADOS or OARS does

In order to maximize our sample size, we included children with past history of a non-ASD DD if they received the full ASD evaluation, even though not all children in this group got the full evaluation. Ideally, we would have data on all children with past history of DD to better estimate sensitivity and specificity of instruments. However, we believe that our approach was valid since we included children with past DD if they screened positive or a clinician suspected ASD. Since DD is heterogeneous and many DDs do not present with any ASD symptoms, we do not think that excluding these children biased our results. If the child did not meet the lowered SCQ cutoff or raise concern in clinicians, it is highly unlikely that there would be discordance, regardless of BAP status. Nonetheless, we conducted analyses restricting our sample just to children with past diagnosis of ASD. This restriction enabled us to evaluate the effect of including these children with DD and inversely assess differences in reporting based on a child having a past diagnosis of ASD. Restricting to this group reduced our sample by 30% (N=495)(**Table 24**). Estimates were much less precise and none met statistical significance (ADOS vs. ADI-R 'over-reporting' was not estimable). We did still see elevated RRs for 'over-reporting'. As mentioned in chapter 4a, the differences in phenotype between DD with ASD symptoms and DD without ASD symptoms are drastic. It would have been ideal to have children with DD without ASD symptoms to have full ASD evaluations to better estimate sensitivity and specificity by BAP status; however; ASD evaluation instruments are primarily used among children with ASD symptoms and we believe that our results are meaningful, even without all DDs.

Influence of culture on the BAP-instrument discordance relationship

As mentioned previously, it could be hypothesized that culture plays a role in the maternal BAP-discordance relationship. We chose to preliminarily explore this by stratifying by race or ethnicity. Results are presented in Figure 6 and Table 25. Due to the amount of comparisons we only present 'over-reporting'. We defined race as white, black, or other, and ethnicity as Hispanic or non-Hispanic. There was a significant increased risk of 'over-reporting'

by BAP on the SCQ vs. ADOS for white mothers (RR: 1.85, 95% CI: 1.10, 3.11). On the SCQ vs. OARS, there was no significant effect for any race or ethnicity. BAP was associated with 'over-reporting' on the ADI-R vs. ADOS for white mothers (RR: 3.55, 95% CI: 1.63, 7.74) and Hispanic mothers (RR: 4.42, 95% CI: 1.32, 14.82). BAP was associated with 'over-reporting' on the ADI-R vs. OARS for Hispanic mothers (RR: 3.25, 95% CI: 1.28, 8.29). These results are difficult to interpret due to the number of comparisons and small sample sizes. Hispanic ethnicity was associated with 'over-reporting' when using the ADI-R, which may suggest that the structured interview may be received differently by ethnicity. Patterns were not clear enough to make any firm statements. As yet, little is known about BAP and race / ethnicity and race /ethnicity and the ASD evaluation process. Once more is known, this type of analysis could be re-examined.

Table 23 Risk differences for 'over-reporting' discordance between maternal reported and clinician observed or estimated instruments and meeting thresholds for broader autism phenotype domains on the Social Responsiveness Scale Adult

		RD	95% CI
SCQ ADOS			
	Overall	**0.12**	0.00, 0.25
	Social awareness	0.06	-0.08, 0.21
	Social cognition	-0.02	-0.14, 0.11
	Social communication	-0.16	-0.34, 0.02
	Autistic mannerisms	0.00	-0.13, 0.12
	Social motivation	0.08	-0.05, 0.21
SCQ OARS			
	Overall	0.10	-0.03, 0.22
	Social awareness	0.05	-0.12, 0.22
	Social cognition	0.10	-0.03, 0.24
	Social communication	0.07	-0.10, 0.25
	Autistic mannerisms	-0.03	-0.17, 0.10
	Social motivation	-0.13	-0.26, 0.004
ADIR ADOS			
	Overall	0.09	-0.03, 0.18
	Social awareness	-0.03	-0.15, 0.09
	Social cognition	-0.02	-0.12, 0.08
	Social communication	0.03	-0.08, 0.14
	Autistic mannerisms	0.08	-0.02, 0.18
	Social motivation	-0.02	-0.08, 0.05
ADIR OARS			
	Overall	0.08	-0.03, 0.19
	Social awareness	0.12	-0.06, 0.30
	Social cognition	0.11	-0.04, 0.25
	Social communication	-0.09	-0.28, 0.10
	Autistic mannerisms	0.02	-0.12, 0.16
	Social motivation	-0.06	-0.16, 0.05

CI 95% confidence interval
SCQ Social Communication Questionnaire
ADOS Autism Diagnostic Observation Schedule
ADI-R Autism Diagnostic Interview-Revised
OARS Ohio State University Autism Rating Scale
'Over reporting' is when the SCQ or ADI-R meets ASD criteria while ADOS or OARS does not

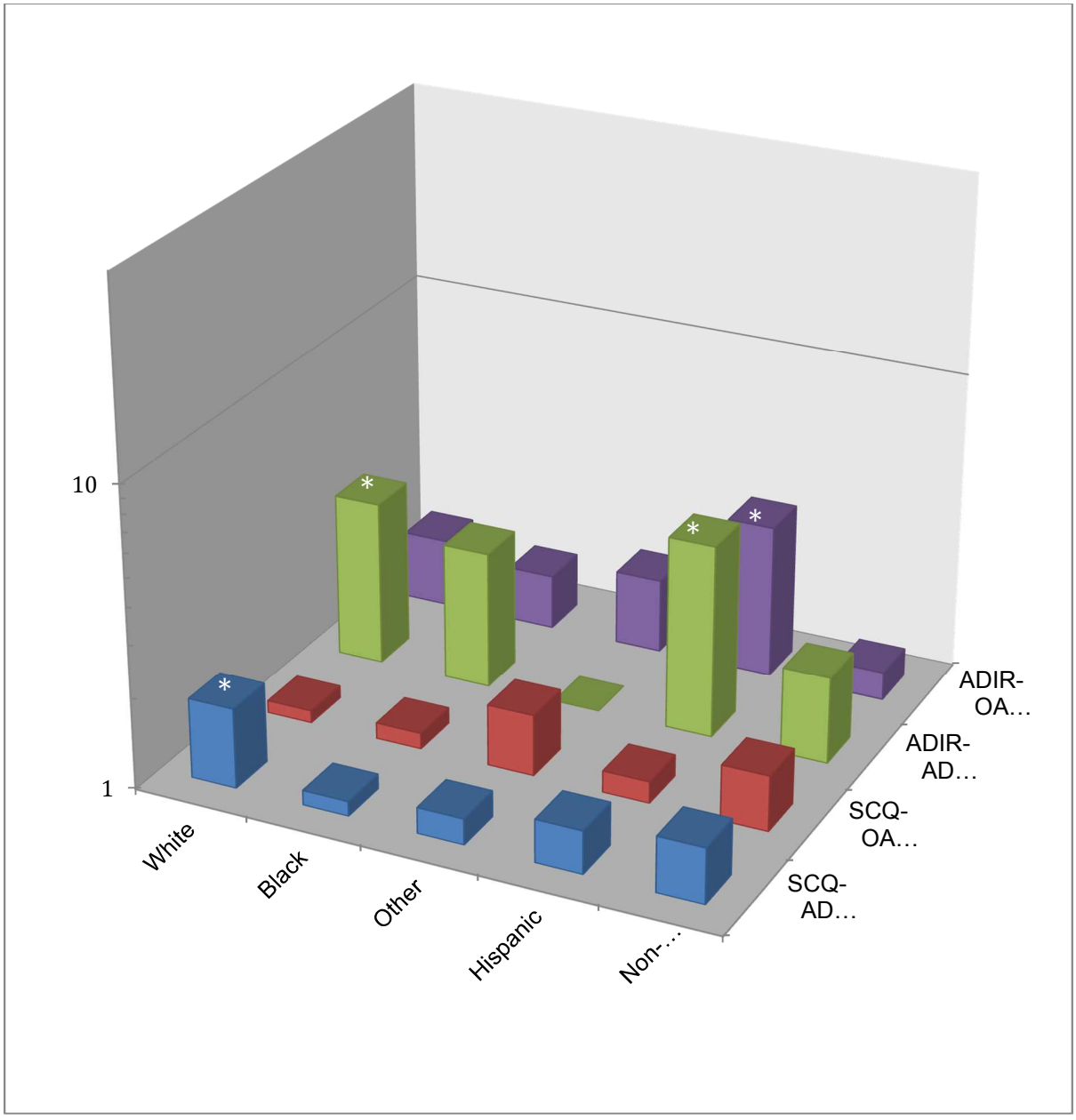
Table 24. Risk ratios and 95% confidence intervals for discordance between maternal and clinician ratings on child autism spectrum disorder screening and evaluation instruments in the Study to Explore Early Development; change by restricting for past ASD diagnosis

	SCQ				ADI-R			
	'Over-reporting'		'Under-reporting'		'Over-reporting'		'Under-reporting'	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
				Past ASD diagnosis only (n=495)				
ADOS	1.41	0.35, 5.73	0.68	0.17, 2.63	**-**	-	1.09	0.65, 1.81
OARS	1.42	0.55, 3.68	0.40	0.06, 2.80	1.47	0.48, 4.49	1.18	0.46, 3.00
				Full sample (n=712)				
ADOS	**1.58**	1.10, 2.20	0.57	0.22, 1.50	**2.52**	1.21, 5.27	1.05	0.64, 1.72
OARS	**1.45**	1.09, 1.90	0.53	0.17, 1.60	1.65	0.97, 2.81	0.99	0.54, 1.79
				Percent difference				
ADOS	-12.1		16.2		-		3.7	
OARS	-2.1		-32.5		-12.2		16.1	

CI 95% confidence interval
SCQ social communication questionnaire
ADI-R autism diagnostic interview revised
ADOS autism diagnostic observation schedule
OARS Ohio State University Autism Rating scale

'Over-reporting' is when the SCQ or ADI-R meets ASD criteria while ADOS or OARS does not
'Under-reporting' is when the SCQ or ADI-R does not meet ASD criteria while ADOS

Figure 6. Effect measure modification on the multiplicative scale for the effect of race/ ethnicity on the association between maternal broader autism phenotype status and 'over-reporting' discordance in ASD evaluation measures



* Indicates statistical significance.
SCQ Social Communication Questionnaire
ADOS Autism Diagnostic Observation Schedule
ADI-R Autism Diagnostic Interview-Revised
OARS Ohio State University Autism Rating Scale
'Over-reporting' is when the SCQ or ADI-R meets ASD criteria while ADOS or OARS does not

Table 25 Race / ethnicity stratified risk ratios and 95% confidence intervals for discordance between maternal and clinician ratings on child autism spectrum disorder screening and evaluation instruments by broader autism phenotype status in the Study to Explore Early Development

Measure	Race/ Ethnicity	RR	95% CI
SCQ-ADOS	White	**1.85**	1.10, 3.11
	Black	1.12	0.62, 2.01
	Other	1.22	0.36, 4.16
	Hispanic	1.39	0.74, 2.62
	Non-Hispanic	1.53	0.97, 2.40
SCQ-OARS	White	1.10	0.65, 1.89
	Black	1.13	0.75, 1.68
	Other	1.6	0.64, 4.00
	Hispanic	1.18	0.80, 1.74
	Non-Hispanic	1.53	0.92, 2.56
ADIR-ADOS	White	**3.55**	1.63, 7.74
	Black	2.88	0.56, 14.84
	Other	-	-
	Hispanic	**4.42**	1.32, 14.82
	Non-Hispanic	1.95	0.78, 4.85
ADIR-OARS	White	1.69	0.75, 3.45
	Black	1.52	0.62, 3.74
	Other	1.77	0.26, 12.21
	Hispanic	**3.25**	1.28, 8.29
	Non-Hispanic	1.24	0.60, 2.55

RR risk ratio
CI confidence interval
SCQ Social Communication Questionnaire
ADOS Autism Diagnostic Observation Schedule
ADI-R Autism Diagnostic Interview-Revised
OARS Ohio State University Autism Rating Scale
'Over-reporting' is when the SCQ or ADI-R meets ASD criteria while ADOS or OARS does not

4B. Association between parental broader autism phenotype and child ASD phenotype subgroup in the Study to Explore Early Development

Overview

Autism spectrum disorder (ASD) is heterogeneous in presentation and etiologic origin. Phenotype varies in level of social and communication ability, associated features, and medical comorbidities. Etiology and genotype are just as diverse, with a myriad of genetic origins and environmental risk factors. Creating more phenotypically similar subgroups and using parental broader autism phenotype (BAP) as a marker for potential genetic predisposition for ASD may improve efficiency in evaluating etiologic factors. Our goal was to assess the association between parental BAP and child phenotype among children age 3-5 years, using latent classes derived from multiple behavioral and developmental measures collected in the multi-site community-based Study to Explore Early Development (N=707). BAP in at least one parent was associated with a child having increased odds of being in a class with average expressive and receptive language, fine motor skills, and visual reception, plus increased co-occurring conditions like anxiety and depression (OR: 2.44, 95% CI: 1.16, 5.09). Results were similar if the father alone had BAP. Child sex did not modify the parental BAP-child ASD phenotype relationship. Children of parents with BAP were more likely to have a phenotype qualitatively similar to BAP presentation; this may have implications for etiologic research and crafting parent-mediated interventions.

Introduction

Autism spectrum disorder, defined by impairment in social communication and social interaction as well as repetitive and restricted behaviors and interests (RRBI)(1), is heterogeneous in phenotype and genotype (1, 25, 234, 235). Verbal ability, age at developmental milestones, and many other diagnostic traits and associated features vary greatly among individuals with ASD (1, 25). Gaugler et al. (26) present a genotypic model with

genetic components explaining 59% of variance in ASD liability. These genetic contributors include chromosomal abnormalities, copy number variants, and rare highly penetrant genes. Other potential causes of ASD include epigenetics, gene by environmental interaction, and environmental risk factors (236). The myriad of potential causes and presentations create challenges when trying to understand etiological mechanisms (11, 29, 103, 234, 235).

Looking at ASD subgroups comprising more phenotypically similar individuals may increase resolution in detecting etiologic associations, provide more clarity on the ASD phenotype, and elucidate developmental trajectories (27, 29, 237). Studies have used singular traits like intellectual disability or developmental regression to parse phenotype (238-240) while data driven techniques like cluster analysis and latent class analysis have been used to create subgroups from a wider range of phenotypic variables (27, 28, 101-103). These subgroups have been used to assess differences in child problem behaviors and to create severity gradients (28), assess differences in child phenotype by IQ (101), explore associations with specific genes (27), and map possible treatment trajectories (102).

Past approaches have focused on families with multiple children with ASD or with familial ASD-like traits to subset their samples (104-107). Mechanisms that cause ASD likely differ by family predisposition for the disorder (107) and sub-setting this group before conducting genetic analysis can increase precision and efficiency. Traits that subset ASD etiology can serve as endophenotypes, which are a measurable phenotypic traits, that allows for a psychiatric disorder to be sub-grouped into more etiologically similar groups. Endophenotypes can be neurophysiological, biochemical, cognitive, or neuropsychological, but must be associated with the disorder in the population, be heritable, state independent (apparent in an individual whether they have the disorder or not), co-segregate in families, and be found in higher rates in unaffected relatives of probands than in the general population (30, 31). Narrowing samples of families with a child with ASD to those with specific traits or groups of traits that meet these guidelines has been effective in increasing the efficiency of linkage

analyses, GWAS, and other techniques that look for specific causal genes or SNPs (108-114, 241, 242).

The broader autism phenotype (BAP) in parents of children with ASD may be a source of endophenotypes that can help improve understanding of some of ASD's core features (243). BAP is a set of sub-clinical characteristics of ASD prevalent in many families of children with ASD. BAP traits include pragmatic difficulties, broadly defined communication difficulties, poor social skills, cognitive rigidity, anxiety, and aloofness (16). BAP and the individual traits that make up BAP may be endophenotypes for ASD since BAP is heritable in the general population (125) and is significantly more prevalent among relatives of probands with ASD (17-20, 23, 130, 164, 180). BAP may serve as a tool to efficiently explore the relationship between ASD genotype and phenotype.

Our objective was to evaluate the association between parental BAP and child ASD phenotype subgroups derived from a wide range of developmental and behavioral traits. Additionally, we explored whether these associations differed by which parent had BAP or the child's sex.

Methods

This study used data from Phase 1 of the Study to Explore Early Development (SEED), a community-based case-control study designed to better understand ASD etiology and phenotypic presentation (196). Six sites (California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania) collected data on maternal pregnancy and health history, child developmental history, and other familial data for children between the ages of 30 and 68 months between 2007 and 2012. Children had to have been born in the study catchment area, lived there at time of first contact, and lived with a caregiver aged >18 years (196). Children were identified and recruited through educational or medical providers who served children with ASD or developmental delay (DD) or through random sampling of birth certificates.

Study sample

This study utilized phenotypic data on all children with ASD as determined by SEED. Child ASD status was determined by first conducting the Social Communication Questionnaire upon study entry. If a child screened positive (scored ≥ 11 to maximize case finding (228)), had a past diagnosis of ASD, or was suspected by a study clinician to have ASD during the child's developmental assessment, the child then had a full ASD evaluation which included the Autism Diagnostic Observation Schedule (ADOS) (198) and the Autism Diagnostic Interview-Revised (ADI-R) (67). Final case status was determined through a SEED-derived algorithm using the standard cut-off scores from the ADI-R and ADOS (Wiggins et al., 2015). In addition to the ASD diagnostic measures, additional phenotypic and demographic descriptions were collected using the Child Behavior Checklist (207), the Mullen Scales of Early Learning (208), the child's birth certificate, and SEED specific caregiver interviews and questionnaires.

For this analysis, siblings of children who were previously enrolled were excluded because they may violate our assumption of independence between observations. When evaluating associations with parental BAP, our inferences are only applicable to children who had BAP measures completed for their biological mother and father.

Creating child phenotypic classes

We used an extended latent class analysis (LCA) to create ASD phenotypic classes based on all ASD cases. We replicated the approach of Wiggins et al. (under review) who previously created latent classes in these data. LCA assumes that there are unobservable subpopulations, often associated with certain patterns of observable data, within the larger study population (213): in this case, we are using ASD phenotype variables to explore if these can be used to categorize people into latent classes. . While standard LCA models can use only categorical observed variables, an extended LCA model allows for use of continuous, dichotomous, and categorical variables to estimate and explore any potential underlying latent classes. For each individual, these models provide probabilities of being in each class based on their observed outcome variables.

Twenty-seven indicators were chosen with the purpose of differentiating the ASD phenotype while differentiating among those with ASD, rather than those with and without ASD. Indicators were selected based on careful literature review and the expertise of psychologists, pediatricians, and epidemiologists (Wiggins et al.) and are presented in Table 26. Gestational age and gastrointestinal issues were dropped as indicators in the LCA due to poor discrimination between classes.

The four-class model was determined to best fit our data after comparing models with up to 5 classes based on the Bayesian Information Criterion (BIC), Lo-Mendel-Rubin Likelihood Ratio Tests (LMR-LRT) and entropy. We also wanted to ensure interpretability of latent classes and adequate class size (no classes including < 2% of the total population). The four-class model had an LMR-LRT P value of 0.001, suggesting a noticeable improvement for 4 versus 3 classes, and entropy of 0.92, which shows good model fit. The smallest class size was 85, roughly 12% of the total sample. A five-class model had a non-significant LMR-LRT P value (0.567), signifying no improvement on the four-class model and no noticeable improvement in BIC. Item response probabilities and means are presented in Table 1 and class descriptions are provided in Table 2. Further details on this LCA method in SEED are provided in Wiggins et al. (under review).

BAP measurement

BAP was measured using the Social Responsiveness Scale-Adult (SRS-A)(123). Although not originally designed to measure BAP, the SRS-A has shown good consistency with other BAP and quantitative autistic trait measures (122, 149). The SRS-A is a 65-item Likert scale questionnaire that a parent was asked to have a friend, spouse, or relative complete on the parent and then return to SEED. This measure has strong internal validity, exhibiting a Cronbach's alpha internal consistency coefficient of 0.95 (122, 123). The SRS-A has been shown to be independent of individual's IQ and age, and the informant's education level (60, 123, 201, 244) with minimal differences due to gender, race or ethnicity, or the identity of the

informant (153). Raw overall and domain SRS-A scores were adjusted to create T-scores, which have a mean of 50 and a standard deviation of 10. For this study we used the standard 'mild range' recommendation of ≥60 to classify a parent with BAP (BAP+) (60). Additionally, we categorized BAP by parent type: mother and father were BAP+, father only was BAP+, mother only was BAP+, or both parents were BAP-.

Analytic approach

We used an inclusive LCA approach to generate odds ratios (ORs) that compare phenotypic class membership by presence of parental BAP. In this method, we first fit the LCA model to determine the appropriate number of latent classes based on model fit and interpretability, as described above, then reran the LCA to include, as predictors of class membership, our BAP covariate and an indicator for missing SRS-A data. We used multinomial logistic regression to derive ORs using estimated model posterior-probabilities for the inclusive classes. This inclusive model improves validity of effect estimates since it incorporates classification error, specifically not requiring the need to assign individuals to latent classes with some uncertainty in a separate step, and accounts for the potential effect of the covariate when deriving latent classes (211). A disadvantage of this approach is that estimated posterior probability for class membership is slightly different when models contain different covariates (e.g. when using BAP as a dichotomous variable versus splitting by parent type or including child sex). To address these issues, we compared our inclusive approach with a 'three-step approach' (which assigns each individual a class then weights for classification error) as a sensitivity analysis (212) (Figure 8). Results were similar between methods and we choose to present results for the inclusive LCA because of the potential reduction in bias and the minimal variation in class make up across models.

There were data missing on parental BAP for approximately 17% of children with ASD in SEED. In order to use data on all cases and ensure that classes were appropriate, we included an indicator for missing BAP in our analyses. Past work has shown that using an

indicator is less biased than restricting to those with complete data for LCA (214). A model with missing indicators creates class distributions for both observed and missing data, which provides information on missing data mechanisms (214). In most cases, a missing indicator approach is biased in epidemiological analyses because it removes the effects covariates have on one another, preventing adequate control of confounding (215, 216). However, there were no confounders in our analysis and our dependent variables (whether dichotomous BAP or BAP by parent type) were exclusive, eliminating the issue of covariance. We ran additional sensitivity analyses to assess the effect of using inverse probability weights to account for missing SRS-As, finding no meaningful differences compared to our missing indicator approach (Figure 8).

We additionally explored the effects of which parent or parents had BAP by rerunning our inclusive LCA using BAP categorized by parent type. Additionally, we explored the effect of child sex as a modifier of the parental BAP-child phenotype association by adding child sex, a child sex by parental BAP status interaction term, and a missing indicator by child sex interaction term to our original inclusive LCA. Child sex was not associated with missing SRS-As (χ^2 P value=0.2); therefore, we believe the missing indicator approach is still unbiased (215). Interaction was tested using a Wald test with an alpha level= 0.05. For all models, class 2 served as the referent class because it was the class with the most cognitive impairment and had lower levels of social and communicative functioning

As a construct, BAP is theorized to be independent of IQ, age, and race (123). Since we consider BAP to be an underlying genetic trait, we do not believe that there are non-genetic characteristics that can cause BAP. Factors like socioeconomic status, parental education, child age at diagnosis, and child service usage are potential mediators because they may be caused by BAP and affect child phenotype and may be examined in future analysis. For these reasons we did not statistically adjust for confounding in these analyses. This is consistent with past work that has assessed the relationship between parental autism-like traits and child phenotype (20, 130, 181).

Analyses were conducted in SAS 9.3 (217) and Mplus 7 (218).

Results

Of 707 children with ASD in our sample, 524 children had available SRS-A data and 100 had at least one parent who was BAP+. Table 28 presents demographics by BAP status (any parent BAP+, both parents BAP-, SRS-A missing for at least one parent). Of mothers in the BAP+ group, 17.8% were black, 16.2% were of Hispanic ethnicity, and 24.2% had less than twelve years of education. Of mothers in the BAP- group, 13.4% were black and 11.0% were of Hispanic ethnicity, while 12.7% had less than twelve years of education. Of mothers missing BAP data (either on themselves or on the child's father, n=183), 39.7% were black, 12.5% were of Hispanic ethnicity, and 6.6% had less than 12 years of education. Paternal and maternal demographics were similar across all three BAP groups.

When at least one parent was BAP+, the odds of the child being in class 4 (average expressive and receptive language, mild language delays, high cognitive rigidity, lower ASD symptom severity, increased co-occurring conditions*)* compared to class 2 (most impairment in cognitive functioning, latest age at language acquisitions) were 2.44 times that of both parents being BAP- (95% CI: 1.16, 5.09) (Figure 7). Compared to class 2, neither class 1 (least impairment in cognitive functioning, high restricted interests) (OR: 0.73, 95% CI: 0.36,1.48), or class 3 (more reported developmental regression, significant impairment in cognitive functioning (OR: 0.86, 95% CI: 0.44, 1.66) were associated with parental BAP status. Missing SRS-A data (compared to not missing data) was not statistically associated with any class (data not shown).

Compared to both parents being BAP-, both parents being BAP+ had an elevated but not statistically significant association with child's membership in class 4 vs. class 2 (OR: 2.4, 95% CI: 0.54, 10.57)(Table 29). When only mothers were BAP+ (N=20), there were no significant associations between classes and maternal BAP, but estimates were imprecise. Fathers being BAP+ alone (N=64) compared to both parents being BAP- was associated with a child being in class 4 compared to class 2 (OR: 2.71, 95% CI: 1.09, 6.77). Because we used an

inclusive LCA model, the model estimated posterior probabilities of class distribution were 0.4% different than when we dichotomized BAP.

There was no evidence that the child's sex modified associations observed between parental BAP and child's phenotypic subgroup based on non-significant P values for interaction terms. Adding child sex and the interaction term into the LCA model shifted the model estimated posterior probability by 0.5% from the LCA with dichotomized BAP. Some suggestive patters of association by sex are present. Among boys, the relationship between any parent being BAP+ and phenotypic class was similar to overall results, as there was a significant effect comparing class 4 to class 2 (OR: 2.68, 95% CI: 1.06, 6.79) (Table 30). Results for girls were imprecise due to small sample size (N=20) but ORS for any parent being BAP+ were elevated for the child being in class 4 compared to class 2 (OR: 3.92, 95% CI: 0.74, 20.76). Class 1 and 3 had ORs that suggest an inverse association (ORs 0.50, 0.44 respectively) but these results were imprecise.

Discussion

In a study of children aged 3-5 years with ASD, having a BAP+ parent was associated with increased odds of having an ASD phenotype marked by mild language and motor delays, average expressive and receptive language, and an increased propensity for co-occurring conditions like anxiety, depression, aggression, and attention problems. Other phenotypic classes had no statistically significant association with parental BAP. Additionally, this positive association remained was statistically significant if fathers alone were BAP+. ORs were elevated but imprecise if both parents were BAP+ or if mother alone was BAP+. The association was similar for both boys and girls.

These results are in agreement with past work that has found that parental BAP is associated with child ASD phenotype which found increased parental scores on a measure of BAP were related to increased scores on a measure of the child's ASD presentation (19, 20, 92, 132, 165). We extend off this prior work by defining child ASD phenotype using latent classes

derived from multiple instruments and data sources (caregiver interview, medical record review, and clinician observation). This improved phenotypic classification enables a wider description of ASD presentation that is not reliant on one instrument or on one informant. Best practices when diagnosing ASD include using multiple informant and multiple instruments to better encompass a child's presentation (10); these methods are also useful to best define phenotype for research studies.

The strong association between parental BAP and a child phenotypic class with less severe social and communication impairments, lower ASD symptom severity, and more co-occurring conditions may support a heritable origin for this subset of children with ASD. Qualitatively, BAP is similar to this class. BAP is a 'milder' presentation of ASD symptoms with average cognitive functioning and high levels of anxiety, depression, and attention issues (24). With the high heritability of ASD (26), these traits may be genetically transmitted (123). The association between parent and child traits that we found is similar to work done by Losh et al. (243) who found that children exhibit ASD traits similar to traits that their parents exhibited during their own childhood. Other studies have found that traits like RRBI (162, 245), anxiety (181), and general social ability (165) present more similarly between parents with BAP and their children with ASD than parents without BAP and their children with ASD. These traits that overlap between parent and child may serve as endophenotypes, as they are associated with the disorder, are state independent, and are likely heritable (30, 31). Conducting genetic analysis among parents with BAP and their phenotypically similar children likely would reduce heterogeneity in both phenotype and genotype, increasing the likelihood of meaningful genetic findings and discovery of etiologic mechanisms for specific ASD traits.

There was an elevated but imprecise association between both parents having BAP and a child being in class 4 compared to class 2. The prevalence of BAP for any parent in our study was 19.0% which is consistent with the literature (10%-50%) (17-19, 21-24) and prevalence of BAP is even lower among mothers of children with BAP (24); consequently, power is an issue

when trying to assess the additive or multiplicative effects of having two parents with BAP. A larger sample may allow for exploration into autosomal recessive inheritance of ASD, which Lim et al. (246) found to explain 3% of liability. Our results for mother alone being BAP+ compared to both parents being BAP-, which were imprecise, were similar in direction, but smaller in magnitude than results when fathers alone or both parents were BAP+. This result is in line with previous studies that found no associations or much weaker associations between maternal BAP and child scores on ASD measures, relative to associations with paternal BAP (19, 20, 92, 170, 185). This difference between parents with BAP could be a result of our limited sample size, or a reflection of differing genetic transmissions of ASD. Parents may transmit genes or epigenetic dysregulation that cause ASD through sex specific pathways (24, 247, 248). If these genes are also associated with BAP in the parent, it is possible that we could see different BAP-child phenotype relationships by parent.

In the full SEED sample there was no statistically significant difference in class distribution between boys and girls (Wiggins et al under review) and our results did not show significant modification of the association between parental BAP and child ASD phenotype by child sex. Child sex may play a role in ASD etiology, based on a 'female protective effect' (249) or differences related to diagnostic practice and under-identification of ASD in females (250). However, our results suggest that pathways associated with parental BAP do not drive sex differences in ASD. However, these findings are limited by small sample size. Further work should explore how parental BAP affects the biological mechanisms that lead to female ASD in a larger sample of girls.

The association of parental BAP with child ASD phenotype may have clinical implications. Parr et al. (183) found that maternal BAP was negatively correlated with outcomes from a parent-mediated intervention. If children of BAP+ parents present differently, it may be necessary to adapt interventions to the child's needs and the parent's socio-communicative ability. Additionally, children of parents with BAP were more likely to be in a class with higher

levels of co-occurring conditions. Further research needs to be done on phenotypic trajectory, but knowing if a parent of a child has BAP may help clinicians and interventionists tailor treatment to prevent development or lessen symptoms of negative co-occurring conditions in children at greater risk.

This study had limitations. There was missing parental SRS-A data for 183 children with ASD. We used a missing indicator approach, which enabled us to use all available information when deriving latent classes. Those with missing data did not differ in class distribution compared to those without missing data, which suggests that these missing data did not cause bias. Additional sensitivity analyses that weighted for this missingness had results similar to the full sample missing indicator approach. We did not know who acted as the informant on the SRS-A for 37.5% of fathers and 75.7% of mothers. It is likely that some mothers and fathers filled out SRS-As on themselves and this could affect accuracy in reporting BAP (92, 251). The SRS-2, which added a self-report version of thee SRS-A, had an inter-rater agreement was moderate between the two versions (r=0.61 to r=0.78)(153). In another study, adults tended to rate his or her own social responsiveness higher than an informant, but this pattern was not associated with gender or ASD case status (92). These properties of the SRS-A suggest that having some parents self-report in our study would lead to non-differential misclassification, since reporting method would not be associated with BAP status or child phenotype. Our lack of data on who acted as the informant prevents us from conducting formal sensitivity analyses but we believe that any effect would only minimally attenuate our results because of moderate correlation between reporting types and the probability that many SRS-As were still filled out by an informant. Few children had both parents BAP+, had only mothers that were BAP+, or were girls. Future work will have to examine these relationships in a sample with larger number of BAP+ mothers and girls with ASD. Although SEED was a community-based, the sample is comprised of six sites that may not fully represent other geographic areas with differing

socioeconomic and demographic distributions. Additionally, this was a sample of children between 3-5 years of age; results may look different for children in a different age range.

Strengths of this study include usage of a large community-based sample of children with ASD. These attributes of SEED gave us more statistical power for analyses and make results more generalizable than clinic-only samples. Additionally, SEED collected extensive phenotypic data that allowed us to better describe child ASD phenotypic subgroups without having to rely solely on one instrument. We have shown that using parental BAP is an improvement on past studies that used multiplex or simplex families to mark increased risk of hereditary ASD because there was no potential for reproductive stoppage to bias our subgrouping. Although sample size was limited for some groups, we were able to explore effects of which parent was BAP+ and interaction by child sex, highlighting avenues for future research.

Conclusion

BAP in parents of children with ASD was significantly associated with the child being in a phenotypic class that presented with average expressive and receptive language, mild language and motor delays, and more co-occurring conditions like anxiety, depression, and sleep problems. Children in this class have a presentation that includes traits qualitatively similar to those that make up BAP in adults. Future work should explore endophenotypes and genetic mechanisms using parental BAP and this more homogenous ASD subgroup to improve efficiency.

Table 26. Indicator variables and item response probabilities or means for children with autism spectrum disorder in the Study to Explore Early Development, using an inclusive latent class analysis approach

	Source	Variable type (range)	Scores indicating impairment	Latent Class response 1	2	3	4
Categorical variables (response probabilities)							
Current diet restrictions	GIQ	Yes / No	Higher	0.26	0.36	0.30	0.40
Early recognition of epilepsy/seizure disorder	Caregiver interview	Yes / No	Higher	0.00	0.13	0.02	0.05
History of regression	ADI-R	Yes / No	Higher	0.16	0.34	0.29	0.27
Insistence on sameness	ADI-R	Yes / No	Higher	0.72	0.63	0.66	0.90
Problems with age at first social smile	EDQ	Yes / No	Higher	0.13	0.24	0.15	0.31
Repetitive behavior with objects	ADI-R	Yes / No	Higher	0.77	0.94	0.82	0.96
Repetitive motor mannerisms	ADI-R	Yes / No	Higher	0.74	0.96	0.78	0.83
Restricted interests	ADI-R	Yes / No	Higher	0.85	0.73	0.81	0.92
Self-injurious behaviors	ADI-R	Yes / No	Higher	0.38	0.58	0.37	0.79
Unusual sensory response	ADI-R	Yes / No	Higher	0.91	0.97	0.94	0.97
Continuous variables (response means)							
Age at verbal language development	ADI-R	Months	Higher	19.92	30.57	25.14	24.25
Age at walking	ADI-R	Months	Higher	13.69	16.32	14.11	13.58
Aggressive behaviors	CBCL	T-scores	Higher	55.92	61.96	57.93	76.07
Anxiety/depression	CBCL	T-scores	Higher	53.58	56.24	53.38	69.37
Attention problems	CBCL	T-scores	Higher	59.03	67.12	61.59	70.90
Autism severity	ADOS	Total severity scores (1-10)	Higher	6.73	7.88	7.21	6.46
Emotionally reactive	CBCL	T-scores	Higher	57.93	61.74	57.35	77.67
Expressive language skills	MSEL	Age equivalent scores (2-70)	Lower	50.77	14.50	34.03	46.10
Fine motor skills	MSEL	Age equivalent scores (4-68)	Lower	54.52	23.08	37.57	49.89
Receptive language skills	MSEL	Age equivalent score (1-69)	Lower	56.98	15.22	34.33	48.24
Sleep problems	Sleep habit questionnaire	Total problem score	Higher	47.38	53.87	49.34	59.65

Social communication abilities	SCQ	Total score (1-35)	Higher	13.04	20.97	16.93	20.53
Somatic complaints	CBCL	Total score (0-91)	Higher	57.18	60.80	58.14	67.70
Visual reception skills	MSEL	Age equivalent score (5-69)	Higher	61.33	23.13	40.50	53.68
Withdrawn behaviors	CBCL	T-scores	Higher	64.89	76.37	67.00	76.54

ADI-R Autism Diagnostic Interview-Revised
ADOS Autism diagnostic observation schedule
EDQ Early Development Questionnaire
CBCL Child Behavior Checklist
MSEL Mullen Scale of Early Learning
SCQ Social communication questionnaire

Table 27. Phenotypic subgroups in the Study to Explore Early Development, derived using latent class analysis

Class	Percent*	Description
1	28.1	Children in this group had the least impairment in terms of cognitive functioning and the youngest age of language development. They were less likely to have developmental regression than children in other classes. This class had high rates of restricted interests and unusual sensory responses
2	26.6	Children in this group had the most impairment in cognitive functioning. Members of this group acquired language at later ages (if at all) and were latest to walk unsupported. This group had the highest rate of seizures, unusual sensory responses, and more repetitive motor mannerisms.
3	33.3	Children in this group had significant impairments in cognitive functioning and were similar to class 1 except that they had more reported developmental regression and delayed language development. This group also had high levels of unusual sensory response.
4	12.0	Children in this group had average nonverbal functioning and mild language and motor delays. This class had high rates of cognitive rigidity, and relatively higher rates of aggressive behaviors, anxiety/depression, attention problems, emotional reactivity, self-injurious behaviors, sleep problems, and somatic complaints than other groups. This group also had high levels of unusual sensory response.

* Percentage is from a latent class model that included our broader autism phenotype covariate

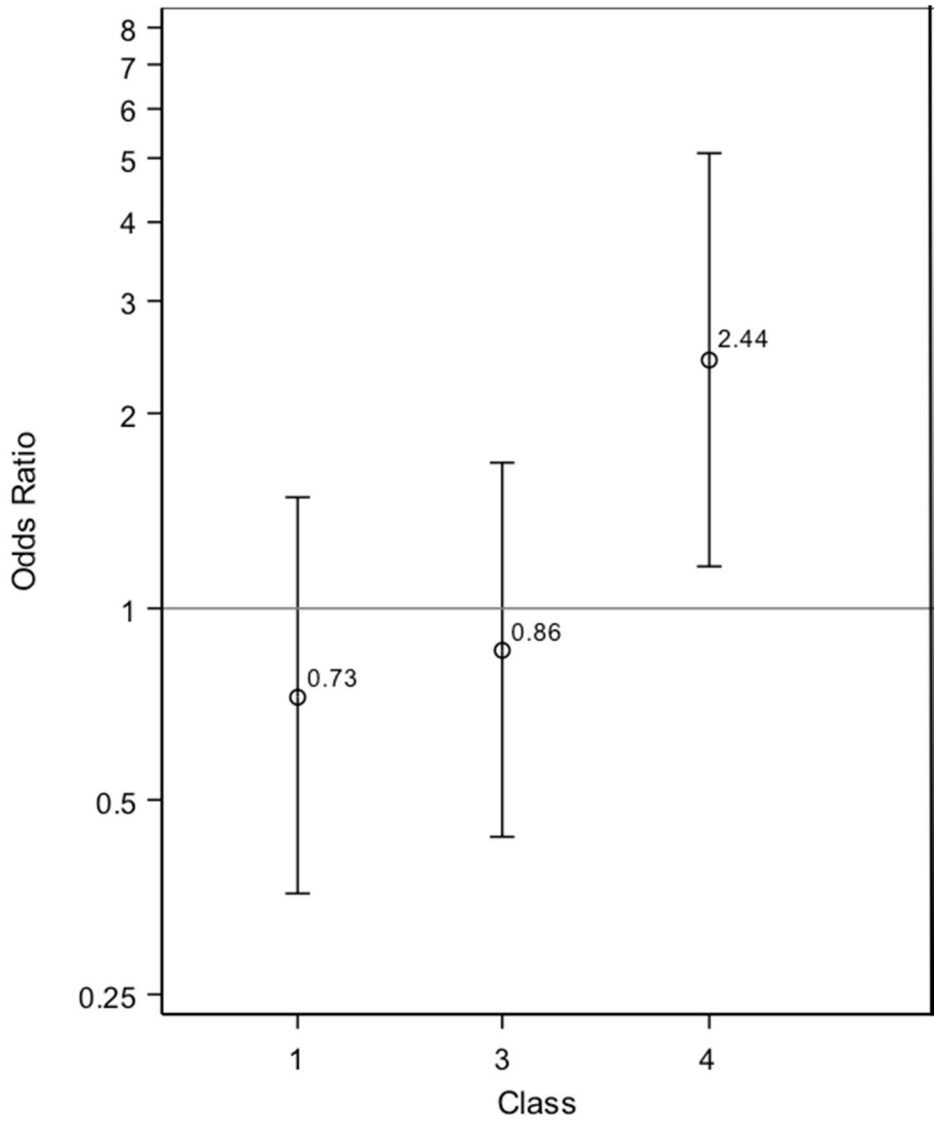
Table 28. Demographic characteristics by parent's broader autism phenotype status in the Study to Explore Early Development

	One or both parents BAP+ N=100		Both parents BAP- N= 424		Missing BAP N=183	
	N	**%**	**n**	**%**	**N**	**%**
Child Sex						
Male	80	80.0	355	83.7	144	78.7
Female	20	20.0	69	16.3	39	21.3
Maternal Race						
White	64	63.4	290	68.4	88	48.1
Black	18	17.8	57	13.4	68	37.2
Asian	9	8.9	43	10.1	8	4.4
Other	6	5.9	18	4.2	9	4.9
Multi-racial	4	4.0	16	3.8	10	5.5
Paternal Race						
White	62	62.0	289	68.2	91	52.3
Black	19	19.0	65	15.3	69	39.7
Asian	7	7.0	39	9.2	8	4.6
Other	9	9.0	19	4.5	6	3.4
Multi-racial	3	3.0	12	2.8	3	1.7
Missing					7	
Maternal Ethnicity						
Hispanic	16	16.2	46	11.0	23	12.6
Not-Hispanic	84	83.8	378	89.0	160	87.4
Paternal Ethnicity						
Hispanic	19	19.4	40	9.5	22	12.6
Not-Hispanic	79	80.6	383	90.5	153	87.4
Missing	2		1		8	
Maternal Education (years)						
<12	24	24.2	54	12.7	12	6.6
12 to <16	58	58.6	266	62.7	101	55.2
>=16	17	17.2	104	24.5	70	38.3
Missing	1					
Paternal Education (years)						
<12	33	33.3	88	20.5	21	12.1
12 to <16	43	43.4	235	54.7	95	54.6
>=16	23	23.2	107	24.9	58	33.3
Missing	1				9	
Site						
California	18	18.0	76	17.9	18	9.8
Colorado	19	19.0	85	20.0	38	20.8

Georgia	18	18.0	81	19.1	39	21.3
Maryland	19	19.0	48	11.3	41	22.4
North Carolina	12	12.0	77	18.2	15	8.2
Pennsylvania	14	14.0	57	13.4	32	17.5
Phenotypic class[a]						
1	26	26.0	106	25.0	56	30.6
2	22	22.0	134	31.6	43	23.5
3	30	30.0	144	34.0	59	32.2
4	22	22.0	38	9.0	25	13.7

BAP Broader autism phenotype
BAP+ defined as a Social Responsiveness-Adult T score ≥ 60
[a] Phenotypic classes were from the inclusive latent class model with any parent BAP+. Classes are assigned by highest posterior probability (analyses did not assign children to classes but used estimated model probabilities).

Figure 7. Odds ratios and 95% confidence intervals comparing child autism spectrum disorder phenotypic classes by parental broader autism phenotype in the Study to Explore Early Development



Class 2 and neither parent having the broader autism phenotype is the referent class.

Table 29. Odds ratios comparing child autism spectrum disorder phenotype class by parental broader autism phenotype status in the Study to Explore Early Development, by parent type

	Both parents BAP+ N=16			Mother only BAP+ N=20			Father only BAP+ N=64		
CLASS	N	OR	95% CI	N	OR	95% CI	N	OR	95% CI
1	2	0.34	0.06, 1.87	9	0.28	0.72, 19.61	19	1.07	0.47, 2.45
2	5	REF		6	REF		15	REF	
3	5	0.77	0.20, 2.94	2	1.06	0.33, 3.46	17	0.82	0.21, 3.12
4	4	2.40	0.54, 10.57	3	1.63	0.34, 7.68	13	**2.71**	1.09, 6.77

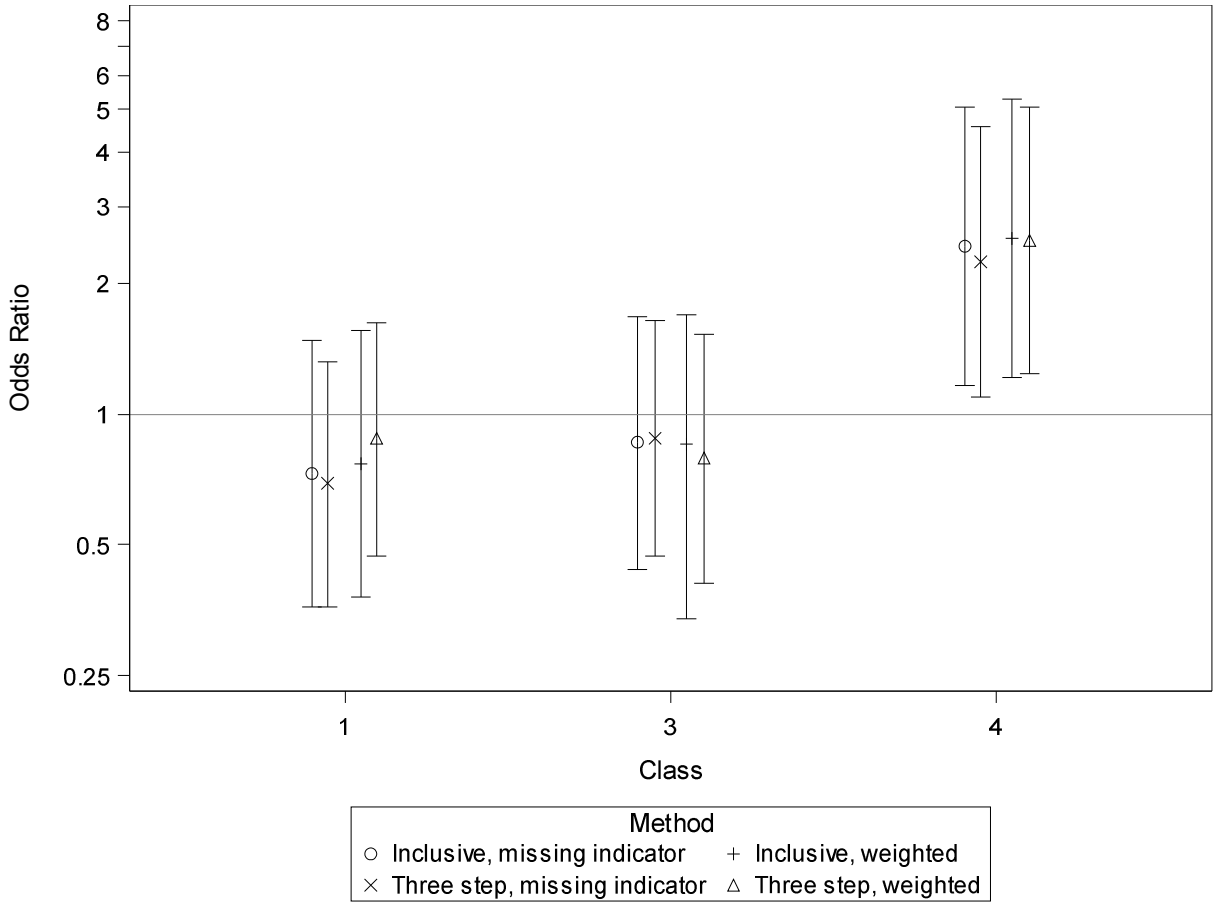
BAP: Broader Autism Phenotype;
OR: Odds Ratio;
CI: Confidence Interval;
Neither parent having BAP is the referent class
Ns were derived using classes assigned by posterior probabilities, analyses used model-estimated probabilities

Table 30. Sex stratified odds ratios comparing child autism spectrum disorder phenotype classes by parental broader autism phenotype in the Study to Explore Early Development

	Boys with any parent BAP+ N=80			Girls with any parent BAP+ N=20			
CLASS	N	OR	95% CI	N	OR	95% CI	P value
1	20	1.22	0.56, 2.65	6	0.50	0.11, 2.34	0.7
2	20	REF		3	REF		
3	25	1.23	0.57, 2.61	5	0.44	0.08, 2.41	0.2
4	15	**2.69**	1.06, 6.79	6	3.92	0.74, 20.76	0.8

BAP: Broader autism phenotype
OR: Odds Ratio,
CI: Confidence Interval,
P value is for the interaction term for child sex and parent broader autism phenotype status
Neither parent having BAP was referent
Ns were derived using classes assigned by posterior probabilities, analyses used model-estimated probabilities

Figure 8. Odds ratios comparing child autism spectrum disorder phenotype classes by any parent having the broader autism phenotype in the Study to Explore Early Development, by latent class and missing data methods



Class 2 with neither parent having BAP is the referent

4B.2. Additional analyses for aim 2.

Additional analyses

Because of the intricacies of latent class modeling and our missing data, we explored a series of additional and sensitivity analyses. These tables and figures are presented here to justify our choices and illustrate the robustness of our results.

Weighting to address missing data

As mentioned previously, SRS-As were missing for some parents. Table 31 presents demographics by parent SRS-A completion for our weighted samples. The group with only one parent SRS-A had mothers that were 43.1% black and 14.9% Hispanic. When neither parent had SRS-A data mothers were 26.9% black and 9.7% of Hispanic. We believe that these missing data are unlikely to be a source of selection bias since it is unlikely that missingness is associated with BAP or child phenotype. Our weighting approach accounted for these demographic differences and this weighted sample has characteristics nearly identical to the total SEED ASD sample. Two slightly different weights were created: one that included estimated posterior probability of class in the weighting model (taken from class derivation using the full N=707) and the other did not include the class variable. Including or excluding the class variable did not greatly change weight values. We used the weights with class included to better account for any associations between missingness and class.

Alternative LCA approaches

As thoroughly discussed in chapter 3f, there were three ways to approach our LCA with covariates. In chapter 4b, we present our results using the inclusive method. Here, we present results for the three-step and classify analyze approaches. Table 32 presents results for our aim 2.1 analysis for all three methods (all with an indicator for missing SRS-A data). Results were qualitatively similar between the three approaches, as all had significant positive association for being in class 4 vs. class 2. As expected, the classify-analyze approach attenuated effects

(class 4 OR 12.5% lower than the three-step, 23.1% lower than the inclusive LCA). Confidence interval ratios were most precise for the classify-analyze approach, then the three-step, and lastly the inclusive. This is to be expected as the classify-analyze approach does not accurately account for variance, and the three-step model includes fewer covariates in the LCA.

Table 31. Aim 2 demographics by SRS-A response and by inverse probability weighting

	ASD cases N=707		No SRS-As N=67		One SRS-A N=116		Both SRS-A N=524		Weighted[a] N=707	Weighted[b] N=707
	N	%	N	%	N	%	N	%	%	%
Child Sex										
Male	579	81.9	51	76.1	93	80.2	435	83.0	82.7	82.6
Female	128	18.1	16	23.9	23	19.8	89	17.0	17.4	17.4
Maternal Race										
White	441	62.4	36	53.7	52	44.8	353	67.4	62.4	62.5
Black	143	20.2	18	26.9	50	43.1	75	14.3	20.8	20.8
Asian	60	8.5	5	7.5	3	2.6	52	9.9	8.8	8.7
Other	33	4.7	4	6.0	5	4.3	24	4.6	4.6	4.6
Multi-racial	30	4.2	4	6.0	6	5.2	20	3.8	3.4	3.4
Paternal Race										
White	442	63.1	40	61.5	51	45.9	351	67.0	61.8	61.9
Black	153	21.9	17	26.2	52	46.8	84	16.0	21.6	21.7
Asian	53	7.6	5	7.7	3	2.7	46	8.8	7.7	7.6
Other	34	4.9	3	4.6	3	2.7	28	5.3	5.9	5.9
Multi-racial	18	2.6	1	1.5	2	1.8	15	2.9	3.0	3.0
Missing	7		2		5					
Maternal Ethnicity										
Hispanic	85	12.4	6	9.7	17	14.9	62	12.0	11.3	11.3
Not-Hispanic	610	89.1	56	90.3	98	86.0	456	88.0	88.7	88.7
Missing	12		5		1		6			
Paternal Ethnicity										
Hispanic	81	11.6	6	9.2	16	14.5	59	11.3	11.3	11.3
Not-Hispanic	615	88.4	59	90.8	94	85.5	462	88.7	88.7	88.7
Missing	11		2		6		3			

	ASD cases N=707		No SRS-As N=67		One SRS-A N=116		Both SRS-A N=524		Weighted[a] N=707	Weighted[b] N=707
	N	%	N	%	N	%	N	%	%	%
Maternal Education (years)										
<12	36	5.1	4	6.0	8	6.9	24	4.6	4.4	4.5
12 to <16	305	43.2	38	56.7	63	54.3	204	39.0	42.8	42.9
>=16	365	51.7	25	37.3	45	38.8	295	56.4	52.7	52.7
Missing	1						1			
Paternal Education (years)										
<12	53	7.6	5	7.9	16	14.4	32	6.1	6.6	6.6
12 to <16	295	42.3	34	54.0	61	55.0	200	38.2	41.9	42.0
>=16	349	50.1	24	38.1	34	30.6	291	55.6	51.5	51.4
Missing	10		4		5		1			
Site										
California	112	15.8	6	6.0	12	10.3	94	17.9	15.1	15.1
Colorado	142	20.1	19	19.0	19	16.4	104	19.8	20.3	20.4
Georgia	138	19.5	14	14.0	25	21.6	99	18.9	19.7	19.6
Maryland	108	15.3	20	20.0	21	18.1	67	12.8	16.6	16.5
North Carolina	104	14.7	2	2.0	13	11.2	89	17.0	14.4	14.5
Pennsylvania	103	14.6	6	6.0	26	22.4	71	13.5	13.9	13.9

[a]Weighted for maternal age, maternal education, maternal race, maternal ethnicity, and site
[b]Includes child ASD phenotypic class in weighting model

Table 32 Comparisons between the three approaches to latent class analysis for overall associations between any parent having the broader autism phenotype and class- weighted

	Missing Indicator								
	Three-step			Inclusive			Classify-analyze		
Class	OR	95% CI	CIR	OR	95% CI	CIR	OR	95% CI	CIR
1	0.69	0.36,1.32	3.67	0.73	0.36, 1.48	4.11	0.81	0.44, 1.47	3.34
3	0.88	0.47, 1.64	3.49	0.86	0.44,1.66	3.77	0.95	0.54, 1.66	3.07
4	**2.23**	1.09, 4.57	4.19	**2.44**	1.16, 5.09	4.38	**1.98**	1.03, 3.80	3.69

	% Change					
	Inclusive vs. Three-step		Inclusive vs. C-A		Three-step vs. C-A	
Class	OR	CIR	OR	CIR	OR	CIR
1	7.04	12.12	-9.27	23.05	-15.23	9.75
3	-1.88	8.12	-9.49	22.73	-7.75	13.51
4	9.42	4.66	23.11	18.94	12.51	13.64

OR Odds ratio;
CI Confidence interval;
CIR Confidence interval ratio
C-A Classify analyze

LCA missing data approaches

We also had two approaches for missing data. We used an indicator for missing SRS-As in our primary analysis and results are presented in chapter 4b. Here we present results weighting our sample to account for this missing data (**Table 33**). Results were similar to results from our primary analysis. All LCA approaches with weighted data had a significant association between parental BAP and being in class 4 compared to class 2 with no other meaningful associations between class 1 or class 3 and class 2. The classify-analyze approach had the lowest estimates (which we know to be biased) but the most precise confidence intervals. The three-step and inclusive approaches differed in point estimate by 12.7% for class 1, 8.22% for class three, and 1.01% for class 4. Confidence intervals were slightly more precise for the three-step compared to the inclusive approach. Again, these differences are to be expected because of the handling of variances and covariates in these approaches. These results agreed with our primary analysis, supporting the robustness of these results.

Change in class distribution due to inclusive LCA

We mentioned in section 4B that the inclusive approach slightly changes class distribution. **Table 34** presents class distribution for our three sub-aims, illustrating these differences. Using indicators for missing SRS-A data, model estimated posterior probabilities between aim 2.1 and aim 2.2 differed for 2.7 children (0.4%), aim 2.1 and aim 2.3 differed for 3.2 children (0.5%), and aim 2.2 and aim 2.3 differed by 0.5 children (0.07%). Weighting our sample to account for missing SRS-As (Table 35) created greater differences. Aim 2.1 differed from aim 2.2 by 12.7 children (2.4%), aim 2.1 differed from aim 2.3 by 21.08 children (4.2%), and aim 2.2 differed from aim 2.3 by 3.4 children (0.6%). Overall, changes were minimal which supports the use of the inclusive LCA. The weighted sample may have more differences because the smaller sample size increases variability in modeling.

Full results using alternative approaches

Lastly we present full results for the other three combinations of methods (LCA inclusive with a weighted sample, three-step with indicators for missing SRS-As, three-step with a weighted sample). As seen in Table 32 and **Table 33**, results for any parent being BAP+ were very similar. As we further categorized BAP and stratified by child sex, results between methods had larger differences. However, our inferences are not different across any of these approaches.

Inclusive LCA with weights

Table 36, Table 37, and Table 38, present results using inclusive LCA with weighting for SRS-A missingness. These results were very similar to the missing indicator approach. Children with any parent BAP+ had 2.54 the odds of being in class 4 vs. class 2 compared to children with two BAP- parents (95% CI: 1.21, 5.31). Results by parent type were similar to our primary analysis: both parents being BAP+ had elevated but non-significant ORs comparing class 4 to class 2 and this association was significant if the father alone was BAP+. Stratifying by child sex also had similar results to our primary analysis. These results further affirm our choice in using a missing indicator.

Three-step approaches

Tables 39-41 present results for the three-step approach with indicators for missing SRS-A data. Tables 42-44 present result from the three-step approach with weighted for missing SRS-A data. These results were similar to results using the inclusive approach with missing indicators, illustrating the robustness of these results

Table 33. Comparisons between the three approaches to latent class analysis for overall associations between any parent having the broader autism phenotype and class- weighted

	Three-Step			Inclusive			Classify-Analyze		
Class	OR	95% CI	CIR	OR	95% CI	CIR	OR	95% CI	CIR
1	0.88	0.47, 1.62	3.45	0.77	0.38, 1.56	4.11	0.68	0.40, 1.15	2.88
3	0.79	0.41, 1.52	3.71	0.85	0.34. 1.69	4.97	0.85	0.52, 1.38	2.65
4	**2.51**	1.24, 5.08	4.10	**2.54**	1.21, 5.31	4.39	**2.24**	1.27, 3.95	3.11

	% Change					
	Inclusive vs. Three-Step		Inclusive vs. C-A		Three-Step vs. C-A	
Class	OR	CIR	OR	CIR	OR	CIR
1	-12.72	19.10	12.71	42.79	29.13	19.89
3	8.22	34.08	0.15	87.30	-7.46	39.70
4	1.01	7.12	13.26	41.10	12.13	31.72

OR Odds ratio;
CI Confidence interval;
CIR Confidence interval ratio
C-A Classify analyze

Table 34. Differences in class distribution between inclusive models with missing indicators

	Aim 2.1		Aim 2.2		Aim 2.3	
Model	Any one parent BAP+		By parent type		Child sex	
Class	N	%	N	%	N	%
1	196.6	27.8	197.6	28.0	197.84	28.0
2	187.5	26.5	187.3	26.5	186.8	26.4
3	237.2	33.5	237.5	33.6	236.23	33.4
4	85.8	12.1	84.6	12.0	86.11	12.2

Table 35 Differences in class distribution between inclusive models, weighting for missingness

	Aim 2.1		Aim 2.2		Aim 2.3	
Model	Any one parent BAP+		By parent type		Child sex	
Class	N	%	N	%	N	%
1	140.31	26.78	131.33	25.06	132.02	25.20
2	137.18	26.18	151.54	28.92	151.39	28.89
3	184.43	35.20	183.38	35.00	181.79	34.84
4	62.06	11.84	57.75	11.02	58.8	11.22

Table 36. Odds ratio for any one parent having BAP, inclusive model weighted for missing SRS-As

CLASS	OR	95% CL
1	0.77	0.38, 1.56
3	0.85	0.34. 1.69
4	**2.54**	1.21, 5.31

Table 37. Odds ratio for classes by which parent has BAP, inclusive model weighted for missing SRS-As

	Both parents BAP+		Mother BAP+		Father BAP+	
CLASS	OR	95% CL	OR	95% CL	OR	95% CL
1	0.43	0.11,3.61	0.21	0.03, 1.51	1.27	0.54, 3.01
3	1.03	0.27, 3.90	0.75	0.22, 2.53	0.89	0.40, 1.97
4	4.34	0.87, 21.63	1.47	0.31, 7.10	**3.24**	1.23, 8.50

Table 38. Odds ratio for classes by child sex and any parent having BAP, inclusive model with weights for SRS-A missingness

	Boys		Girls		
CLASS	OR	95% CI	OR	95% CI	P value
1	0.85	0.37, 1.95	0.48	0.10, 2.28	0.5
3	0.91	0.44, 1.88	0.67	0.15, 2.88	0.7
4	2.31	0.93, 5.72	**6.57**	1.01, 42.43	0.3

Referent class is class 2, no parent with BAP
P value for interaction term between child sex and parent BAP
OR Odds ratio;
CI: Confidence interval

Table 39 Class distribution for three-step approach with missing indicators

	Total	
	N=707	
Class	N	%
1	197.74	27.97
2	187.46	26.51
3	237.51	33.59
4	84.29	11.92

Table 40 Odds ratios by parent BAP type and class, three-step approach with missing indicators

	Both parents BAP+		Mother BAP+		Father BAP+	
CLASS	OR	95% CL	OR	95% CL	OR	95% CL
1	0.28	0.04, 1.87	0.23	0.03, 1.57	1.00	0.47, 2.13
3	0.73	0.19, 2.87	1.15	0.36, 3.60	0.82	0.37, 1.83
4	2.33	0.57, 9.50	1.44	0.32, 6.48	**2.50**	1.05, 5.93

Table 41 Odds ratios by child sex for any parent with BAP, three-step approach with missing indicators

	Boys		Girls		
CLASS	OR	95% CI	OR	95% CI	P value
1	0.76	0.37, 1.55	0.43	0.08, 2.23	0.5
3	0.97	0.48, 1.95	0.59	0.15, 2.36	0.9
4	2.01	0.89. 4.51	4.13	0.73, 21.21	0.2

Referent class is class 2, no parent with BAP
P value for interaction term for child sex times parent BAP
OR Odds ratio;
CI Confidence interval

Table 42. Class distribution for three-step approach weighted for missingness

CLASS	Total	
	N	%
1	137.90	26.32
2	140.48	26.81
3	184.52	35.21
4	61.09	11.66

Table 43. Odds ratio for any parent with BAP, three step-approach weighted for missingness

CLASS	OR	95% CL
1	0.88	0.57, 2.17
3	0.79	0.66, 2.46
4	**2.51**	1.24, 5.08

Table 44. Odds ratios by which parent had BAP, three step-approach weighted for missingness

	Both parents BAP+		Mother BAP+		Father BAP+	
CLASS	OR	95% CL	OR	95% CL	OR	95% CL
1	2.73	0.43, 17.02	3.38	0.52, 21.61	0.89	0.41, 1.92
3	2.01	0.30, 13.41	3.90	0.62, 24.50	0.73	0.33, 1.60
4	6.84	0.98, 47.81	5.29	0.64, 42.66	**2.58**	1.10, 6.02

Table 45. Odds ratio for any parent with BAP by child sex, three-step approach weighted for missingness

	Boys		Girls		
CLASS	OR	95% CI	OR	95% CI	P Value
1	0.89	0.42, 1.89	0.41	0.07, 2.39	0.4
3	0.89	0.43, 1.86	0.73	0.18, 2.88	0.8
4	2.26	0.95, 5.36	**7.01**	1.30, 37.92	0.2

Referent class is 2 with no parent with BAP
P value is for interaction between child sex and any parent having BAP
OR odds ratio
CI confidence interval

CHAPTER 5. DISCUSSION

5A. Aim 1 Discussion

Summary of findings

The diagnostic process for ASD is complex and involves multiple instruments and informants. We assessed whether disagreement between these instruments was associated with maternal BAP in a sample of children with past history of ASD or DD identified in SEED. The broader autism phenotype is a set of subclinical ASD traits more prevalent in families of children with ASD. Mothers with BAP were at significantly higher risk of reporting that their child met instrument ASD risk (based on the SCQ) or ASD diagnostic thresholds when a clinician reported otherwise. (based on the ADOS or OARS) Risk ratios for these associations ranged from 1.30 (SCQ vs. OARS) to 2.85 (ADI-R vs. ADOS). Risk ratios were higher when the maternal reported instrument was a semi-structured interview compared to a brief screener. We did not see any 'under-reporting' effects, although there was a suggestion of an inverse association when looking at the SCQ. Overall, our results were unchanged after sensitivity analyses adjusted for Spanish language use, study site, a more conservative SCQ cut-off, or weighting for missing BAP data.

Maternal BAP sub-domains were not meaningfully associated with reporting discordance. This may suggest that the entire constellation of BAP leads to discordance, rather than one specific trait or group of traits. Alternatively, there may not have been adequate sample size to detect associations in these subdomains, or, associations with these domains are more specific to reporting on certain child ASD traits, rather than meeting instrument cut-off scores.

Maternal self-reported history of past depression diagnosis was not associated with reporting discordance. This indicates that reporting discordance may be due to the autism-like traits of BAP, rather than larger maternal psychopathology. Self-reported history of a diagnosis of an anxiety disorder had an elevated association for 'over-reporting' on the ADI-R vs. ADOS, but did not meet statistical significance. This may be an effect of anxiety as a state based trait that might present more in the one-on-one maternal interview then a brief telephone questionnaire. Risk ratios for anxiety and 'over-' or 'under-reporting' were still much lower than for BAP, which again supports the specificity of these results to BAP.

In regards to our hypotheses for aim 1:

Hypothesis 1.1: Mothers with BAP, compared to those without, will be more likely to report that a child reaches the threshold for ASD risk on screening instruments when a clinician does not observe or deduce that the child has ASD.

Results 1.1: Mothers with BAP were at increased risk of 'over-reporting' on the SCQ vs. ADOS or OARS as compared to mothers without BAP. There was no significant association between BAP and 'under-reporting', although effect estimates were below one.

Hypothesis 1.2: Compared to mothers without BAP, mothers with BAP will be more likely to report on an ASD interview instrument that their child meets ASD thresholds when a clinician observation or best estimate does not meet ASD thresholds.

Results 1.2: Mothers with BAP were at elevated risk for 'over-reporting' on the ADI-R vs. ADOS or OARS compared to mothers without. These effect estimates were higher than when the screening instrument was used. Further, there were no significant associations for 'under-reporting'.

Hypothesis 1.3: There will be no clinical difference in discordance between maternal-reported and clinician-observed or estimated instruments with regard to maternal self-reported history of a depression or anxiety disorder diagnosis.

Results 1.3: Mothers with self-reported history of depression diagnosis did not differ from those without in regards to 'over-' or 'under-reporting' on any combination of measures. For self-reported history of an anxiety disorder diagnosis, there were no significant associations with 'over' reporting, but effect estimates were elevated.

Results in context of study design and past literature

Sampling approach

These results need to be interpreted in context of study design and limitations. SEED is a large community-based case-control study. For this work, the case-control design was not utilized but rather, we derived our sample from children identified as most likely cases. Therefore, this sample consisted of only mothers whose children had past evaluations for ASD or DD, preventing us from making inferences on mothers who had never experienced a child's neurodevelopment diagnostic process. Having experienced previous evaluations may lead to a reduction in anxiety and better ability to remember child developmental milestones. It would be important to assess these patterns in mothers who have children at high risk for ASD with no past history of ASD or DD evaluation to determine whether these effects are magnified in a more stressful setting. Further, since SEED was for research purposes and no formal diagnoses were given, results are not translatable to the diagnostic process. Replicating this study in a clinical sample may illuminate these effects in a more stressful, meaningful environment. Alternatively, SEED enabled us to assess these associations in a broader sample with more variety in ASD severity. SEED was designed to examine younger children (3-5 years) so results are specific to that age range. This age range is ideal for improving early interventions, but children are still evaluated at lager ages. When a child is older a mother has to report on more past symptoms and a differing array of current symptoms and any discordances may delay diagnosis further. Future work should replicate this study in an older group of children.

Consistency with past literature

The fact that there is discordance between ASD reporting instruments is consistent with past work in SEED (197) and in specific studies comparing the ADI-R and ADOS (62, 64). Few studies have assessed predictors of this discordance; as yet, a study found that the child's level of repetitive and restricted behaviors was not associated with discordance in SEED instruments (197) nor was child age associated with ADI-R ADOS discordance(224). We believe that this is the first work to assess maternal characteristics as a source of discordance in ASD evaluations. These results agree with the literature on 'over-reporting' for child psychiatric conditions among mothers who have those conditions. This 'depression-distortion' literature is slightly different in that the mother usually has a confirmed diagnosis and the child has less severe traits that are being reported on. Our study was the inverse, but there still was an increased likelihood that maternal reported instruments reached ASD thresholds compared to clinician measures when the mother had BAP.

Exposure and outcome misclassification

There is the possibility that BAP was misclassified. As described in chapter 2, there are many different methods and instruments to measure BAP. We used the SRS-A, which is a brief informant-reported questionnaire, but it has limitations. We were missing who the informant was for a majority of our sample (~75%). A mother was asked to have a friend or spouse report on her, but could have self-reported her traits, which the SRS-A was not designed for. A study by Ingersoll et al. (122) adapted the wording of the SRS-A to be self-report (by changing the pronouns) and found that it still met criterion validity and was in line with other self-report BAP measures. The SRS-2 added a self-report version of the SRS-A, again only adjusting the wording to enable self-administration. This version showed lower intra-class correlation with the informant version than the intra-class correlations between two different informants; however, standardized mean differences in score were small and the SRS-2 manual standardizes both versions to the same set of scores (153). De La Marche et al. (92) evaluated difference between

self- and informant reporting on the SRS-2 and found that parents over-reported their social ability, and this was not associated with gender or ASD case status. Based on that result, we would expect the effect of our mixed informant type to be non-differential and minimal; we do not expect mothers with BAP to be more likely to self-report and scoring does not appear to differ by level of ASD traits (92). Our results would likely be attenuated, as mothers with and without BAP will look more similar due to overall over-reporting. However, based on the effect sizes seen in the SRS-2, we expect minimal attenuation. We were unable to simulate these effects due to the extent of our missingness and the series of assumptions we would need to make to test these effects (e.g. of those missing, who was a self-report, then, of those who self-report, who was inaccurate). Ideally, we would have had a BAP measure that incorporates multiple informants including clinicians to best capture BAP, but that type of measurement may not be feasible in a study with the size and goals of SEED.

The cutoffs we used for evaluation instruments were well validated and standardized, but they were dichotomized. We were unable to assess discordance using a continuous measure. The four instruments that we used all had continuous scales, but they did not easily align such that we could calculate differences. In the future, this work should be replicated using instruments that more easily align or by creating a way to compare continuous scores across instruments. This would allow us to examine the magnitude of difference in reporting.

Recommendations

Future research needs

Since this work is novel and has some limitations, results are not generalizable to populations outside SEED. Therefore, recommendations for future action are conservative. We still have many questions about BAP and the diagnostic process: Do people with and without BAP report differently on the same set of events? Does mode of an interview (in person interview, self-report, over the phone interview) affect response differentially through BAP? How

heterogeneous is the BAP phenotype and does this heterogeneity affect reporting? In the prior section we listed a series of future analyses that could build off this work. Hopefully our results will foster others to pursue these promising projects.

Our results are in agreement with past literature that ASD evaluation measures are not always concordant. In this study, maternal BAP was associated with this discordance across instruments and methods. We recommend that clinicians continue to use their best judgment during the diagnostic process when trying to incorporate information that may be in opposition to what they observe. Continued research into parental BAP and its manifestation will be useful in clarifying how clinicians should respond to this differential diagnostic discordance by BAP. There is also the possibility that children who have a parent with BAP present differently. In aim 2 we found that there were differences in child presentation by parental BAP status. A more subtle presentation may be more difficult for a clinician to observe in the limited time for an instrument like the ADOS. Better understanding the relationship between parent BAP and child phenotype may reduce some diagnostic discordance.

Intervention planning

This work may have implications for further research that incorporates child behavioral intervention. A preliminary study by Parr et al. (183) found that effectiveness of a parent-mediated intervention was negatively impacted by a mothers level of BAP traits. Many interventions are crafted to a child's specific needs; the reporting ability of a parent in communicating a child's needs may affect the programs prescribed. If parental BAP affects informant ability, then these interventions may be negatively impacted because of miscommunication between parent and interventionist. Studies that repeat our approach to try and quantify reporting discordance for intervention creation may provide insight into improving intervention design.

In summation, more work is needed that explores how maternal BAP affects the ASD diagnostic process. Our study is the first to find differential reporting by BAP status, but the

extent of this impact on time to diagnosis or intervention planning is not yet known. At this point, there is no biomarker or test for ASD. Even if one were found to be valid, the heterogeneity of ASD will likely inhibit the usefulness of a 'magic bullet' diagnostic test from being able to diagnose all children with ASD. For the foreseeable future, the diagnostic process and treatment development and implementation for young children with ASD will be heavily reliant on a caregiver reporting the child's developmental and medical history, and strengths and challenges. The utility of our specific findings may not yet affect clinical practice; however, figuring out better methods of interpreting parents' reports regarding the child's behaviors for the brief period that a caregiver has with a clinician or interventionist, are vital. We believe that this work is a small step in that direction.

5B. Aim 2 Discussions

Summary of findings

Our goal was to determine whether parental BAP was associated with child ASD phenotype classes derived from extensive data collected from children aged 3-5 years in SEED. We found that children with ASD who had parents with BAP had increased odds of being in a phenotypic class marked by typical non-verbal functioning, mild language and motor delays, and increased levels of co-occurring conditions. There were no associations with other classes. These results were robust across latent class methods and approaches to handling missing data. Although our sample size was low, we explored how this effect differed by which parent had BAP and by child sex. Results suggest that having a BAP+ father was associated with being in a class with average expressive and receptive language, mild language and motor delays, and increased levels of co-occurring conditions like anxiety or depression. Child sex did not modify the relationship between parental BAP and child class.

In regard to our specific hypotheses:

Hypothesis 2.1 a. parental BAP will be associated with child phenotype subgroups that have a less severe ASD presentation.

Results 2.1 a. BAP was associated with a class that had less severe impairment in non-verbal functioning with milder language and motor delays. It could be said that this class had a less severe presentation in regards to social communication; however, this class had more co-occurring conditions like self-injurious behavior and aggression that can be burdensome and make intervention difficult.

Hypothesis 2.1.b. Parental BAP will be associated with subgroups of ASD in children that are qualitatively similar to those defining the parent BAP.

Results 2.1 b. The class that was associated with BAP included traits commonly seen in BAP, like mild language impairment, anxiety, and depression. This result highlights potential endophenotypes that can be further studied to find specific genetic mechanisms for ASD by harnessing increased homogeneity between parents with BAP and children with ASD in this class.

Hypothesis 2.2: Fathers with BAP will be more strongly associated with less severe child ASD subgroups compared to mothers with BAP.

Results 2.2: The association between fathers with BAP and the class with typical non-verbal functioning and mild language delay was elevated and statistically significant. In regards to mothers, sample size was low, but our results do not suggest that there is an association with child phenotypic class. Further work with a larger number of BAP+ mothers will need to be done to explore this relationship.

Hypothesis 2.3: Associations between parental BAP and child ASD will be stronger among boys compared to girls.

Results 2.3: This objective was more exploratory in nature due to the limited sample of girls. We found no statistical differences between sex in regards to the relationship between parental BAP and class. Both sexes had increased associations with the average receptive and expressive language ability and mild language delay class.

Results in context of study design

Using the SEED sample

These results are drawn from a sample that was recruited or volunteered to participate in a research study. Almost all of these children were identified from educational and health agencies that typically serve children with DDs. Children with ASD in the SEED sample were socio-economically and racially diverse (206); however, response rate for SEED was low (64-68% non-response)(196). Although our sample was diverse, this response rate gives pause to

the generalizability of our results. Additionally, SEED only collected data on children 3-5 years of age so our results are applicable only to that age range. Although natural history of ASD has not been extensively studied, phenotypic classes would likely differ greatly in an older sample. We have stressed the phenotypic diversity of ASD, but this diversity extends to demographics. Families of all races, ethnicities, education levels, and socio-economic statuses can have children with ASD. These factors may affect the ASD phenotype through service usage, identification, or genetic predisposition. We acknowledge that our results are dependent on the type of sample we evaluated. Future work should assess these questions in differing populations.

Improvement on class building

This work is bolstered by the usage of multiple measures and informants in creating phenotypic classes. As evaluated in aim 1, a parent with BAP may differentially report child ASD symptoms; relying on a sole informant report on child phenotype may lead to inaccurate phenotypic classification. This study creates classes from maternal interviews, medical records, and clinician observation. Past work relied only one parental reported measure (Table 4). This work is an improvement on those studies because the child phenotype is not defined from one perspective. When diagnosing ASD, a multi-informant multi-instrument evaluation is recommended because of the comprehensive description of child ASD (10); using that same approach also improves description of ASD phenotype for research studies.

Use of the SRS-A

This study relied on the SRS-A, which was an informant reported measure for BAP. As discussed in section 5a, we had missingness for informant type (75.7% missing in mothers, 37.5% missing in fathers). There is a high likelihood that some of this missingness indicates that the respondent self-reported (based on discussions with SEED staff). Adapting the SRS-A to be in the second person was shown to be valid in comparison to other self-reported BAP measures (122). A self-report was added for the SRS-2 and was moderately correlated with the informant

report (inter-rater agreement between 0.61 and 0.78) (92, 153). Inter-rater agreements were weaker than when comparing two informant reports (153). Ultimately, we believe that misclassification due to informant effects would be non-differential, as SRS-A informant effects are not associated with gender or level of ASD traits (92). Any misclassification would make our BAP+ and BAP- groups look more similar, attenuating effects. Based on the SRS-2, differences in SRS score is minimally affected by informant type and any affect on our results would be small. Using the SRS-2 and allowing the respondent the option to complete a self-report will improve our measurement of BAP, but the ideal measure of BAP would synthesize multiple informants and clinical opinion.

Recommendations

Finding etiologic origins

These results support the usage of heterogeneity reducing techniques to improve ASD research. There was a strong relationship between parental BAP and a child phenotype that had higher cognitive functioning, lower ASD severity, and co-occurring conditions that are also prevalent in people with BAP. Additional steps could look at specific traits that line up between parents and children to identify etiologic pathways. Using a sample of parents with BAP who have children with an ASD phenotype marked by average expressive and receptive language, mild language and motor delays, and increased co-occurring conditions, may be an efficient way to explore genetic origins. Because ASD has similar characteristics to other disorders (like DD, ID, obsessive compulsive disorder, anxiety), examining these traits may be insightful for the larger field of psychiatric genetics. The National Institutes of Mental Health launched the Research Domain Criteria to look at features of mental health disorders that may present across different conditions (252). Identifying etiologic pathways can contribute to identifying multiple traits/conditions shared by people with different formal diagnoses.

Looking at older ages

Additionally, the majority of the ASD research focuses on a younger age range. There is still much to learn about the ASD phenotype in adolescence and adulthood. It will be important to better understand how the parent-child phenotype lines up as the child develops into adolescence and adulthood. Preliminary research suggests high level of psychological burden and suicidal tendencies in adults with ASD (43). Determining whether these traits are linked to parent traits could be a way to preemptively intervene.

Effecting intervention

The relationship between parental BAP and child phenotype has implications for intervention. Parr et al. (183) found that children had poorer outcomes in a parent-mediated intervention if the mother was in the upper 50th percentile of BAP scores. This study was limited by sample size and by dichotomizing groups by greater than or less than mean BAP score. Nonetheless, this suggests BAP may be a factor in intervention efficacy. This makes sense, as a parent may be asked to teach skills and traits that they themselves may not fully grasp. If parent traits align with child traits, adapting these interventions to accommodate these parental traits could increase their effectiveness. Additionally, timing of ASD diagnosis is a key factor for optimal outcomes (11); work is being done in SEED to evaluate age at first concern for child ASD and service usage by parental BAP status. If BAP is a factor in age at identification, presentation may differ due to increased or decreased service usage during the important early developmental window. Lastly, knowing that co-occurring conditions may track between parent and child, clinicians and interventionists should be hyper-aware for the development of conditions like depression or anxiety in these children who are likely at a higher risk for these conditions.

Future work

Our results suggest further work needs to be done on the association between mothers with BAP and child phenotypic classes. BAP in mothers is less common than in fathers (Table

3), which necessitates large samples for adequate power. In addition, our sample of girls with ASD was low and future work should delve deeper into potential sex differences. SEED is a relatively large sample of children with ASD, but with estimated prevalence of identified ASD in girls being 5.3 in 1000 (32) finding girls is difficult. Utilizing online registries like the Interactive Autism Network or Simons Simplex Collection could provide enough power for analyses, but there is a likely trade-off in having to rely on self- or informant-reported measures of BAP and child phenotype. With more BAP+ mothers and girls with ASD, we could explore whether associations between which parent had BAP and child class was modified by child sex. Examining mothers and girls could be useful for exploring X-linked transmission ASD sex differences.

In conclusion, any parent being BAP+ was associated with a child having an ASD phenotype defined by average receptive and expressive language, mild language and motor delays, and increased co-occurring conditions. This work is meaningful in its implications for efficiently studying ASD etiology. Results support parental BAP as an ASD endophenotype, and further suggest that the traits of BAP can be used as individual endophenotypes. Future work should explore potential genetic etiologies in this parent BAP- child ASD class subgroup.

CHAPTER 6. CONCLUSIONS

It may be redundant, but autism spectrum disorder exists on a spectrum. This dissertation goes into great detail on how this spectrum exists beyond the criteria that lead to a formal diagnosis. It is important for researchers to use the full extent of the spectrum to better understand the mechanisms that cause ASD and find ways to craft interventions that can alleviate some of the disorders more negative aspects.

Our two main findings are that mothers with BAP are more likely to report on ASD evaluations that their child meets ASD risk or ASD thresholds on evaluation instruments when a clinician's report does not, and that having a parent with BAP is associated with the child having an ASD phenotype defined by average receptive and expressive language, mild language and motor delays, and increased co-occurring conditions like anxiety and depression. These results are significant. Maternal report is vital for accurately diagnosing ASD; understanding factors that affect discordance with clinician reports will improve ability to make an accurate final diagnosis. Identifying a strong association between parental BAP and a specific child ASD phenotypic class allows for efficient genetic research using this more homogenous sample to assess endophenotypes.

Our society is slowly shifting into one that is more accepting of people with ASD rather than trying to 'cure' or marginalize them. With this being the case, it is not farfetched to think that the prevalence of autistic traits in the population will increase. As we emphasize the strengths of people with autism, we will likely see more of these traits accumulate in future generations through assortative mating and acceptance of the traits that make people with autism unique. It will be imperative that we identify children that have significant impairment

associated with their ASD so we can prevent negative outcomes through targeted genetic and biologically based therapies or early intervention. In bettering our understanding of diagnostic discordance and finding efficient ways to conduct etiologic research, we move closer to creating a world where ASD is no longer a disability but a difference.

APPENDIX 1. STUDY TO EXPLORE EARLY DETETICION DATA COLLECTION TOOLS (from Schendel et al. 2014 (196))

Study contacts and instruments	Type of quality control assessment(s) and requirements	Specific quality control training requirements[a]	Ongoing quality control (frequency)	Results ongoing quality control[b]
Invitation telephone call, including eligibility screener and Social Communication Questionnaire	Semiqualitative call rating form—a priori criteria established for acceptable score.[c]	Acceptable scores on 4 role-playing (mock) calls and first 2 "live" calls.	5% per interviewer	88% acceptable rating scores overall, with improvements over time; >90% after first 6 months.
Follow-up call, including structured pregnancy dates questionnaire for caregiver interview	Semiqualitative call rating form—a priori criteria established for acceptable score.[c]	Acceptable scores on 3 role playing (mock) calls.	5% per interviewer	93% acceptable rating scores overall, with improvements over time; >90% after first 6 months and 100% after first 12 months.
Caregiver interview	(1) Semiqualitative call rating form—a priori criteria established for acceptable score.[c] (2) Quantitative inter-rater reliability assessment of selected interview items. Acceptable score is ≥95% concordance.	Acceptable scores for both assessments on 3 role-playing (mock) interviews and first 2 "live" calls.	5% per interviewer	99% acceptable call rating scores; 98% acceptable inter-rater reliability assessments throughout study.
Questionnaire packets I, II, and III (self-administered forms)[d]	No specific systematic QC requirements, but continual supervisor oversight and all forms reviewed for missing or illegible data or contradictory entries. Participants are recontacted as needed.	None. General training provided on forms and appropriate responses to participant queries.	NA	NA
Autism Diagnostic Observation Schedule (ADOS)	Intersite: Supervising clinicians establish reliability by scoring the same ADOS exam videotapes. Acceptable score is ≥80% concordance on algorithm items. Intrasite: All clinicians establish reliability with supervising clinician. Acceptable score is ≥80% concordance on algorithm items	Both intersite and intrasite reliability established in advance of study start.	Quarterly intersite and intrasite reliability exercises	Intersite: 99% acceptable scores on "first pass" quarterly exercises and 100% acceptable scores on "second pass" Intrasite: 99% acceptable scores on "first pass" quarterly exercises and 100% acceptable scores on "second pass".
Autism Diagnostic Interview-Revised (ADI-R)	Intersite: Supervising clinicians establish reliability by scoring the same ADI-R interview videotapes. Acceptable score is ≥90% concordance on algorithm items. Intrasite: All clinicians establish reliability with supervising clinician. Acceptable score is ≥90% concordance on algorithm items.	Both intersite and intrasite reliability established in advance of study start.	Quarterly intersite and intrasite reliability exercises.	Intersite: 99% acceptable scores on "first pass" quarterly exercises and 100% acceptable scores on "second pass". Intrasite: 87% acceptable rating scores on "first pass" quarterly exercises and 100% acceptable scores on "second pass".
Mullen Scales of Early Learning	No specific systematic QC requirements, but continual supervisor oversight and all forms reviewed for missing or illegible data or contradictory entries.	None. Supervising site clinicians monitor initial assessments until competency determined.	NA	NA
Vineland Adaptive Behavioral Scales	No specific systematic QC requirements, but continual supervisor oversight and all forms reviewed for missing or illegible data or contradictory entries.	None. Supervising site clinicians monitor initial assessments until competency determined.	NA	NA

Dysmorphology physical examination: examination, photography, and anthropometric measurements.	Intersite: Examiners review common set of photos and compare measurements. Acceptable score is >80% concordance. Intrasite: Examiners certified as meeting acceptable levels of reliability (80% or higher depending on component) on performance standards in several areas.	Acceptable intrasite scores in all areas on 5 practice examinations and first 3 "live" examinations.	Intersite: 1 exercise/month Intrasite: 10% per examiner	Intersite: 100% acceptable scores on monthly exercises. Intrasite: 95% acceptable scores.
Biologic specimens: buccal swabs and blood specimens (child, mother, father) and hair specimen (child).	All: Central laboratory staff processes specimens upon receipt and performs preliminary QC (gross visual inspection). Sample of participants: Second blood specimen obtained for duplicate processing and analysis	None. Extensive staff training on study protocol for obtaining and processing biologic specimens	2% sample of duplicate blood specimens	Will assess analyte concordance (e.g., genotypes) among duplicates
Medical record abstraction (4 forms: prenatal, labor and delivery, neonatal, pediatric).	Intersite: Common reliability abstraction exercises, each focusing on different sections/forms. Acceptable score is ≥90% concordance across sites. Intrasite: Quantitative inter-rater reliability assessment of selected items on each form. Acceptable score is ≥90% concordance.	Acceptable intrasite scores on first 2 "live" abstractions for each form type (8 total abstractions).	Intersite: Quarterly reliability exercises. Intrasite: 5% per abstractor (across form types)	Intersite: Exercises revealed minor inconsistencies in abstraction process; no major substantive differences noted. Intrasite: 91–100% acceptable rating scores across the 4 form types

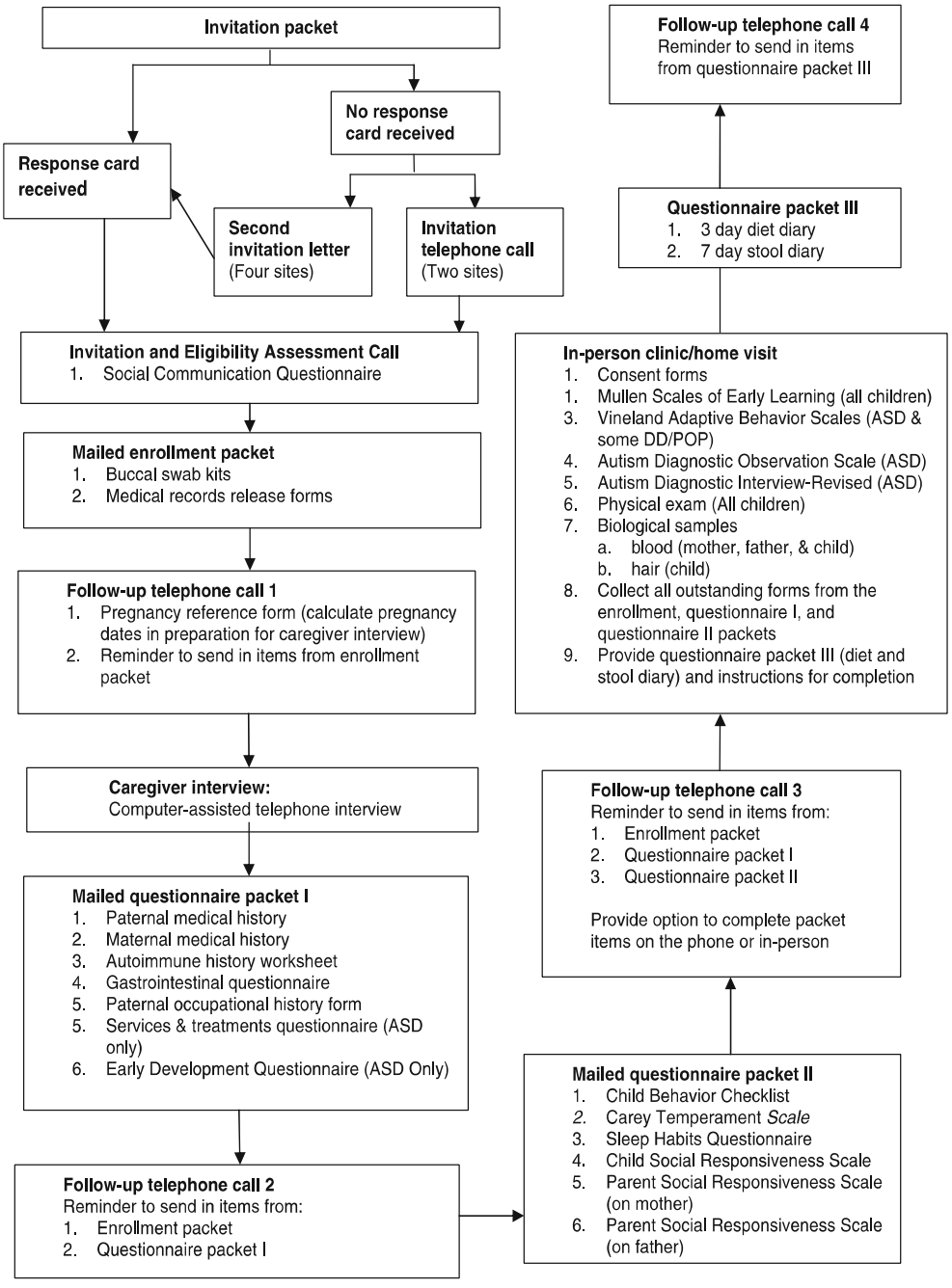
[a] Training QC requirements consisted of requirement for staff to pass formal reliability or other QC assessment on mock exercises in advance of "live" field work and initial QC requirement on first instruments/examinations once in the field

[b] For each instrument, if a study staff member did not meet criteria for acceptable score during ongoing QC, retraining and training QC requirements were instituted

[c] Semiqualitative call rating forms for invitation, follow-up, and caregiver interview calls included items such as use of call script, coverage of essential points, ability to respond to participant questions, probing on unclear or neutral responses, professionalism, and delivery and response recording for applicable study instruments (Social Communications Questionnaire, pregnancy reference form, or caregiver interview). For each item, QC supervisor rated interviewer as "good", "fair", or "poor". Criteria for acceptable score consisted of: no item rated as "poor" and 20% or fewer rated as "fair"; and mandatory ratings of "good" for select items (dependent on type of call)

[d] Questionnaire packet I included maternal medical history form, paternal medical history form, family autoimmune disease history form, paternal occupational exposure questionnaire, child services and treatments questionnaire, child early development questionnaire, and child gastrointestinal function questionnaire. Questionnaire packet II included Child Behavior Checklist, Carey Temperament Scale, Child Sleep Habits questionnaire, Child Social Responsiveness Scale, and Parent Social Responsiveness Scale. Questionnaire packet III included child diet diary and child stool diary

APPENDIX 2. STUDY TO EXPLORE EARLY DEVELOPMENT DATA COLLECTION PROCEDURE (from Schendel et al. (196))



APPENDIX 3. SOCIAL RESPONSIVENESS SCALE-ADULT QUESTIONNAIRE (from Constantino et al. (107))

WESTERN PSYCHOLOGICAL SERVICES
wps 12031 Wilshire Boulevard Los Angeles, CA 90025-1251
Publishers and Distributors

Social Responsiveness Scale –Adult Research Version

John N. Constantino, M.D.

Instructions: This form is about the child's **biological mother**. Someone who knows the mother well and sees her every day should fill out this form about the mother.

Fill in the date this form is completed: _____/_____/_____
Fill in your relationship to the mother: _____

For each question please check the box that best describes her behavior over the last six months.

	Not True	Some-times True	Often True	Almost Always True
1. Seems much more uncomfortable in social situations than when alone	☐	☐	☐	☐
2. Expressions on his or her face don't match what he or she is saying	☐	☐	☐	☐
3. Seems self-confident when interacting with others	☐	☐	☐	☐
4. When under stress, he or she shows rigid or inflexible patterns of behavior that seem odd	☐	☐	☐	☐
5. Doesn't recognize when others are trying to take advantage of him or her	☐	☐	☐	☐
6. Would rather be alone than with others	☐	☐	☐	☐
7. Is aware of what others are thinking or feeling	☐	☐	☐	☐
8. Behaves in ways that seem strange or bizarre	☐	☐	☐	☐
9. Seems too dependent on others for help with meeting basic needs	☐	☐	☐	☐
10. Takes things too literally and doesn't get the real meaning of a conversation	☐	☐	☐	☐
11. Has good self-confidence	☐	☐	☐	☐
12. Is able to communicate his or her feelings to others	☐	☐	☐	☐
13. Is awkward in turn-taking interactions with others (e.g., doesn't seem to understand the give-and-take of conversations)	☐	☐	☐	☐
14. Is not well coordinated	☐	☐	☐	☐
15. Recognizes and appropriately responds to changes in other people's tone of voice and facial expressions	☐	☐	☐	☐
16. Avoids eye contact or has unusual eye contact	☐	☐	☐	☐
17. Recognizes when something is unfair	☐	☐	☐	☐
18. Has difficulty making friends, even when trying his or her best	☐	☐	☐	☐
19. Gets frustrated trying to get ideas across in conversations	☐	☐	☐	☐
20. Shows unusual sensory interests (e.g., smelling his or her fingers frequently) or strange, repetitive ways of handling or manipulating small items within reach	☐	☐	☐	☐
21. Is able to imitate others' actions and demeanor when it is socially appropriate to do so	☐	☐	☐	☐
22. Interacts appropriately with other adults	☐	☐	☐	☐
23. Does not join group activities or social events unless forced to do so	☐	☐	☐	☐
24. Has more difficulty than others with changes in his or her routine	☐	☐	☐	☐
25. Doesn't seem to mind being out of step with or "not on the same wavelength" as others	☐	☐	☐	☐

	Not True	Some-times True	Often True	Almost Always True
26. Offers comfort to others when they are sad	❑	❑	❑	❑
27. Avoids starting social interactions with other adults	❑	❑	❑	❑
28. Thinks or talks about the same thing over and over	❑	❑	❑	❑
29. Is regarded by others as odd or weird	❑	❑	❑	❑
30. Becomes upset in a situation with lots of things going on	❑	❑	❑	❑
31. Can't get his or her mind off something once he or she starts thinking about it	❑	❑	❑	❑
32. Has good personal hygiene	❑	❑	❑	❑
33. Is socially awkward, even when trying to be polite	❑	❑	❑	❑
34. Avoids people who want to be emotionally close to him or her	❑	❑	❑	❑
35. Has trouble keeping up with the flow of a normal conversation	❑	❑	❑	❑
36. Has difficulty relating to family members	❑	❑	❑	❑
37. Has difficulty relating to other adults	❑	❑	❑	❑
38. Responds appropriately to mood changes in others (e.g., when a friend's mood changes from happy to sad)	❑	❑	❑	❑
39. Has an unusually narrow range of interests	❑	❑	❑	❑
40. Is imaginative without losing touch with reality	❑	❑	❑	❑
41. Wanders aimlessly from one activity to another	❑	❑	❑	❑
42. Seems overly sensitive to sounds, textures, or smells	❑	❑	❑	❑
43. Enjoys and is competent with small talk (casual conversation with others)	❑	❑	❑	❑
44. Doesn't understand how events relate to one another (cause and effect) the way other adults do	❑	❑	❑	❑
45. Generally gets interested in what others nearby are paying attention to	❑	❑	❑	❑
46. Has overly serious facial expressions	❑	❑	❑	❑
47. Laughs at inappropriate times	❑	❑	❑	❑
48. Has a sense of humor, understands jokes	❑	❑	❑	❑
49. Does extremely well at a few intellectual or computational tasks, but does not do as well at most other tasks	❑	❑	❑	❑
50. Has repetitive, odd behaviors	❑	❑	❑	❑
51. Has difficulty answering questions directly and ends up talking around the subject	❑	❑	❑	❑
52. Knows when he or she is talking too loud or making too much noise	❑	❑	❑	❑
53. Talks to people with an unusual tone of voice (e.g., talks like a robot or like he or she is giving a lecture)	❑	❑	❑	❑
54. Seems to react to people as if they are objects	❑	❑	❑	❑
55. Knows when he or she is too close to someone or is invading someone's space	❑	❑	❑	❑
56. Walks in between two people who are talking	❑	❑	❑	❑
57. Isolative; tends not to leave his or her home	❑	❑	❑	❑
58. Concentrates too much on parts of things rather than seeing the whole picture	❑	❑	❑	❑
59. Is overly suspicious	❑	❑	❑	❑
60. Is emotionally distant, doesn't show his or her feelings	❑	❑	❑	❑
61. Is inflexible, has a hard time changing his or her mind	❑	❑	❑	❑
62. Gives unusual or illogical reasons for doing things	❑	❑	❑	❑
63. Touches or greets others in an unusual way	❑	❑	❑	❑
64. Is too tense in social settings	❑	❑	❑	❑
65. Stares or gazes off into space	❑	❑	❑	❑

APPENDIX 4. LATENT CLASS FIT STATISTICS FOR CHILDREN WITH AUTISM SPECTRUM DISORDER ENROLLED IN THE STUDY TO EXPLORE EARLY DEVELOPMENT From Wiggins et al. (under review)

	Latent Class Distributions					Entropy	BIC[1]	SABIC[1]	LMR-LRT p values[1]
Number of classes	1	2	3	4	5				
1	100	NA	NA	NA	NA	NA	80528	80401	NA
2	55	45	NA	NA	NA	0.93	78305	78096	<0.001
3	40	44	16	NA	NA	0.92	77379	77087	0.018
4	28	26	34	12	NA	0.92	76722	76347	0.001
5	21	25	25	19	10	0.91	76493	76036	0.567

[1] Bayesian Information Criterion (BIC), Sample adjusted BIC (SABIC), and Lo-Mendel-Rubin Likelihood Ratio Test (LMR-LRT)

APPENDIX 5. ITEM RESPONSE PROBABILITIES AND ITEM RESPONSE MEANS (95% CONFIDENCE INTERVAL) BY LATENT CLASS FOR CHILDREN WITH AUTISM SPECTRUM DISORDER ENROLLED IN THE STUDY TO EXPLORE EARLY DEVELOPMENT From Wiggins et al (under review)

	Latent Class			
	1	2	3	4
Categorical variables (response probabilities)				
Current diet restrictions	0.26(0.19-0.33)$_{A}$	0.36(0.29-0.43)$_{A}$	0.30(0.23-0.37)$_{A}$	0.40(0.28-0.52)$_{A}$
Early recognition of epilepsy/seizure disorder	0.00(0.00-0.00)$_{A}$	0.13(0.07-0.18)$_{B}$	0.02(#0.00-0.04)$_{A}$	0.05(#0.00-0.10)$_{AB}$
History of regression	0.17(0.11-0.23)$_{A}$	0.34(0.27-0.42)$_{B}$	0.29(0.22-0.36)$_{AB}$	0.25(0.13-0.38)$_{AB}$
Insistence on sameness	0.72(0.65-0.79)$_{A}$	0.63(0.55-0.71)$_{A}$	0.66(0.59-0.74)$_{A}$	0.90(0.83-0.97)$_{B}$
Problems with age at first social smile	0.13(0.08-0.18)$_{A}$	0.24(0.16-0.31)$_{AB}$	0.15(0.10-0.20)$_{AB}$	0.31(0.19-0.42)$_{B}$
Repetitive behavior with objects	0.77(0.71-0.84)$_{A}$	0.94(0.91-0.98)$_{B}$	0.82(0.77-0.88)$_{A}$	0.96(0.91-#1.00)$_{B}$
Repetitive motor mannerisms	0.74(0.67-0.80)$_{A}$	0.96(0.92-1.00)$_{B}$	0.78(0.72-0.84)$_{A}$	0.83(0.74-0.93)$_{AB}$
Restricted interests	0.86(0.80-0.91)$_{AB}$	0.73(0.66-0.80)$_{A}$	0.81(0.75-0.87)$_{AB}$	0.92(0.84-0.99)$_{B}$
Self-injurious behaviors	0.38(0.31-0.46)$_{A}$	0.58(0.50-0.66)$_{B}$	0.37(0.30-0.44)$_{A}$	0.78(0.68-0.89)$_{C}$
Unusual sensory response	0.91(0.87-0.96)$_{A}$	0.97(0.94-1.00)$_{A}$	0.94(0.91-0.97)$_{A}$	0.97(0.93-#1.00)$_{A}$
Continuous variables (response means)				
Age at verbal language development	19.89(18.62-21.16)$_{A}$	30.58(27.81-33.35)$_{B}$	25.16(23.32-26.99)$_{C}$	24.32(21.79-26.86)$_{C}$

Age at walking	13.69(13.22-14.16)$_A$	16.31(15.09-17.53)$_B$	14.11(13.38-14.84)$_A$	13.60(12.86-14.34)$_A$
Aggressive behaviors	55.94(54.66-57.23)$_A$	61.94(60.02-63.86)$_B$	57.98(56.24-59.71)$_A$	76.18(71.96-80.41)$_C$
Anxiety/depression	53.60(52.55-54.65)$_A$	56.24(54.92-57.55)$_B$	53.38(52.33-54.43)$_A$	69.56(65.96-73.16)$_C$
Attention problems	59.05(57.73-60.37)$_A$	67.11(65.60-68.61)$_B$	61.61(60.20-63.03)$_A$	70.95(68.94-72.97)$_C$
Autism severity	6.73(6.51-6.95)$_A$	7.89(7.64-8.13)$_B$	7.21(6.98-7.44)$_C$	6.47(6.11-6.82)$_A$
Emotionally reactive	57.96 (56.49-59.44)$_A$	61.72(59.89-63.55)$_B$	57.39(55.75-59.02)$_A$	77.79(74.13-81.45)$_C$
Expressive language skills	50.73(48.69-52.76)$_A$	14.49(12.77-16.21)$_B$	34.03(31.98-36.08)$_C$	46.23(42.47-49.99)$_A$
Fine motor skills	54.49(52.90-56.09)$_A$	23.07(21.78-24.37)$_B$	37.56(35.21-39.90)$_C$	49.98(46.46-53.51)$_A$
Receptive language skills	56.97(54.92-59.01)$_A$	15.21(13.40-17.02)$_B$	34.32(32.04-36.60)$_C$	48.27(43.91-52.62)$_D$
Sleep problems	47.39(45.88-48.91)$_A$	53.86(51.95-55.78)$_B$	49.38(47.65-51.11)$_A$	59.66(56.02-63.29)$_C$
Social communication abilities	13.08(12.08-14.08)$_A$	20.97(20.10-21.83)$_B$	16.94(15.95-17.94)$_C$	20.51(19.14-21.88)$_B$
Somatic complaints	57.20(56.05-58.36)$_A$	60.79(59.42-62.17)$_B$	58.16(57.02-59.30)$_A$	67.72(65.24-70.21)$_C$
Visual reception skills	61.33(59.81-62.84)$_A$	23.13(21.90-24.36)$_B$	40.50(37.46-43.54)$_C$	53.66(49.89-

				57.44)$_D$
Withdrawn behaviors	64.92(63.36-66.47)$_A$	76.38(74.59-78.16)$_B$	66.98(65.23-68.72)$_A$	76.66(74.05-79.26)$_B$

Note: subscripts indicate between-class differences based on confidence intervals that do not overlap; # For interval estimates, a lower bound was reported as 0.00 when the lower bound estimate was <0.00 and an upper bound was reported as 1.00 when the upper bound estimate was > 1.00.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (5th ed.). Arlington, VA: American Psychiatric Publishing; 2013.

2. Autism and Developmental Disabilities Monitoring Network 2010 Principal Investigators. Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2010. MMWR Surveill Summ. 2014;63(2):1-22.

3. Buescher AVS, Cidav Z, Knapp M, Mandell D. Costs of autism spectrum disorders in the United Kingdom and the United States. JAMA pediatrics. 2014;168(8):721-8. doi: 10.1001/jamapediatrics.2014.210.

4. Kogan MD, Blumberg SJ, Schieve LA, Boyle CA, Perrin JM, Ghandour RM, Singh GK, Strickland BB, Trevathan E, van Dyck PC. Prevalence of parent-reported diagnosis of autism spectrum disorder among children in the US, 2007. Pediatrics. 2009;124(5):1395-403. doi: 10.1542/peds.2009-1522. PubMed PMID: 19805460.

5. Leigh JP, Du J. Brief Report: Forecasting the Economic Burden of Autism in 2015 and 2025 in the United States. J Autism Dev Disord. 2015;45(12):4135-9. doi: 10.1007/s10803-015-2521-7. PubMed PMID: 26183723.

6. Fernell E, Eriksson MA, Gillberg C. Early diagnosis of autism and impact on prognosis: a narrative review. Clin Epidemiol. 2013;5:33-43. doi: 10.2147/CLEP.S41714. PubMed PMID: 23459124; PMCID: 3583438.

7. Fava L, Strauss K. Response to Early Intensive Behavioral Intervention for autism—An umbrella approach to issues critical to treatment individualization. Int J Dev Neurosci. 2014;39:49-58. doi: 10.1016/j.ijdevneu.2014.05.004. PubMed PMID: 24866707.

8. Eldevik S, Hastings RP, Hughes JC, Jahr E, Eikeseth S, Cross S. Meta-analysis of Early Intensive Behavioral Intervention for children with autism. J Clin Child Adolesc Psychol. 2009;38(3):439-50. doi: 10.1080/15374410902851739. PubMed PMID: 19437303.

9. Shattuck PT, Durkin M, Maenner M, Newschaffer C, Mandell DS, Wiggins L, Lee LC, Rice C, Giarelli E, Kirby R, Baio J, Pinto-Martin J, Cuniff C. Timing of identification among children with an autism spectrum disorder: findings from a population-based surveillance study. J Am Acad Child Adolesc Psychiatry. 2009;48(5):474-83. doi: 10.1097/CHI.0b013e31819b3848. PubMed PMID: 19318992; PMCID: 3188985.

10. Huerta M, Lord C. Diagnostic evaluation of autism spectrum disorders. Pediatr Clin North Am. 2012;59(1):103-11, xi. doi: 10.1016/j.pcl.2011.10.018. PubMed PMID: 22284796; PMCID: 3269006.

11. Koegel LK, Koegel RL, Ashbaugh K, Bradshaw J. The importance of early identification and intervention for children with or at risk for autism spectrum disorders. Int J Speech Lang Pathol. 2014;16(1):50-6. doi: 10.3109/17549507.2013.861511. PubMed PMID: 24328352.

12. Vandeleur CL, Rothen S, Lustenberger Y, Glaus J, Castelao E, Preisig M. Inter-informant agreement and prevalence estimates for mood syndromes: direct interview vs. family history method. J Affect Disord. 2015;171:120-7. doi: 10.1016/j.jad.2014.08.048. PubMed PMID: 25303028.

13. Rothen S, Vandeleur CL, Lustenberger Y, Jeanpretre N, Ayer E, Gamma F, Halfon O, Fornerod D, Ferrero F, Preisig M. Parent-child agreement and prevalence estimates of diagnoses in childhood: direct interview versus family history method. Int J Methods Psychiatr Res. 2009;18(2):96-109. doi: 10.1002/mpr.281. PubMed PMID: 19507167.

14. Pereira AI, Muris P, Barros L, Goes R, Marques T, Russo V. Agreement and discrepancy between mother and child in the evaluation of children's anxiety symptoms and anxiety life interference. Eur Child Adolesc Psychiatry. 2015;24(3):327-37. doi: 10.1007/s00787-014-0583-2. PubMed PMID: 25059797.

15. De Los Reyes A, Kazdin AE. Informant discrepancies in the assessment of childhood psychopathology: a critical review, theoretical framework, and recommendations for further study. Psychol Bull. 2005;131(4):483-509. doi: 10.1037/0033-2909.131.4.483. PubMed PMID: 16060799.

16. Sucksmith E, Roth I, Hoekstra RA. Autistic traits below the clinical threshold: re-examining the broader autism phenotype in the 21st century. Neuropsychol Rev. 2011;21(4):360-89. doi: 10.1007/s11065-011-9183-9. PubMed PMID: 21989834.

17. Lyall K, Constantino JN, Weisskopf MG, Roberts AL, Ascherio A, Santangelo SL. Parental social responsiveness and risk of autism spectrum disorder in offspring. JAMA Psychiatry. 2014;71(8):936-42. doi: 10.1001/jamapsychiatry.2014.476. PubMed PMID: 25100167; PMCID: 4126195.

18. Seidman I, Yirmiya N, Milshtein S, Ebstein RP, Levi S. The Broad Autism Phenotype Questionnaire: mothers versus fathers of children with an autism spectrum disorder. J Autism Dev Disord. 2012;42(5):837-46. doi: 10.1007/s10803-011-1315-9. PubMed PMID: 21706249.

19. Maxwell CR, Parish-Morris J, Hsin O, Bush JC, Schultz RT. The broad autism phenotype predicts child functioning in autism spectrum disorders. J Neurodev Disord. 2013;5(1):25. doi: 10.1186/1866-1955-5-25. PubMed PMID: 24053506; PMCID: 3848833.

20. Schwichtenberg AJ, Young GS, Sigman M, Hutman T, Ozonoff S. Can family affectedness inform infant sibling outcomes of autism spectrum disorders? J Child Psychol Psychiatry. 2010;51(9):1021-30. doi: 10.1111/j.1469-7610.2010.02267.x. PubMed PMID: 20546079; PMCID: 2922056.

21. Dawson G, Estes A, Munson J, Schellenberg G, Bernier R, Abbott R. Quantitative assessment of autism symptom-related traits in probands and parents: Broader Phenotype Autism Symptom Scale. J Autism Dev Disord. 2007;37(3):523-36. doi: 10.1007/s10803-006-0182-2. PubMed PMID: 16868845.

22. Lainhart JE, Ozonoff S, Coon H, Krasny L, Dinh E, Nice J, McMahon W. Autism, regression, and the broader autism phenotype. Am J Med Genet. 2002;113(3):231-7. doi: 10.1002/ajmg.10615. PubMed PMID: 12439889.

23. Sasson NJ, Lam KS, Childress D, Parlier M, Daniels JL, Piven J. The broad autism phenotype questionnaire: prevalence and diagnostic classification. Autism Research. 2013;6(2):134-43. doi: 10.1002/aur.1272. PubMed PMID: 23427091; PMCID: 3661685.

24. Gerdts J, Bernier R. The broader autism phenotype and its implications on the etiology and treatment of autism spectrum disorders. Autism Research and Treatment. 2011;2011:545901. doi: 10.1155/2011/545901. PubMed PMID: 22937250; PMCID: 3420416.

25. Lai MC, Lombardo MV, Baron-Cohen S. Autism. Lancet. 2014;383(9920):896-910. doi: 10.1016/s0140-6736(13)61539-1.

26. Gaugler T, Klei L, Sanders SJ, Bodea CA, Goldberg AP, Lee AB, Mahajan M, Manaa D, Pawitan Y, Reichert J, Ripke S, Sandin S, Sklar P, Svantesson O, Reichenberg A, Hultman CM, Devlin B, Roeder K, Buxbaum JD. Most genetic risk for autism resides with common variation. Nat Genet. 2014;46(8):881-5. doi: 10.1038/ng.3039. PubMed PMID: 25038753; PMCID: 4137411.

27. Veatch OJ, Veenstra-Vanderweele J, Potter M, Pericak-Vance MA, Haines JL. Genetically meaningful phenotypic subgroups in autism spectrum disorders. Genes, Brain, and Behavior. 2014;13(3):276-85. doi: 10.1111/gbb.12117. PubMed PMID: 24373520.

28. Cholemkery H, Medda J, Lempp T, Freitag CM. Classifying Autism Spectrum Disorders by ADI-R: Subtypes or Severity Gradient? J Autism Dev Disord. 2016;46(7):2327-39. doi: 10.1007/s10803-016-2760-2. PubMed PMID: 26956715.

29. Lai MC, Lombardo MV, Chakrabarti B, Baron-Cohen S. Subgrouping the autism "spectrum": reflections on DSM-5. PLoS Biol. 2013;11(4):e1001544. doi: 10.1371/journal.pbio.1001544. PubMed PMID: 23630456; PMCID: 3635864.

30. Gould TD, Gottesman, II. Psychiatric endophenotypes and the development of valid animal models. Genes, Brain, and Behavior. 2006;5(2):113-9. doi: 10.1111/j.1601-183X.2005.00186.x. PubMed PMID: 16507002.

31. Gottesman, II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 2003;160(4):636-45. doi: 10.1176/appi.ajp.160.4.636. PubMed PMID: 12668349.

32. Christensen DL, Baio J, Van Naarden Braun K, Bilder D, Charles J, Constantino JN, Daniels J, Durkin MS, Fitzgerald RT, Kurzius-Spencer M, Lee LC, Pettygrove S, Robinson C, Schulz E, Wells C, Wingate MS, Zahorodny W, Yeargin-Allsopp M, Centers for Disease C, Prevention. Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years--Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. MMWR Surveill Summ. 2016;65(3):1-23. doi: 10.15585/mmwr.ss6503a1. PubMed PMID: 27031587.

33. Blumberg SJ, Bramlett MD, Kogan MD, Schieve LA, Jones JR, Lu MC. Changes in prevalence of parent-reported autism spectrum disorder in school-aged U.S. children: 2007 to 2011-2012. Natl Health Stat Report. 2013;65(65):1-11, 1 p following PubMed PMID: 24988818.

34. Levy SE, Giarelli E, Lee LC, Schieve LA, Kirby RS, Cunniff C, Nicholas J, Reaven J, Rice CE. Autism spectrum disorder and co-occurring developmental, psychiatric, and medical conditions among children in multiple populations of the United States. J Dev Behav Pediatr. 2010;31(4):267-75. doi: 10.1097/DBP.0b013e3181d5d03b. PubMed PMID: 20431403.

35. Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, Miller J, Fedele A, Collins J, Smith K, Lotspeich L, Croen LA, Ozonoff S, Lajonchere C, Grether JK, Risch N. Genetic heritability and shared environmental factors among twin pairs with autism. Arch Gen Psychiatry. 2011;68(11):1095-102. doi: 10.1001/archgenpsychiatry.2011.76. PubMed PMID: 21727249.

36. Colvert E, Tick B, McEwen F, Stewart C, Curran SR, Woodhouse E, Gillan N, Hallett V, Lietz S, Garnett T, Ronald A, Plomin R, Rijsdijk F, Happe F, Bolton P. Heritability of Autism Spectrum Disorder in a UK Population-Based Twin Sample. JAMA Psychiatry. 2015;72(5):415-23. doi: 10.1001/jamapsychiatry.2014.3028. PubMed PMID: 25738232; PMCID: 4724890.

37. Nordenbaek C, Jorgensen M, Kyvik KO, Bilenberg N. A Danish population-based twin study on autism spectrum disorders. Eur Child Adolesc Psychiatry. 2014;23(1):35-43. doi: 10.1007/s00787-013-0419-5. PubMed PMID: 23661220.

38. Rosenberg RE, Law JK, Yenokyan G, McGready J, Kaufmann WE, Law PA. Characteristics and concordance of autism spectrum disorders among 277 twin pairs. Arch Pediatr Adolesc Med. 2009;163(10):907-14. doi: 10.1001/archpediatrics.2009.98. PubMed PMID: 19805709.

39. Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, Reichenberg A. The familial risk of autism. JAMA. 2014;311(17):1770-7. doi: 10.1001/jama.2014.4144. PubMed PMID: 24794370; PMCID: 4381277.

40. Parellada M, Penzol MJ, Pina L, Moreno C, Gonzalez-Vioque E, Zalsman G, Arango C. The neurobiology of autism spectrum disorders. Eur Psychiatry. 2014;29(1):11-9. doi: 10.1016/j.eurpsy.2013.02.005. PubMed PMID: 24275633.

41. Geschwind DH. Genetics of autism spectrum disorders. Trends Cogn Sci. 2011;15(9):409-16. doi: 10.1016/j.tics.2011.07.003. PubMed PMID: 21855394; PMCID: 3691066.

42. Kassebaum NJ, Arora M, Barber RM, Bhutta ZA, Brown J, Carter A, Casey DC, Charlson FJ, Coates MM, Coggeshall M, Cornaby L, Dandona L, Dicker DJ, Erskine HE, Ferrari AJ, Fitzmaurice C, Foreman K, Forouzanfar MH, Fullman N, Gething PW, Goldberg EM, Graetz N, Haagsma JA, Johnson CO, Kemmer L, Khalil IA, Kinfu Y, Kutz MJ, Kyu HH, Leung J, Liang X, Lim SS, Lozano R, Mensah GA, Mikesell J, Mokdad AH, Mooney MD, Naghavi M, Nguyen G, Nsoesie E, Pigott DM, Pinho C, Rankin Z, Reinig N, Salomon JA, Sandar L, Smith A, Sorensen RJD, Stanaway J, Steiner C, Teeple S, Thomas BA, Troeger C, VanderZanden A, Wagner JA, Wanga V, Whiteford HA, Zhou M, Zoeckler L, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, Abraham B, Abubakar I, Abu-Raddad LJ, Abu-Rmeileh NME, Achoki T, Ackerman IN, Adebiyi AO, Adedeji IA, Adsuar JC, Afanvi KA, Afshin A, Agardh EE, Agarwal A, Agarwal SK, Ahmed MB, Kiadaliri AA, Ahmadieh H, Akseer N, Al-Aly Z, Alam K, Alam NKM, Aldhahri SF, Alegretti MA, Aleman AV, Alemu ZA, Alexander LT, Ali R, Alkerwi Aa, Alla F, Allebeck P, Alsharif U, Altirkawi KA, Martin EA, Alvis-Guzman N, Amare AT, Amberbir A, Amegah AK, Amini H, Ammar W, Amrock SM, Anderson GM, Anderson BO, Antonio CAT, Anwari P, Ärnlöv J, Arsenijevic VSA, Artaman A, Asayesh H, Asghar RJ, Avokpaho EFGA, Awasthi A, Quintanilla BPA, Azzopardi P, Bacha U, Badawi A, Balakrishnan K, Banerjee A, Barac A, Barker-Collo SL, Bärnighausen T, Barregard L, Barrero LH, Basu S, Bayou TA, Beardsley J, Bedi N, Beghi E, Bell B, Bell ML, Benjet C, Bennett DA, Bensenor IM, Berhane A, Bernabé E, Betsu BD, Beyene AS, Bhala N, Bhansali A, Bhatt S, Biadgilign S, Bienhoff K, Bikbov B, Abdulhak AAB, Bisanzio D, Bjertness E, Blore JD, Borschmann R, Boufous S, Bourne RRA, Brainin M, Brazinova A, Breitborde NJK, Brugha TS, Buchbinder R, Buckle GC, Butt ZA, Calabria B, Campos-Nonato IR, Campuzano JC, Carabin H, Carapetis JR, Cárdenas R, Carrero JJ, Castañeda-Orjuela CA, Rivas JC, Catalá-López F, Cavalleri F, Chang J-C, Chiang PP-C, Chibalabala M, Chibueze CE, Chisumpa VH, Choi J-YJ, Choudhury L, Christensen H, Ciobanu LG, Colistro V, Colomar M, Colquhoun SM, Cortinovis M, Crump JA, Damasceno A, Dandona R, Dargan PI, das Neves J, Davey G, Davis AC, Leo DD, Degenhardt L, Gobbo LCD, Derrett S, Jarlais DCD, deVeber GA, Dharmaratne SD, Dhillon PK, Ding EL, Doyle KE, Driscoll TR, Duan L, Dubey M, Duncan BB, Ebrahimi H, Ellenbogen RG, Elyazar I, Endries AY, Ermakov SP, Eshrati B, Esteghamati A, Estep K, Fahimi S, Farid TA, Farinha CSeS, Faro A, Farvid MS, Farzadfar F, Feigin VL, Fereshtehnejad S-M, Fernandes JG, Fernandes JC, Fischer F, Fitchett JRA, Foigt N, Fowkes

FGR, Franklin RC, Friedman J, Frostad J, Fürst T, Futran ND, Gabbe B, Gankpé FG, Garcia-Basteiro AL, Gebrehiwot TT, Gebremedhin AT, Geleijnse JM, Gibney KB, Gillum RF, Ginawi IAM, Giref AZ, Giroud M, Gishu MD, Godwin WW, Gomez-Dantes H, Gona P, Goodridge A, Gopalani SV, Gotay CC, Goto A, Gouda HN, Guo Y, Gupta R, Gupta R, Gupta V, Gutiérrez RA, Hafezi-Nejad N, Haile D, Hailu AD, Hailu GB, Halasa YA, Hamadeh RR, Hamidi S, Hammami M, Handal AJ, Hankey GJ, Harb HL, Harikrishnan S, Haro JM, Hassanvand MS, Hassen TA, Havmoeller R, Hay RJ, Hedayati MT, Heredia-Pi IB, Heydarpour P, Hoek HW, Hoffman DJ, Horino M, Horita N, Hosgood HD, Hoy DG, Hsairi M, Huang H, Huang JJ, Iburg KM, Idrisov BT, Innos K, Inoue M, Jacobsen KH, Jauregui A, Jayatilleke AU, Jeemon P, Jha V, Jiang G, Jiang Y, Jibat T, Jimenez-Corona A, Jin Y, Jonas JB, Kabir Z, Kajungu DK, Kalkonde Y, Kamal R, Kan H, Kandel A, Karch A, Karema CK, Karimkhani C, Kasaeian A, Katibeh M, Kaul A, Kawakami N, Kazi DS, Keiyoro PN, Kemp AH, Kengne AP, Keren A, Kesavachandran CN, Khader YS, Khan AR, Khan EA, Khang Y-H, Khoja TAM, Khubchandani J, Kieling C, Kim C-i, Kim D, Kim YJ, Kissoon N, Kivipelto M, Knibbs LD, Knudsen AK, Kokubo Y, Kolte D, Kopec JA, Koul PA, Koyanagi A, Defo BK, Kuchenbecker RS, Bicer BK, Kuipers EJ, Kumar GA, Kwan GF, Lalloo R, Lallukka T, Larsson A, Latif AA, Lavados PM, Lawrynowicz AEB, Leasher JL, Leigh J, Leung R, Li Y, Li Y, Lipshultz SE, Liu PY, Liu Y, Lloyd BK, Logroscino G, Looker KJ, Lotufo PA, Lucas RM, Lunevicius R, Lyons RA, Razek HMAE, Mahdavi M, Majdan M, Majeed A, Malekzadeh R, Malta DC, Marcenes W, Martinez-Raga J, Masiye F, Mason-Jones AJ, Matzopoulos R, Mayosi BM, McGrath JJ, McKee M, Meaney PA, Mehari A, Melaku YA, Memiah P, Memish ZA, Mendoza W, Meretoja A, Meretoja TJ, Mesfin YM, Mhimbira FA, Miller TR, Mills EJ, Mirarefin M, Mirrakhimov EM, Mitchell PB, Mock CN, Mohammad KA, Mohammadi A, Mohammed S, Monasta L, Hernandez JCM, Montico M, Moradi-Lakeh M, Mori R, Mueller UO, Mumford JE, Murdoch ME, Murthy GVS, Nachega JB, Naheed A, Naldi L, Nangia V, Newton JN, Ng M, Ngalesoni FN, Nguyen QL, Nisar MI, Pete PMN, Nolla JM, Norheim OF, Norman RE, Norrving B, Obermeyer CM, Ogbo FA, Oh I-H, Oladimeji O, Olivares PR, Olusanya BO, Olusanya JO, Oren E, Ortiz A, Ota E, Oyekale AS, Pa M, Park E-K, Parsaeian M, Patten SB, Patton GC, Pedro JM, Pereira DM, Perico N, Pesudovs K, Petzold M, Phillips MR, Piel FB, Pillay JD, Pishgar F, Plass D, Polinder S, Popova S, Poulton RG, Pourmalek F, Prasad NM, Qorbani M, Rabiee RHS, Radfar A, Rafay A, Rahimi K, Rahimi-Movaghar V, Rahman M, Rahman MHU, Rahman SU, Rai D, Rai RK, Rajsic S, Raju M, Ram U, Ranganathan K, Refaat AH, Reitsma MB, Remuzzi G, Resnikoff S, Reynolds A, Ribeiro AL, Ricci S, Roba HS, Rojas-Rueda D, Ronfani L, Roshandel G, Roth GA, Roy A, Sackey BB, Sagar R, Sanabria JR, Sanchez-Niño MD, Santos IS, Santos JV, Sarmiento-Suarez R, Sartorius B, Satpathy M, Savic M, Sawhney M, Schmidt MI, Schneider IJC, Schutte AE, Schwebel DC, Seedat S, Sepanlou SG, Servan-Mori EE, Shahraz S, Shaikh MA, Sharma R, She J, Sheikhbahaei S, Shen J, Sheth KN, Shibuya K, Shigematsu M, Shin M-J, Shiri R, Sigfusdottir ID, Silva DAS, Silverberg JI, Simard EP, Singh A, Singh JA, Singh PK, Skirbekk V, Skogen JC, Soljak M, Søreide K, Sorensen RJD, Sreeramareddy CT, Stathopoulou V, Steel N, Stein DJ, Stein MB, Steiner TJ, Stovner LJ, Stranges S, Stroumpoulis K, Sunguya BF, Sur PJ, Swaminathan S, Sykes BL, Szoeke CEI, Tabarés-Seisdedos R, Tandon N, Tanne D, Tavakkoli M, Taye B, Taylor HR, Ao BJT, Tegegne TK, Tekle DY, Terkawi AS, Tessema GA, Thakur JS, Thomson AJ, Thorne-Lyman AL, Thrift AG, Thurston GD, Tobe-Gai R, Tonelli M, Topor-Madry R, Topouzis F, Tran BX, Dimbuene ZT, Tsilimbaris M, Tura AK, Tuzcu EM, Tyrovolas S, Ukwaja KN, Undurraga EA, Uneke CJ, Uthman OA, van Gool CH, van Os J, Vasankari T, Vasconcelos AMN, Venketasubramanian N, Violante FS, Vlassov VV, Vollset SE, Wagner GR, Wallin MT, Wang L, Weichenthal S, Weiderpass E, Weintraub RG, Werdecker A, Westerman R, Wijeratne T, Wilkinson JD, Williams HC, Wiysonge CS, Woldeyohannes SM, Wolfe CDA, Won S, Xu G, Yadav AK, Yakob B, Yan LL, Yano Y, Yaseri M, Ye P, Yip P, Yonemoto N, Yoon S-J, Younis MZ, Yu C, Zaidi Z, Zaki MES, Zeeb H, Zodpey S, Zonies D, Zuhlke LJ, Vos T, Lopez AD, Murray CJL. Global, regional, and national disability-adjusted life-years (DALYs) for 315

diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet.388(10053):1603-58. doi: http://dx.doi.org/10.1016/S0140-6736(16)31460-X.

43. Croen LA, Zerbo O, Qian Y, Massolo ML, Rich S, Sidney S, Kripke C. The health status of adults on the autism spectrum. Autism. 2015;19(7):814-23. Epub 2015/04/26. doi: 10.1177/1362361315577517. PubMed PMID: 25911091.

44. Kohane IS, McMurry A, Weber G, MacFadden D, Rappaport L, Kunkel L, Bickel J, Wattanasin N, Spence S, Murphy S, Churchill S. The co-morbidity burden of children and young adults with autism spectrum disorders. PLoS One. 2012;7(4):e33224. doi: 10.1371/journal.pone.0033224. PubMed PMID: 22511918; PMCID: 3325235.

45. Chiang HM, Wineman I. Factors associated with quality of life in individuals with autism spectrum disorders: A review of literature. Res Autism Spectr Disord. 2014;8(8):974-86. doi: 10.1016/j.rasd.2014.05.003. PubMed PMID: WOS:000337982600006.

46. Reichow B, Barton EE, Boyd BA, Hume K. Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). Cochrane Database Syst Rev. 2012;10:CD009260. Epub 2012/10/19. doi: 10.1002/14651858.CD009260.pub2. PubMed PMID: 23076956.

47. Horlin C, Falkmer M, Parsons R, Albrecht MA, Falkmer T. The cost of autism spectrum disorders. PLoS One. 2014;9(9):e106552. doi: 10.1371/journal.pone.0106552. PubMed PMID: 25191755; PMCID: 4156354.

48. Cidav Z, Marcus SC, Mandell DS. Implications of childhood autism for parental employment and earnings. Pediatrics. 2012;129(4):617-23. doi: 10.1542/peds.2011-2700. PubMed PMID: 22430453; PMCID: 3356150.

49. Lavelle TA, Weinstein MC, Newhouse JP, Munir K, Kuhlthau KA, Prosser LA. Economic burden of childhood autism spectrum disorders. Pediatrics. 2014;133(3):e520-9. doi: 10.1542/peds.2013-0763. PubMed PMID: 24515505.

50. Leigh JP, Grosse SD, Cassady D, Melnikow J, Hertz-Picciotto I. Spending by California's Department of Developmental Services for Persons with Autism across Demographic and Expenditure Categories. PLoS One. 2016;11(3):e0151970. doi: 10.1371/journal.pone.0151970. PubMed PMID: 27015098; PMCID: 4807877.

51. Peters-Scheffer N, Didden R, Korzilius H, Matson J. Cost comparison of early intensive behavioral intervention and treatment as usual for children with autism spectrum disorder in The Netherlands. Res Dev Disabil. 2012;33(6):1763-72. doi: 10.1016/j.ridd.2012.04.006. PubMed PMID: 22705454.

52. Anderson GM. Autism biomarkers: challenges, pitfalls and possibilities. J Autism Dev Disord. 2015;45(4):1103-13. doi: 10.1007/s10803-014-2225-4. PubMed PMID: 25193140.

53. Jordan BR, Tsai DF. Whole-genome association studies for multigenic diseases: ethical dilemmas arising from commercialization--the case of genetic testing for autism. J Med Ethics. 2010;36(7):440-4. doi: 10.1136/jme.2009.031385. PubMed PMID: 20558435.

54. Baird G, Douglas HR, Murphy MS. Recognising and diagnosing autism in children and young people: summary of NICE guidance. BMJ. 2011;343:d6360. doi: 10.1136/bmj.d6360. PubMed PMID: 22021468.

55. Zwaigenbaum L, Bauman ML, Fein D, Pierce K, Buie T, Davis PA, Newschaffer C, Robins DL, Wetherby A, Choueiri R, Kasari C, Stone WL, Yirmiya N, Estes A, Hansen RL, McPartland JC, Natowicz MR, Carter A, Granpeesheh D, Mailloux Z, Smith Roley S, Wagner S. Early Screening of Autism Spectrum Disorder: Recommendations for Practice and Research. Pediatrics. 2015;136 Suppl 1:S41-59. Epub 2015/10/03. doi: 10.1542/peds.2014-3667D. PubMed PMID: 26430169.

56. Mandell D, Mandy W. Should all young children be screened for autism spectrum disorder? Autism. 2015;19(8):895-6. doi: 10.1177/1362361315608323.

57. US Preventative Services Task Force. Draft Recommendations Statement: Autism Spectrum Disorder in Young Children: Screening. 2015 [December, 21, 2015]. Available from: http://www.uspreventiveservicestaskforce.org/.

58. Council on Children With D, Section on Developmental Behavioral P, Bright Futures Steering C, Medical Home Initiatives for Children With Special Needs Project Advisory C. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. Pediatrics. 2006;118(1):405-20. doi: 10.1542/peds.2006-1231. PubMed PMID: 16818591.

59. Robins DL, Fein D. Modified Checklist for Autism in Toddlers. 1999.

60. Constantino JN. Social responsiveness scale. Los Angeles, CA: Western Psychological Services; 2002.

61. Rutter M, Bailey A, Lord C. SCQ: Social Communication Questionnaire. Los Angeles, CA: Western Psychological Services; 2003.

62. Kim SH, Lord C. Combining information from multiple sources for the diagnosis of autism spectrum disorders for toddlers and young preschoolers from 12 to 47 months of age. J Child

Psychol Psychiatry. 2012;53(2):143-51. doi: 10.1111/j.1469-7610.2011.02458.x. PubMed PMID: 21883205; PMCID: 3235227.

63. Le Couteur A, Haden G, Hammal D, McConachie H. Diagnosing autism spectrum disorders in pre-school children using two standardised assessment instruments: the ADI-R and the ADOS. J Autism Dev Disord. 2008;38(2):362-72. doi: 10.1007/s10803-007-0403-3. PubMed PMID: 17605097.

64. Mazefsky CA, Oswald DP. The discriminative ability and diagnostic utility of the ADOS-G, ADI-R, and GARS for children in a clinical setting. Autism. 2006;10(6):533-49. doi: 10.1177/1362361306068505. PubMed PMID: 17088271.

65. Leekam SR, Libby SJ, Wing L, Gould J, Taylor C. The Diagnostic Interview for Social and Communication Disorders: algorithms for ICD-10 childhood autism and Wing and Gould autistic spectrum disorder. J Child Psychol Psychiatry. 2002;43(3):327-42. doi: 10.1111/1469-7610.00024. PubMed PMID: 11944875.

66. Skuse D, Warrington R, Bishop D, Chowdhury U, Lau J, Mandy W, Place M. The developmental, dimensional and diagnostic interview (3di): a novel computerized assessment for autism spectrum disorders. J Am Acad Child Adolesc Psychiatry. 2004;43(5):548-58. Epub 2004/04/22. doi: 10.1097/00004583-200405000-00008. PubMed PMID: 15100561.

67. Rutter M, Le Couteur A, Lord C. ADI-R: the Autism Diagnostic Interview-Revised2003.

68. Schopler E, Rechler R, Rochen Renner B. The child autism rating scale. Western Psychological Services; 1988.

69. Lord C, Risi S, Lambrecht L, Cook EH, Jr., Leventhal BL, DiLavore PC, Pickles A, Rutter M. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord. 2000;30(3):205-23. doi: 10.1023/A:1005592401947. PubMed PMID: 11055457.

70. Aggarwal S, Angus B. Misdiagnosis versus missed diagnosis: diagnosing autism spectrum disorder in adolescents. Australas Psychiatry. 2015;23(2):120-3. doi: 10.1177/1039856214568214. PubMed PMID: 25653302.

71. Van Schalkwyk GI, Peluso F, Qayyum Z, McPartland JC, Volkmar FR. Varieties of misdiagnosis in ASD: an illustrative case series. J Autism Dev Disord. 2015;45(4):911-8. doi: 10.1007/s10803-014-2239-y. PubMed PMID: 25218849.

72. Jones RM, Risi S, Wexler D, Anderson D, Corsello C, Pickles A, Lord C. How interview questions are placed in time influences caregiver description of social communication symptoms

on the ADI-R. J Child Psychol Psychiatry. 2015;56(5):577-85. doi: 10.1111/jcpp.12325. PubMed PMID: 25243378; PMCID: 4369461.

73. Hus V, Lord C. Effects of child characteristics on the Autism Diagnostic Interview-Revised: implications for use of scores as a measure of ASD severity. J Autism Dev Disord. 2013;43(2):371-81. doi: 10.1007/s10803-012-1576-y. PubMed PMID: 22729382; PMCID: 3493749.

74. Vanegas SB, Magana S, Morales M, McNamara E. Clinical Validity of the ADI-R in a US-Based Latino Population. J Autism Dev Disord. 2016;46(5):1623-35. doi: 10.1007/s10803-015-2690-4. PubMed PMID: 26742934; PMCID: 4826821.

75. Chilcoat HD, Breslau N. Does psychiatric history bias mothers' reports? An application of a new analytic approach. J Am Acad Child Adolesc Psychiatry. 1997;36(7):971-9. doi: 10.1097/00004583-199707000-00020. PubMed PMID: 9204676.

76. Hughes EK, Gullone E. Discrepancies between adolescent, mother, and father reports of adolescent internalizing symptom levels and their association with parent symptoms. J Clin Psychol. 2010;66(9):978-95. doi: 10.1002/jclp.20695. PubMed PMID: 20694961.

77. Verweij KH, Derks EM, Hendriks EJ, Cahn W. The influence of informant characteristics on the reliability of family history interviews. Twin Res Hum Genet. 2011;14(3):217-20. doi: 10.1375/twin.14.3.217. PubMed PMID: 21623650.

78. Ringoot AP, Tiemeier H, Jaddoe VW, So P, Hofman A, Verhulst FC, Jansen PW. Parental depression and child well-being: young children's self-reports helped addressing biases in parent reports. J Clin Epidemiol. 2015;68(8):928-38. doi: 10.1016/j.jclinepi.2015.03.009. PubMed PMID: 25900418.

79. Heun R, Muller H, Papassotiropoulos A. Differential validity of informant-based diagnoses of dementia and depression in index subjects and in their first-degree relatives. Soc Psychiatry Psychiatr Epidemiol. 1998;33(10):510-3. doi: Doi 10.1007/S001270050087. PubMed PMID: WOS:000075878000008.

80. Gartstein MA, Bridgett DJ, Dishion TJ, Kaufman NK. Depressed Mood and Maternal Report of Child Behavior Problems: Another Look at the Depression-Distortion Hypothesis. J Appl Dev Psychol. 2009;30(2):149-60. doi: 10.1016/j.appdev.2008.12.001. PubMed PMID: 20161323; PMCID: 2678740.

81. Kendler KS, Silberg JL, et al. The Family History Method: Whose Psychiatric History Is Measured? Am J Psychiatry. 1991;148(11):1501-4. PubMed PMID: 220480806; 1928463; 00929020.

82. Briggs-Gowan MJ, Carter AS, Schwab-Stone M. Discrepancies among mother, child, and teacher reports: examining the contributions of maternal depression and anxiety. J Abnorm Child Psychol. 1996;24(6):749-65. Epub 1996/12/01. PubMed PMID: 8970908.

83. Daryanani I, Hamilton JL, Shapero BG, Burke TA, Abramson LY, Alloy LB. Differential Reporting of Adolescent Stress as a Function of Maternal Depression History. Cognit Ther Res. 2015;39(2):110-9. doi: 10.1007/s10608-014-9654-4. PubMed PMID: 25798018; PMCID: 4361769.

84. Torbjörn Ohrt ISL-HT. Cognitive distortions in panic disorder and major depression: Specificity for depressed mood. Nord J Psychiatry. 1999;53(6):459-64. doi: 10.1080/080394899427719.

85. Richters JE. Depressed mothers as informants about their children: A critical review of the evidence for distortion. Psychol Bull. 1992;112(3):485-99. doi: 10.1037/0033-2909.112.3.485. PubMed PMID: 1993-13744-001.

86. Hoza B, Pelham WE, Jr., Dobbs J, Owens JS, Pillow DR. Do boys with attention-deficit/hyperactivity disorder have positive illusory self-concepts? J Abnorm Psychol. 2002;111(2):268-78. doi: 10.1037/0021-843x.111.2.268.

87. De Los Reyes A, Kazdin AE. Informant Discrepancies in Assessing Child Dysfunction Relate to Dysfunction Within Mother-Child Interactions. Journal of child and family studies. 2006;15(5):643-61. doi: 10.1007/s10826-006-9031-3. PubMed PMID: 21243074; PMCID: 3020626.

88. Lerner MD, Calhoun CD, Mikami AY, De Los Reyes A. Understanding parent-child social informant discrepancy in youth with high functioning autism spectrum disorders. J Autism Dev Disord. 2012;42(12):2680-92. doi: 10.1007/s10803-012-1525-9. PubMed PMID: 22456819.

89. Mikami AY, Calhoun CD, Abikoff HB. Positive illusory bias and response to behavioral treatment among children with attention-deficit/hyperactivity disorder. J Clin Child Adolesc Psychol. 2010;39(3):373-85. doi: 10.1080/15374411003691735. PubMed PMID: 20419578.

90. De Los Reyes A, Kazdin AE. When the Evidence Says, "Yes, No, and Maybe So": Attending to and Interpreting Inconsistent Findings Among Evidence-Based Interventions. Curr Dir Psychol Sci. 2008;17(1):47-51. Epub 2008/02/01. doi: 10.1111/j.1467-8721.2008.00546.x. PubMed PMID: 21243087; PMCID: PMC3021137.

91. Noterdaeme M, Mildenberger K, Sitter S, Amorosa H. Parent information and direct observation in the diagnosis of pervasive and specific developmental disorders. Autism. 2002;6(2):159-68. doi: 10.1177/1362361302006002003. PubMed PMID: 12083282.

92. De la Marche W, Noens I, Kuppens S, Spilt JL, Boets B, Steyaert J. Measuring quantitative autism traits in families: informant effect or intergenerational transmission? Eur Child Adolesc Psychiatry. 2015;24(4):385-95. doi: 10.1007/s00787-014-0586-z. PubMed PMID: 25086652.

93. Chapman TF, Mannuzza S, Klein DF, Fyer AJ. Effects of informant mental disorder on psychiatric family history data. Am J Psychiatry. 1994;151(4):574-9. doi: 10.1176/ajp.151.4.574. PubMed PMID: 8147456.

94. Collishaw S, Goodman R, Ford T, Rabe-Hesketh S, Pickles A. How far are associations between child, family and community factors and child psychopathology informant-specific and informant-general? J Child Psychol Psychiatry. 2009;50(5):571-80. doi: 10.1111/j.1469-7610.2008.02026.x. PubMed PMID: 19207620.

95. Muller JM, Achtergarde S, Furniss T. The influence of maternal psychopathology on ratings of child psychiatric symptoms: an SEM analysis on cross-informant agreement. Eur Child Adolesc Psychiatry. 2011;20(5):241-52. doi: 10.1007/s00787-011-0168-2. PubMed PMID: 21416135.

96. De Los Reyes A, Youngstrom EA, Pabon SC, Youngstrom JK, Feeny NC, Findling RL. Internal consistency and associated characteristics of informant discrepancies in clinic referred youths age 11 to 17 years. J Clin Child Adolesc Psychol. 2011;40(1):36-53. doi: 10.1080/15374416.2011.533402. PubMed PMID: 21229442; PMCID: 3078639.

97. Randazzo KV, Landsverk J, Ganger W. Three informants' reports of child behavior: parents, teachers, and foster parents. J Am Acad Child Adolesc Psychiatry. 2003;42(11):1343-50. doi: 10.1097/01.chi.0000085753.71002.da. PubMed PMID: 14566172.

98. Boyle MH, Pickles AR. Influence of maternal depressive symptoms on ratings of childhood behavior. J Abnorm Child Psychol. 1997;25(5):399-412. doi: 10.1023/A:1025737124888. PubMed PMID: 9421748.

99. Zablotsky B, Bramlett M, Blumberg SJ. Factors associated with parental ratings of condition severity for children with autism spectrum disorder. Disabil Health J. 2015;8(4):626-34. doi: 10.1016/j.dhjo.2015.03.006. PubMed PMID: 25910554; PMCID: 4652641.

100. Persico AM, Napolioni V. Autism genetics. Behav Brain Res. 2013;251:95-112. doi: 10.1016/j.bbr.2013.06.012. PubMed PMID: 23769996.

101. Munson J, Dawson G, Sterling L, Beauchaine T, Zhou A, Elizabeth K, Lord C, Rogers S, Sigman M, Estes A, Abbott R. Evidence for latent classes of IQ in young children with autism spectrum disorder. Am J Ment Retard. 2008;113(6):439-52. doi: 10.1352/2008.113:439-452. PubMed PMID: 19127655; PMCID: 2991056.

102. Georgiades S, Boyle M, Szatmari P, Hanna S, Duku E, Zwaigenbaum L, Bryson S, Fombonne E, Volden J, Mirenda P, Smith I, Roberts W, Vaillancourt T, Waddell C, Bennett T, Elsabbagh M, Thompson A, Pathways in ASDST. Modeling the phenotypic architecture of autism symptoms from time of diagnosis to age 6. J Autism Dev Disord. 2014;44(12):3045-55. doi: 10.1007/s10803-014-2167-x. PubMed PMID: 24958435.

103. Georgiades S, Szatmari P, Boyle M, Hanna S, Duku E, Zwaigenbaum L, Bryson S, Fombonne E, Volden J, Mirenda P, Smith I, Roberts W, Vaillancourt T, Waddell C, Bennett T, Thompson A, Pathways in ASDST. Investigating phenotypic heterogeneity in children with autism spectrum disorder: a factor mixture modeling approach. J Child Psychol Psychiatry. 2013;54(2):206-15. doi: 10.1111/j.1469-7610.2012.02588.x. PubMed PMID: 22862778.

104. Bernier R, Gerdts J, Munson J, Dawson G, Estes A. Evidence for broader autism phenotype characteristics in parents from multiple-incidence autism families. Autism Research. 2012;5(1):13-20. doi: 10.1002/aur.226. PubMed PMID: 21905246; PMCID: 3237782.

105. Duvall JA, Lu A, Cantor RM, Todd RD, Constantino JN, Geschwind DH. A quantitative trait locus analysis of social responsiveness in multiplex autism families. Am J Psychiatry. 2007;164(4):656-62. Epub 2007/04/04. doi: 10.1176/ajp.2007.164.4.656. PubMed PMID: 17403980.

106. Gerdts J, Bernier R, Dawson G, Estes A. The broader autism phenotype in simplex and multiplex families. J Autism Dev Disord. 2013;43(7):1597-605. doi: 10.1007/s10803-012-1706-6. PubMed PMID: 23117424.

107. Virkud YV, Todd RD, Abbacchi AM, Zhang Y, Constantino JN. Familial aggregation of quantitative autistic traits in multiplex versus simplex autism. Am J Med Genet B Neuropsychiatr Genet. 2009;150B(3):328-34. doi: 10.1002/ajmg.b.30810. PubMed PMID: 18618672; PMCID: 2819431.

108. Lowe JK, Werling DM, Constantino JN, Cantor RM, Geschwind DH. Social responsiveness, an autism endophenotype: genomewide significant linkage to two regions on chromosome 8. Am J Psychiatry. 2015;172(3):266-75. doi: 10.1176/appi.ajp.2014.14050576. PubMed PMID: 25727539; PMCID: 4523091.

109. Losh M, Piven J. Social-cognition and the broad autism phenotype: identifying genetically meaningful phenotypes. J Child Psychol Psychiatry. 2007;48(1):105-12. doi: 10.1111/j.1469-7610.2006.01594.x. PubMed PMID: 17244276.

110. Connolly JJ, Glessner JT, Hakonarson H. A genome-wide association study of autism incorporating autism diagnostic interview-revised, autism diagnostic observation schedule, and social responsiveness scale. Child Dev. 2013;84(1):17-33. doi: 10.1111/j.1467-8624.2012.01838.x. PubMed PMID: 22935194.

111. Butler MG, Dasouki MJ, Zhou XP, Talebizadeh Z, Brown M, Takahashi TN, Miles JH, Wang CH, Stratton R, Pilarski R, Eng C. Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. J Med Genet. 2005;42(4):318-21. doi: 10.1136/jmg.2004.024646. PubMed PMID: 15805158; PMCID: 1736032.

112. Francis SM, Kistner-Griffin E, Yan Z, Guter S, Cook EH, Jacob S. Variants in Adjacent Oxytocin/Vasopressin Gene Region and Associations with ASD Diagnosis and Other Autism Related Endophenotypes. Front Neurosci. 2016;10:195. doi: 10.3389/fnins.2016.00195. PubMed PMID: 27242401; PMCID: 4863894.

113. Alarcon M, Yonan AL, Gilliam TC, Cantor RM, Geschwind DH. Quantitative genome scan and Ordered-Subsets Analysis of autism endophenotypes support language QTLs. Mol Psychiatry. 2005;10(8):747-57. doi: 10.1038/sj.mp.4001666. PubMed PMID: 15824743.

114. Liu XQ, Paterson AD, Szatmari P, Autism Genome Project C. Genome-wide linkage analyses of quantitative and categorical autism subphenotypes. Biol Psychiatry. 2008;64(7):561-70. doi: 10.1016/j.biopsych.2008.05.023. PubMed PMID: 18632090; PMCID: 2670970.

115. Kanner L. Autistic Disturbances of Affective Contact. Nervous Child. 1943;2(3):217-50. Epub PubMed PMID: WOS:000205224200001.

116. Wolff S, Narayan S, Moyes B. Personality characteristics of parents of autistic children: a controlled study. J Child Psychol Psychiatry. 1988;29(2):143-53. Epub 1988/03/01. PubMed PMID: 3372611.

117. Landa R, Folstein SE, Isaacs C. Spontaneous narrative-discourse performance of parents of autistic individuals. J Speech Hear Res. 1991;34(6):1339-45. Epub 1991/12/01. PubMed PMID: 1787716.

118. Landa R, Piven J, Wzorek MM, Gayle JO, Chase GA, Folstein SE. Social language use in parents of autistic individuals. Psychol Med. 1992;22(1):245-54. Epub 1992/02/01. PubMed PMID: 1574562.

119. Piven J, Wzorek M, Landa R, Lainhart J, Bolton P, Chase GA, Folstein S. Personality characteristics of the parents of autistic individuals. Psychol Med. 1994;24(3):783-95. Epub 1994/08/01. PubMed PMID: 7991760.

120. Piven J, Palmer P. Psychiatric disorder and the broad autism phenotype: evidence from a family study of multiple-incidence autism families. Am J Psychiatry. 1999;156(4):557-63. doi: 10.1176/ajp.156.4.557. PubMed PMID: 10200734.

121. Bolton P, Macdonald H, Pickles A, Rios P, Goode S, Crowson M, Bailey A, Rutter M. A case-control family history study of autism. J Child Psychol Psychiatry. 1994;35(5):877-900. Epub 1994/07/01. PubMed PMID: 7962246.

122. Ingersoll B, Hopwood CJ, Wainer A, Brent Donnellan M. A comparison of three self-report measures of the broader autism phenotype in a non-clinical sample. J Autism Dev Disord. 2011;41(12):1646-57. doi: 10.1007/s10803-011-1192-2. PubMed PMID: 21331821.

123. Constantino JN, Todd RD. Intergenerational transmission of subthreshold autistic traits in the general population. Biol Psychiatry. 2005;57(6):655-60. doi: 10.1016/j.biopsych.2004.12.014. PubMed PMID: 15780853.

124. Constantino JN. The quantitative nature of autistic social impairment. Pediatr Res. 2011;69(5 Pt 2):55R-62R. Epub 2011/02/04. doi: 10.1203/PDR.0b013e318212ec6e. PubMed PMID: 21289537; PMCID: 3086844.

125. Robinson EB, Koenen KC, McCormick MC, Munir K, Hallett V, Happe F, Plomin R, Ronald A. Evidence that autistic traits show the same etiology in the general population and at the quantitative extremes (5%, 2.5%, and 1%). Arch Gen Psychiatry. 2011;68(11):1113-21. doi: 10.1001/archgenpsychiatry.2011.119. PubMed PMID: 22065527; PMCID: 3708488.

126. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The Autism-Spectrum Quotient (AQ): Evidence from Asperger Syndrome/High-Functioning Autism, Malesand Females, Scientists and Mathematicians. J Autism Dev Disord. 2001;31(1):5-17. doi: 10.1023/a:1005653411471.

127. Hoekstra RA, Bartels M, Verweij CJ, Boomsma DI. Heritability of autistic traits in the general population. Arch Pediatr Adolesc Med. 2007;161(4):372-7. doi: 10.1001/archpedi.161.4.372. PubMed PMID: 17404134.

128. Berthoz S, Lalanne C, Crane L, Hill EL. Investigating emotional impairments in adults with autism spectrum disorders and the broader autism phenotype. Psychiatry Res. 2013;208(3):257-64. doi: 10.1016/j.psychres.2013.05.014. PubMed PMID: 23747233.

129. Bishop DVM, Maybery M, Maley A, Wong D, Hill W, Hallmayer J. Using self-report to identify the broad phenotype in parents of children with autistic spectrum disorders: a study using the Autism-Spectrum Quotient. Journal of Child Psychology and Psychiatry. 2004;45(8):1431-6. doi: 10.1111/j.1469-7610.2004.00325.x. PubMed PMID: WOS:000224678100011.

130. De la Marche W, Noens I, Luts J, Scholte E, Van Huffel S, Steyaert J. Quantitative autism traits in first degree relatives: evidence for the broader autism phenotype in fathers, but

not in mothers and siblings. Autism. 2012;16(3):247-60. doi: 10.1177/1362361311421776. PubMed PMID: 21949002.

131. Grove R, Baillie A, Allison C, Baron-Cohen S, Hoekstra RA. Exploring the quantitative nature of empathy, systemising and autistic traits using factor mixture modelling. Br J Psychiatry. 2015;207(5):400-6. Epub 2015/09/19. doi: 10.1192/bjp.bp.114.155101. PubMed PMID: 26382949.

132. Hasegawa C, Kikuchi M, Yoshimura Y, Hiraishi H, Munesue T, Nakatani H, Higashida H, Asada M, Oi M, Minabe Y. Broader autism phenotype in mothers predicts social responsiveness in young children with autism spectrum disorders. Psychiatry Clin Neurosci. 2015;69(3):136-44. doi: 10.1111/pcn.12210. PubMed PMID: 24902617.

133. Ingersoll B, Meyer K, Becker MW. Increased rates of depressed mood in mothers of children with ASD associated with the presence of the broader autism phenotype. Autism Research. 2011;4(2):143-8. doi: 10.1002/aur.170. PubMed PMID: 21480539.

134. Kadak MT, Demirel OF, Yavuz M, Demir T. Recognition of emotional facial expressions and broad autism phenotype in parents of children diagnosed with autistic spectrum disorder. Compr Psychiatry. 2014;55(5):1146-51. doi: 10.1016/j.comppsych.2014.03.004. PubMed PMID: 24742718.

135. Kose S, Bora E, Erermis S, Ozbaran B, Bildik T, Aydin C. Broader autistic phenotype in parents of children with autism: Autism Spectrum Quotient-Turkish version. Psychiatry Clin Neurosci. 2013;67(1):20-7. Epub 2013/01/22. doi: 10.1111/pcn.12005. PubMed PMID: 23331285.

136. Losh M, Childress D, Lam K, Piven J. Defining key features of the broad autism phenotype: a comparison across parents of multiple- and single-incidence autism families. Am J Med Genet B Neuropsychiatr Genet. 2008;147B(4):424-33. doi: 10.1002/ajmg.b.30612. PubMed PMID: 17948871; PMCID: 2746421.

137. Meera SS, Girimaji SC, Seshadri SP, Philip M, Shivashankar N, Morgan P, Piven J. Translation of the Broad Autism Phenotype Questionnaire to an Indian language: A description of the process. Asian J Psychiatr. 2015;15:62-7. doi: 10.1016/j.ajp.2015.04.013. PubMed PMID: 26003779.

138. Mohammadi MR, Zarafshan H, Ghasempour S. Broader Autism Phenotype in Iranian Parents of Children with Autism Spectrum Disorders vs. Normal Children. Iranian Journal of Psychiatry. 2012;7(4):157-63. Epub 2013/02/15. PubMed PMID: 23408558; PMCID: 3570573.

139. Pickles A, Starr E, Kazak S, Bolton P, Papanikolaou K, Bailey A, Goodman R, Rutter M. Variable expression of the autism broader phenotype: findings from extended pedigrees. J Child Psychol Psychiatry. 2000;41(4):491-502. Epub 2000/06/03. PubMed PMID: 10836679.

140. Piven J, Palmer P, Jacobi D, Childress D, Arndt S. Broader autism phenotype: evidence from a family history study of multiple-incidence autism families. Am J Psychiatry. 1997;154(2):185-90. Epub 1997/02/01. doi: 10.1176/ajp.154.2.185. PubMed PMID: 9016266.

141. Ruta L, Mazzone D, Mazzone L, Wheelwright S, Baron-Cohen S. The Autism-Spectrum Quotient--Italian version: a cross-cultural confirmation of the broader autism phenotype. J Autism Dev Disord. 2012;42(4):625-33. doi: 10.1007/s10803-011-1290-1. PubMed PMID: 21626054.

142. Scheeren AM, Stauder JE. Broader autism phenotype in parents of autistic children: reality or myth? J Autism Dev Disord. 2008;38(2):276-87. doi: 10.1007/s10803-007-0389-x. PubMed PMID: 17588199.

143. Starr E, Berument SK, Pickles A, Tomlins M, Bailey A, Papanikolaou K, Rutter M. A family genetic study of autism associated with profound mental retardation. J Autism Dev Disord. 2001;31(1):89-96. Epub 2001/07/07. PubMed PMID: 11439758.

144. Shi LJ, Ou JJ, Gong JB, Wang SH, Zhou YY, Zhu FR, Liu XD, Zhao JP, Luo XR. Broad autism phenotype features of Chinese parents with autistic children and their associations with severity of social impairment in probands. BMC Psychiatry. 2015;15:168. doi: 10.1186/s12888-015-0568-9. PubMed PMID: 26202327; PMCID: 4511534.

145. Wheelwright S, Auyeung B, Allison C, Baron-Cohen S. Defining the broader, medium and narrow autism phenotype among parents using the Autism Spectrum Quotient (AQ). Mol Autism. 2010;1(1):10. doi: 10.1186/2040-2392-1-10. PubMed PMID: 20678260; PMCID: 2913943.

146. Zhang L, Sun Y, Chen F, Wu D, Tang J, Han X, Ye J, Wang K. Psychometric properties of the Autism-Spectrum Quotient in both clinical and non-clinical samples: Chinese version for mainland China. BMC Psychiatry. 2016;16(1):213. doi: 10.1186/s12888-016-0915-5. PubMed PMID: 27388335; PMCID: 4936315.

147. Hurley RS, Losh M, Parlier M, Reznick JS, Piven J. The broad autism phenotype questionnaire. J Autism Dev Disord. 2007;37(9):1679-90. doi: 10.1007/s10803-006-0299-3. PubMed PMID: 17146701.

148. Davidson J, Goin-Kochel RP, Green-Snyder LA, Hundley RJ, Warren Z, Peters SU. Expression of the broad autism phenotype in simplex autism families from the Simons Simplex

Collection. J Autism Dev Disord. 2014;44(10):2392-9. doi: 10.1007/s10803-012-1492-1. PubMed PMID: 22382605.

149. Nishiyama T, Suzuki M, Adachi K, Sumi S, Okada K, Kishino H, Sakai S, Kamio Y, Kojima M, Suzuki S, Kanne SM. Comprehensive comparison of self-administered questionnaires for measuring quantitative autistic traits in adults. J Autism Dev Disord. 2014;44(5):993-1007. doi: 10.1007/s10803-013-2020-7. PubMed PMID: 24342972.

150. Parr JR, De Jonge MV, Wallace S, Pickles A, Rutter ML, Le Couteur AS, van Engeland H, Wittemeyer K, McConachie H, Roge B, Mantoulan C, Pedersen L, Isager T, Poustka F, Bolte S, Bolton P, Weisblatt E, Green J, Papanikolaou K, Baird G, Bailey AJ. New Interview and Observation Measures of the Broader Autism Phenotype: Description of Strategy and Reliability Findings for the Interview Measures. Autism Research. 2015;8(5):522-33. doi: 10.1002/aur.1466. PubMed PMID: 25959701; PMCID: 4690162.

151. Constantino JN, Todd RD. Autistic traits in the general population: a twin study. Arch Gen Psychiatry. 2003;60(5):524-30. doi: 10.1001/archpsyc.60.5.524. PubMed PMID: 12742874.

152. Ruzich E, Allison C, Smith P, Watson P, Auyeung B, Ring H, Baron-Cohen S. Measuring autistic traits in the general population: a systematic review of the Autism-Spectrum Quotient (AQ) in a nonclinical population sample of 6,900 typical adult males and females. Mol Autism. 2015;6:2. doi: 10.1186/2040-2392-6-2. PubMed PMID: 25874074; PMCID: 4396128.

153. Constantino JN, Gruber CP. Social Responsiveness Scale, Second Edition. Los Angeles, CA: Western Psychological Services; 2012.

154. Page J, Constantino JN, Zambrana K, Martin E, Tunc I, Zhang Y, Abbacchi A, Messinger D. Quantitative autistic trait measurements index background genetic risk for ASD in Hispanic families. Molecular Autism. 2016;7(1):39. doi: 10.1186/s13229-016-0100-1. PubMed PMID: 27606047; PMCID: 5013609.

155. Pickles A, Parr JR, Rutter ML, De Jonge MV, Wallace S, Le Couteur AS, van Engeland H, Wittemeyer K, McConachie H, Roge B, Mantoulan C, Pedersen L, Isager T, Poustka F, Bolte S, Bolton P, Weisblatt E, Green J, Papanikolaou K, Bailey AJ. New interview and observation measures of the broader autism phenotype: impressions of interviewee measure. J Autism Dev Disord. 2013;43(9):2082-9. doi: 10.1007/s10803-013-1810-2. PubMed PMID: 23547019.

156. de Jonge M, Parr J, Rutter M, Wallace S, Kemner C, Bailey A, van Engeland H, Pickles A. New interview and observation measures of the broader autism phenotype: group differentiation. J Autism Dev Disord. 2015;45(4):893-901. doi: 10.1007/s10803-014-2230-7. PubMed PMID: 25245786.

157. Losh M, Adolphs R, Poe MD, Couture S, Penn D, Baranek GT, Piven J. Neuropsychological profile of autism and the broad autism phenotype. Arch Gen Psychiatry. 2009;66(5):518-26. doi: 10.1001/archgenpsychiatry.2009.34. PubMed PMID: 19414711; PMCID: 2699548.

158. Piven J, Palmer P, Landa R, Santangelo S, Jacobi D, Childress D. Personality and language characteristics in parents from multiple-incidence autism families. Am J Med Genet. 1997;74(4):398-411. Epub 1997/07/25. PubMed PMID: 9259376.

159. Whitehouse AJ, Coon H, Miller J, Salisbury B, Bishop DV. Narrowing the broader autism phenotype: a study using the Communication Checklist-Adult Version (CC-A). Autism. 2010;14(6):559-74. doi: 10.1177/1362361310382107. PubMed PMID: 20923891; PMCID: 3008969.

160. Whitehouse AJO, Coon H, Miller J, Salisbury B, Bishop DVM. Narrowing the broader autism phenotype: A study using the Communication Checklist - Adult Version (CC-A). Autism. 2010;14(6):559-74. doi: 10.1177/1362361310382107.

161. Fombonne E, Bolton P, Prior J, Jordan H, Rutter M. A family study of autism: cognitive patterns and levels in parents and siblings. J Child Psychol Psychiatry. 1997;38(6):667-83. Epub 1997/10/08. PubMed PMID: 9315977.

162. Uljarevic M, Evans DW, Alvares GA, Whitehouse AJ. Short report: relationship between restricted and repetitive behaviours in children with autism spectrum disorder and their parents. Mol Autism. 2016;7:29. doi: 10.1186/s13229-016-0091-y. PubMed PMID: 27303619; PMCID: 4906972.

163. Bishop DVM, Maybery M, Wong D, Maley A, Hill W, Hallmayer J. Are phonological processing deficits part of the broad autism phenotype? Am J Med Genet B Neuropsychiatr Genet. 2004;128B(1):54-60. doi: 10.1002/ajmg.b.30039. PubMed PMID: 15211632.

164. Bora E, Aydin A, Sarac T, Kadak MT, Kose S. Heterogeneity of subclinical autistic traits among parents of children with autism spectrum disorder: Identifying the broader autism phenotype with a data-driven method. Autism Research. 2016. doi: 10.1002/aur.1661. PubMed PMID: 27383033.

165. Sasson NJ, Lam KS, Parlier M, Daniels JL, Piven J. Autism and the broad autism phenotype: familial patterns and intergenerational transmission. J Neurodev Disord. 2013;5(1):11. Epub 2013/05/04. doi: 10.1186/1866-1955-5-11. PubMed PMID: 23639131; PMCID: 3651284.

166. Szatmari P, MacLean JE, Jones MB, Bryson SE, Zwaigenbaum L, Bartolucci G, Mahoney WJ, Tuff L. The familial aggregation of the lesser variant in biological and

nonbiological relatives of PDD probands: a family history study. J Child Psychol Psychiatry. 2000;41(5):579-86. Epub 2000/08/18. PubMed PMID: 10946750.

167. Ghaziuddin M. A family history study of Asperger syndrome. J Autism Dev Disord. 2005;35(2):177-82. doi: 10.1007/s10803-004-1996-4. PubMed PMID: 15909404.

168. Levin-Decanini T, Maltman N, Francis SM, Guter S, Anderson GM, Cook EH, Jacob S. Parental broader autism subphenotypes in ASD affected families: relationship to gender, child's symptoms, SSRI treatment, and platelet serotonin. Autism Res. 2013;6(6):621-30. doi: 10.1002/aur.1322. PubMed PMID: 23956104; PMCID: 3869872.

169. Baron-Cohen S, Lombardo MV, Auyeung B, Ashwin E, Chakrabarti B, Knickmeyer R. Why are autism spectrum conditions more prevalent in males? PLoS Biol. 2011;9(6):e1001081. doi: 10.1371/journal.pbio.1001081. PubMed PMID: 21695109; PMCID: 3114757.

170. Smith CJ, Lang CM, Kryzak L, Reichenberg A, Hollander E, Silverman JM. Familial associations of intense preoccupations, an empirical factor of the restricted, repetitive behaviors and interests domain of autism. J Child Psychol Psychiatry. 2009;50(8):982-90. doi: 10.1111/j.1469-7610.2009.02060.x. PubMed PMID: 19298470.

171. Klusek J, Losh M, Martin GE. Sex differences and within-family associations in the broad autism phenotype. Autism. 2014;18(2):106-16. doi: 10.1177/1362361312464529. PubMed PMID: 23188882; PMCID: 3703490.

172. Taylor LJ, Maybery MT, Wray J, Ravine D, Hunt A, Whitehouse AJ. Brief report: do the nature of communication impairments in autism spectrum disorders relate to the broader autism phenotype in parents? J Autism Dev Disord. 2013;43(12):2984-9. doi: 10.1007/s10803-013-1838-3. PubMed PMID: 23619954.

173. Goin-Kochel RP, Mazefsky CA, Riley BP. Level of functioning in autism spectrum disorders: Phenotypic congruence among affected siblings. J Autism Dev Disord. 2008;38(6):1019-27. doi: 10.1007/s10803-007-0476-z.

174. Mazefsky CA, Williams DL, Minshew NJ. Variability in adaptive behavior in autism: evidence for the importance of family history. J Abnorm Child Psychol. 2008;36(4):591-9. doi: 10.1007/s10802-007-9202-8. PubMed PMID: 18188537; PMCID: 2373259.

175. Klin A, Pauls D, Schultz R, Volkmar F. Three diagnostic approaches to Asperger syndrome: implications for research. J Autism Dev Disord. 2005;35(2):221-34. doi: 10.1007/s10803-004-2001-y. PubMed PMID: 15909408.

176. Ruser TF, Arin D, Dowd M, Putnam S, Winklosky B, Rosen-Sheidley B, Piven J, Tomblin B, Tager-Flusberg H, Folstein S. Communicative competence in parents of children with autism and parents of children with specific language impairment. J Autism Dev Disord. 2007;37(7):1323-36. Epub 2006/12/21. doi: 10.1007/s10803-006-0274-z. PubMed PMID: 17180460.

177. Whitehouse AJ, Barry JG, Bishop DV. The broader language phenotype of autism: a comparison with specific language impairment. J Child Psychol Psychiatry. 2007;48(8):822-30. doi: 10.1111/j.1469-7610.2007.01765.x. PubMed PMID: 17683454; PMCID: 2835861.

178. Coon H, Villalobos ME, Robison RJ, Camp NJ, Cannon DS, Allen-Brady K, Miller JS, McMahon WM. Genome-wide linkage using the Social Responsiveness Scale in Utah autism pedigrees. Molecular autism. 2010;1(1):8. Epub 2010/08/04. doi: 10.1186/2040-2392-1-8. PubMed PMID: 20678250; PMCID: 2913945.

179. Ingersoll B, Hambrick DZ. The relationship between the broader autism phenotype, child severity, and stress and depression in parents of children with autism spectrum disorders. Research in Autism Spectrum Disorders. 2011;5(1):337-44. doi: 10.1016/j.rasd.2010.04.017. PubMed PMID: WOS:000283953800037.

180. Sasson NJ, Faso DJ, Parlier M, Daniels JL, Piven J. When father doesn't know best: selective disagreement between self-report and informant report of the broad autism phenotype in parents of a child with autism. Autism Research. 2014;7(6):731-9. doi: 10.1002/aur.1425. PubMed PMID: 25339495.

181. Duvekot J, van der Ende J, Constantino JN, Verhulst FC, Greaves-Lord K. Symptoms of autism spectrum disorder and anxiety: shared familial transmission and cross-assortative mating. J Child Psychol Psychiatry. 2016;57(6):759-69. doi: 10.1111/jcpp.12508. PubMed PMID: 26714925.

182. Yucel GH, Belger A, Bizzell J, Parlier M, Adolphs R, Piven J. Abnormal Neural Activation to Faces in the Parents of Children with Autism. Cereb Cortex. 2015;25(12):4653-66. Epub 2014/07/25. doi: 10.1093/cercor/bhu147. PubMed PMID: 25056573; PMCID: PMC4635912.

183. Parr JR, Gray L, Wigham S, McConachie H, Le Couteur A. Measuring the relationship between the parental Broader Autism Phenotype, parent-child interaction, and children's progress following parent mediated intervention. Research in Autism Spectrum Disorders. 2015;20:24-30. doi: 10.1016/j.rasd.2015.07.006. PubMed PMID: WOS:000362930000003.

184. Mazefsky CA, Goin-Kochel RP, Riley BP, Maes HH, The Autism Genetic Resource Exchange C. Genetic and Environmental Influences on Symptom Domains in Twins and Siblings with Autism. Research in Autism Spectrum Disorders. 2008;2(2):320-31. Epub 2008/04/01. doi: 10.1016/j.rasd.2007.08.002. PubMed PMID: 19718281; PMCID: 2734093.

185. Losh M, Klusek J, Martin GE, Sideris J, Parlier M, Piven J. Defining genetically meaningful language and personality traits in relatives of individuals with fragile X syndrome and relatives of individuals with autism. Am J Med Genet B Neuropsychiatr Genet. 2012;159B(6):660-8. doi: 10.1002/ajmg.b.32070. PubMed PMID: 22693142; PMCID: 3740587.

186. Ronconi L, Facoetti A, Bulf H, Franchin L, Bettoni R, Valenza E. Paternal autistic traits are predictive of infants visual attention. J Autism Dev Disord. 2014;44(7):1556-64. doi: 10.1007/s10803-013-2018-1
10.1093/cercor/bhs319; Ronconi, L., Gori, S., Giora, E., Ruffino, M., Molteni, M., Facoetti, A., Deeper attentional masking by lateral objects in children with autism (2013) Brain and Cognition, 82 (2), pp. 213-218; Ronconi, L., Gori, S., Ruffino, M., Franceschini, S., Urbani, B., Molteni, M., Decreased coherent motion discrimination in autism spectrum disorder: The role of attentional zoom-out deficit (2012) PLoS ONE, 7 (11), pp. e49019. , doi:10.1371/journal.pone.0049019; Ronconi, L., Gori, S., Ruffino, M., Molteni, M., Facoetti, A., Zoom-out attentional impairment in children with autism spectrum disorder (2013) Cortex, , doi: 10.1016/j.cortex.2012.03.005; Saalmann, Y.B., Pigarev, I.N., Vidyasagar, T.R., Neural mechanisms of visual attention: How top-down feedback highlights relevant locations (2007) Science, 316 (5831), pp. 1612-1615. , DOI 10.1126/science.1139140; Sacrey, L.R., Bryson, S.E., Zwaigenbaum, L., Prospective examination of visual attention during play in infants at high-risk for autism spectrum disorder: A longitudinal study from 6 to 36 months of age (2013) Behavioural Brain Research, 256, pp. 441-450; Sucksmith, E., Roth, I., Hoekstra, R., Autistic traits below the clinical threshold: Re-examining the broader autism phenotype in the 21st century (2011) Neuropsychology Review, 21 (4), pp. 360-389; Sutherland, A., Crewther, D.P., Magnocellular visual evoked potential delay with high autism spectrum quotient yields a neural mechanism for altered perception (2010) Brain, 133 (7), pp. 2089-2097; Townsend, J., Courchesne, E., Egaas, B., Slowed orienting of covert visual-spatial attention in autism: Specific deficits associated with cerebellar and parietal abnormality (1996) Development and Psychopathology, 8 (3), pp. 563-584; Wainwright-Sharp, J.A., Bryson, S.E., Visual orienting deficits in high-functioning people with autism (1993) Journal of Autism and Developmental Disorders, 23 (1), pp. 1-13; Wass, S., Porayska-Pomsta, K., Johnson, M.H., Training attentional control in infancy (2011) Current Biology, 21, pp. 1543-1547; Zwaigenbaum, L., Bryson, S., Rogers, T., Roberts, W., Brian, J., Szatmari, P., Behavioral manifestations of autism in the first year of life (2005) International Journal of Developmental Neuroscience, 23 (2-3 SPEC. ISS.), pp. 143-152. , DOI 10.1016/j.ijdevneu.2004.05.001.

187. Lamport D, Zlomke KR. The Broader Autism Phenotype, Social Interaction Anxiety, and Loneliness: Implications for Social Functioning. Curr Psychol. 2014;33(3):246-55. doi: 10.1007/s12144-014-9210-0.

188. Crocetti E, Moscatelli S, Van der Graaff J, Keijsers L, van Lier P, Koot HM, Rubini M, Meeus W, Branje S. The Dynamic Interplay among Maternal Empathy, Quality of Mother-Adolescent Relationship, and Adolescent Antisocial Behaviors: New Insights from a Six-Wave Longitudinal Multi-Informant Study. PLoS One. 2016;11(3):e0150009. doi: 10.1371/journal.pone.0150009.

189. Deoliveira CA, Moran G, Pederson DR. Understanding the link between maternal adult attachment classifications and thoughts and feelings about emotions. Attachment & human development. 2005;7(2):153-70. doi: 10.1080/14616730500135032. PubMed PMID: 16096191.

190. Derguy C, M'Bailara K, Michel G, Roux S, Bouvard M. The Need for an Ecological Approach to Parental Stress in Autism Spectrum Disorders: The Combined Role of Individual and Environmental Factors. J Autism Dev Disord. 2016;46(6):1895-905. doi: 10.1007/s10803-016-2719-3. PubMed PMID: 26858031.

191. Lau WY, Gau SS, Chiu YN, Wu YY. Autistic traits in couple dyads as a predictor of anxiety spectrum symptoms. J Autism Dev Disord. 2014;44(11):2949-63. doi: 10.1007/s10803-014-2151-5. PubMed PMID: 24907095.

192. Cuccaro ML, Czape K, Alessandri M, Lee J, Deppen AR, Bendik E, Dueker N, Nations L, Pericak-Vance M, Hahn S. Genetic testing and corresponding services among individuals with autism spectrum disorder (ASD). Am J Med Genet A. 2014;164A(10):2592-600. doi: 10.1002/ajmg.a.36698. PubMed PMID: 25131847.

193. Wood CL, Warnell F, Johnson M, Hames A, Pearce MS, McConachie H, Parr JR. Evidence for ASD recurrence rates and reproductive stoppage from large UK ASD research family databases. Autism Research. 2015;8(1):73-81. Epub 2014/10/03. doi: 10.1002/aur.1414. PubMed PMID: 25273900.

194. Gronborg TK, Hansen SN, Nielsen SV, Skytthe A, Parner ET. Stoppage in Autism Spectrum Disorders. J Autism Dev Disord. 2015;45(11):3509-19. doi: 10.1007/s10803-015-2497-3. PubMed PMID: 26077953.

195. Hoffmann TJ, Windham GC, Anderson M, Croen LA, Grether JK, Risch N. Evidence of reproductive stoppage in families with autism spectrum disorder: a large, population-based cohort study. JAMA Psychiatry. 2014;71(8):943-51. doi: 10.1001/jamapsychiatry.2014.420. PubMed PMID: 24942798.

196. Schendel DE, Diguiseppi C, Croen LA, Fallin MD, Reed PL, Schieve LA, Wiggins LD, Daniels J, Grether J, Levy SE, Miller L, Newschaffer C, Pinto-Martin J, Robinson C, Windham GC, Alexander A, Aylsworth AS, Bernal P, Bonner JD, Blaskey L, Bradley C, Collins J, Ferretti CJ, Farzadegan H, Giarelli E, Harvey M, Hepburn S, Herr M, Kaparich K, Landa R, Lee LC, Levenseller B, Meyerer S, Rahbar MH, Ratchford A, Reynolds A, Rosenberg S, Rusyniak J, Shapira SK, Smith K, Souders M, Thompson PA, Young L, Yeargin-Allsopp M. The Study to Explore Early Development (SEED): a multisite epidemiologic study of autism by the Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) network. J Autism Dev Disord. 2012;42(10):2121-40. doi: 10.1007/s10803-012-1461-8. PubMed PMID: 22350336; PMCID: 4455890.

197. Wiggins LD, Reynolds A, Rice CE, Moody EJ, Bernal P, Blaskey L, Rosenberg SA, Lee LC, Levy SE. Using standardized diagnostic instruments to classify children with autism in the study to explore early development. J Autism Dev Disord. 2015;45(5):1271-80. doi: 10.1007/s10803-014-2287-3. PubMed PMID: 25348175; PMCID: 4486213.

198. Lord C, Rutter M, DiLavore PC, Risi S. Autism Diagnostic Observation Schedule (2nd Edition) 2012.

199. Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord. 1994;24(5):659-85. doi: 10.1007/BF02172145. PubMed PMID: 7814313.

200. The Ohio State University (OSU) Research Unit on Pediatric Psychopharmacology. OSU Autism Rating Scale (OARS; adapted for SEED) an Clinical Global Impression (CGI; adapted for SEED) 2005 [August 30, 2010]. Available from: http://psychmed.osu.edu/resources.htm.

201. Constantino JN, Abbacchi AM, Lavesser PD, Reed H, Givens L, Chiang L, Gray T, Gross M, Zhang Y, Todd RD. Developmental course of autistic social impairment in males. Dev Psychopathol. 2009;21(1):127-38. doi: 10.1017/S095457940900008X. PubMed PMID: 19144226; PMCID: 2893041.

202. Seidman I, Yirmiya N, Milshtein S, Ebstein RP, Levi S. The broad autism phenotype questionnaire: Mothers versus fathers of children with an autism spectrum disorder. Journal of Autism and Developmental Disorders. 2012;42(5):837-46. doi: 10.1007/s10803-011-1315-9.

203. Duvekot J, van der Ende J, Constantino JN, Verhulst FC, Greaves-Lord K. Symptoms of autism spectrum disorder and anxiety: shared familial transmission and cross-assortative mating. J Child Psychol Psychiatry. 2015. doi: 10.1111/jcpp.12508. PubMed PMID: 26714925.

204. de Jonge M, Parr J, Rutter M, Wallace S, Kemner C, Bailey A, van Engeland H, Pickles A. New Interview and Observation Measures of the Broader Autism Phenotype: Group Differentiation. Journal of Autism and Developmental Disorders. 2015;45(4):893-901. doi: 10.1007/s10803-014-2230-7.

205. Wiggins LD, Levy SE, Daniels J, Schieve L, Croen LA, DiGuiseppi C, Blaskey L, Giarelli E, Lee LC, Pinto-Martin J, Reynolds A, Rice C, Rosenberg CR, Thompson P, Yeargin-Allsopp M, Young L, Schendel D. Autism Spectrum Disorder Symptoms Among Children Enrolled in the Study to Explore Early Development (SEED). J Autism Dev Disord. 2015. doi: 10.1007/s10803-015-2476-8. PubMed PMID: 26048040.

206. DiGuiseppi CG, Daniels JL, Fallin DM, Rosenberg SA, Schieve LA, Thomas KC, Windham GC, Goss CW, Soke GN, Currie DW, Singer AB, Lee LC, Bernal P, Croen LA, Miller

LA, Pinto-Martin JA, Young LM, Schendel DE. Demographic profile of families and children in the Study to Explore Early Development (SEED): Case-control study of autism spectrum disorder. Disabil Health J. 2016;9(3):544-51. doi: 10.1016/j.dhjo.2016.01.005. PubMed PMID: 26917104; PMCID: 4903880.

207. Achenbach BS. Child behavior checklist. Burlington, VT: Achenbach System of Empirically based Assessment; 1992.

208. Mullen E. Mullen scales of early learning. San Antonio, TX: Pearson; 1995.

209. Ozonoff S, Williams BJ, Landa R. Parental report of the early development of children with regressive autism: the delays-plus-regression phenotype. Autism. 2005;9(5):461-86. doi: 10.1177/1362361305057880. PubMed PMID: 16287700.

210. Lanza ST, Rhoades BL. Latent class analysis: an alternative perspective on subgroup analysis in prevention and treatment. Prev Sci. 2013;14(2):157-68. doi: 10.1007/s11121-011-0201-1. PubMed PMID: 21318625; PMCID: 3173585.

211. Bray BC, Lanza ST, Tan X. Eliminating Bias in Classify-Analyze Approaches for Latent Class Analysis. Structural Equation Modeling. 2015;22(1):1-11. doi: 10.1080/10705511.2014.935265. PubMed PMID: 25614730; PMCID: 4299667.

212. Vermunt JK. Latent Class Modeling with Covariates: Two Improved Three-Step Approaches. Political Analysis. 2010;18(4):450-69. doi: 10.1093/pan/mpq025.

213. Hagenaars JA, McCutcheon AL. Applied Latent Class Analysis. Cambridge; New York: Cambridge University Press; 2002. 454 p.

214. Formann AK. Mixture analysis of multivariate categorical data with covariates and missing entries. Computational Statistics & Data Analysis. 2007;51(11):5236-46. doi: http://dx.doi.org/10.1016/j.csda.2006.08.020.

215. Groenwold RHH, White IR, Donders ART, Carpenter JR, Altman DG, Moons KGM. Missing covariate data in clinical research: when and when not to use the missing-indicator method for analysis. Can Med Assoc J. 2012;184(11):1265-9. doi: 10.1503/cmaj.110977. PubMed PMID: PMC3414599.

216. Jones MP. Indicator and Stratification Methods for Missing Explanatory Variables in Multiple Linear Regression. Journal of the American Statistical Association. 1996;91(433):222-30. doi: 10.2307/2291399.

217. SAS Institute Inc. SAS/STAT Software, Version 9.3. 2011.

218. Muthen LK, Muthen BO. Mplus User's Guide. Los Angeles, CA: Muthen & Muthen; 1998-2012.

219. Vermunt JK, Magidson J. Latent Class Analysis With Sampling Weights. Socio Meth Res. 2007;36(1):87-111. doi: 10.1177/0049124107301965.

220. Hofler M, Pfister H, Lieb R, Wittchen HU. The use of weights to account for non-response and drop-out. Soc Psychiatry Psychiatr Epidemiol. 2005;40(4):291-9. Epub 2005/04/19. doi: 10.1007/s00127-005-0882-5. PubMed PMID: 15834780.

221. Westman Andersson G, Miniscalco C, Johansson U, Gillberg C. Autism in toddlers: can observation in preschool yield the same information as autism assessment in a specialised clinic? The Scientific World Journal. 2013;2013:384745. doi: 10.1155/2013/384745. PubMed PMID: 23476129; PMCID: 3582094.

222. Boshoff K, Gibbs D, Phillips RL, Wiles L, Porter L. Parents' voices: 'why and how we advocate'. A meta-synthesis of parents' experiences of advocating for their child with autism spectrum disorder. Child Care Health Dev. 2016;42(6):784-97. doi: 10.1111/cch.12383. PubMed PMID: 27445227.

223. DePape AM, Lindsay S. Parents' experiences of caring for a child with autism spectrum disorder. Qual Health Res. 2015;25(4):569-83. doi: 10.1177/1049732314552455. PubMed PMID: 25246329.

224. de Bildt A, Sytema S, Ketelaars C, Kraijer D, Mulder E, Volkmar F, Minderaa R. Interrelationship Between Autism Diagnostic Observation Schedule-Generic (ADOS-G), Autism Diagnostic Interview-Revised (ADI-R), and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) Classification in Children and Adolescents with Mental Retardation. J Autism Dev Disord. 2004;34(2):129-37. doi: http://dx.doi.org/10.1023/B:JADD.0000022604.22374.5f. PubMed PMID: 205298760; 15162932.

225. Falkmer T, Anderson K, Falkmer M, Horlin C. Diagnostic procedures in autism spectrum disorders: a systematic literature review. Eur Child Adolesc Psychiatry. 2013;22(6):329-40. doi: 10.1007/s00787-013-0375-0. PubMed PMID: 23322184.

226. Ventola PE, Kleinman J, Pandey J, Barton M, Allen S, Green J, Robins D, Fein D. Agreement among four diagnostic instruments for autism spectrum disorders in toddlers. J Autism Dev Disord. 2006;36(7):839-47. doi: 10.1007/s10803-006-0128-8. PubMed PMID: 16897398.

227. Bishop DVM, Maybery M, Maley A, Wong D, Hill W, Hallmayer J. Using self-report to identify the broad phenotype in parents of children with autistic spectrum disorders: a study using the Autism-Spectrum Quotient. J Child Psychol Psychiatry. 2004;45(8):1431-6. doi: 10.1111/j.1469-7610.2004.00325.x. PubMed PMID: WOS:000224678100011.

228. Wiggins LD, Bakeman R, Adamson LB, Robins DL. The Utility of the Social Communication Questionnaire in Screening for Autism in Children Referred for Early Intervention. Focus on Autism and Other Developmental Disabilities. 2007;22(1):33-8. doi: 10.1177/10883576070220010401.

229. Ryan S, Runswick‐Cole K. Repositioning mothers: mothers, disabled children and disability studies. Disability & Society. 2008;23(3):199-210. doi: 10.1080/09687590801953937.

230. McKeever P, Miller KL. Mothering children who have disabilities: a Bourdieusian interpretation of maternal practices. Soc Sci Med. 2004;59(6):1177-91. doi: 10.1016/j.socscimed.2003.12.023. PubMed PMID: 15210090.

231. Tracey TJ. A note on socially desirable responding. J Couns Psychol. 2016;63(2):224-32. doi: 10.1037/cou0000135. PubMed PMID: 26689626.

232. Henderson C, Evans-Lacko S, Flach C, Thornicroft G. Responses to mental health stigma questions: the importance of social desirability and data collection method. Can J Psychiatry. 2012;57(3):152-60. Epub 2012/03/09. PubMed PMID: 22398001.

233. Tran US, Stieger S, Voracek M. Psychometric analysis of Stober's social desirability scale (SDS-17): an item response theory perspective. Psychol Rep. 2012;111(3):870-84. doi: 10.2466/03.09.PR0.111.6.870-884. PubMed PMID: 23402053.

234. Miles JH. Autism spectrum disorders--a genetics review. Genet Med. 2011;13(4):278-94. doi: 10.1097/GIM.0b013e3181ff67ba. PubMed PMID: 21358411.

235. An JY, Claudianos C. Genetic heterogeneity in autism: From single gene to a pathway perspective. Neurosci Biobehav Rev. 2016;68:442-53. doi: 10.1016/j.neubiorev.2016.06.013. PubMed PMID: 27317861.

236. Lyall K, Croen L, Daniels J, Fallin MD, Ladd-Acosta C, Lee BK, Park BY, Snyder NW, Schendel D, Volk HE, Windham GC, Newschaffer C. The Changing Epidemiology of Autism Spectrum Disorders. Annu Rev Public Health. 2016. doi: 10.1146/annurev-publhealth-031816-044318. PubMed PMID: 28068486.

237. Landa RJ, Gross AL, Stuart EA, Bauman M. Latent class analysis of early developmental trajectory in baby siblings of children with autism. J Child Psychol Psychiatry.

2012;53(9):986-96. doi: 10.1111/j.1469-7610.2012.02558.x. PubMed PMID: 22574686; PMCID: 3432306.

238. Bernabei P, Cerquiglini A, Cortesi F, D'Ardia C. Regression versus no regression in the autistic disorder: developmental trajectories. J Autism Dev Disord. 2007;37(3):580-8. doi: 10.1007/s10803-006-0201-3. PubMed PMID: 16909312.

239. Gadow KD, Perlman G, Weber RJ. Parent-Reported Developmental Regression in Autism: Epilepsy, IQ, Schizophrenia Spectrum Symptoms, and Special Education. J Autism Dev Disord. 2017. doi: 10.1007/s10803-016-3004-1. PubMed PMID: 28074354.

240. Rai D, Lee BK, Dalman C, Golding J, Lewis G, Magnusson C. Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. BMJ. 2013;346:f2059. doi: 10.1136/bmj.f2059. PubMed PMID: 23604083; PMCID: 3630989.

241. Flint J, Munafo MR. The endophenotype concept in psychiatric genetics. Psychol Med. 2007;37(2):163-80. doi: 10.1017/S0033291706008750. PubMed PMID: 16978446; PMCID: 2829981.

242. Hall MH, Smoller JW. A new role for endophenotypes in the GWAS era: functional characterization of risk variants. Harv Rev Psychiatry. 2010;18(1):67-74. doi: 10.3109/10673220903523532. PubMed PMID: 20047462; PMCID: 3586547.

243. Losh M, Martin GE, Lee M, Klusek J, Sideris J, Barron S, Wassink T. Developmental Markers of Genetic Liability to Autism in Parents: A Longitudinal, Multigenerational Study. J Autism Dev Disord. 2017. doi: 10.1007/s10803-016-2996-x. PubMed PMID: 28070788.

244. Constantino JN, Zhang Y, Holzhauer K, Sant S, Long K, Vallorani A, Malik L, Gutmann DH. Distribution and Within-Family Specificity of Quantitative Autistic Traits in Patients with Neurofibromatosis Type I. J Pediatr. 2015;167(3):621-6 e1. Epub 2015/06/09. doi: 10.1016/j.jpeds.2015.04.075. PubMed PMID: 26051969; PMCID: PMC4792262.

245. Evans DW, Uljarevic M, Lusk LG, Loth E, Frazier T. Development of Two Dimensional Measures of Restricted and Repetitive Behavior in Parents and Children. J Am Acad Child Adolesc Psychiatry. 2017;56(1):51-8. doi: 10.1016/j.jaac.2016.10.014. PubMed PMID: 27993229.

246. Lim ET, Raychaudhuri S, Sanders SJ, Stevens C, Sabo A, MacArthur DG, Neale BM, Kirby A, Ruderfer DM, Fromer M, Lek M, Liu L, Flannick J, Ripke S, Nagaswamy U, Muzny D, Reid JG, Hawes A, Newsham I, Wu Y, Lewis L, Dinh H, Gross S, Wang LS, Lin CF, Valladares O, Gabriel SB, dePristo M, Altshuler DM, Purcell SM, Project NES, State MW, Boerwinkle E, Buxbaum JD, Cook EH, Gibbs RA, Schellenberg GD, Sutcliffe JS, Devlin B, Roeder K, Daly MJ.

Rare complete knockouts in humans: population distribution and significant role in autism spectrum disorders. Neuron. 2013;77(2):235-42. doi: 10.1016/j.neuron.2012.12.029. PubMed PMID: 23352160; PMCID: 3613849.

247. Flashner BM, Russo ME, Boileau JE, Leong DW, Gallicano GI. Epigenetic factors and autism spectrum disorders. Neuromolecular Med. 2013;15(2):339-50. doi: 10.1007/s12017-013-8222-5.

248. Keverne EB. Genomic imprinting in the brain. Curr Opin Neurobiol. 1997;7(4):463-8. doi: http://dx.doi.org/10.1016/S0959-4388(97)80023-2.

249. Jacquemont S, Coe BP, Hersch M, Duyzend MH, Krumm N, Bergmann S, Beckmann JS, Rosenfeld JA, Eichler EE. A higher mutational burden in females supports a "female protective model" in neurodevelopmental disorders. Am J Hum Genet. 2014;94(3):415-25. doi: 10.1016/j.ajhg.2014.02.001. PubMed PMID: 24581740; PMCID: 3951938.

250. Begeer S, Mandell D, Wijnker-Holmes B, Venderbosch S, Rem D, Stekelenburg F, Koot HM. Sex differences in the timing of identification among children and adults with autism spectrum disorders. J Autism Dev Disord. 2013;43(5):1151-6. doi: 10.1007/s10803-012-1656-z. PubMed PMID: 23001766.

251. Sasson NJ, Faso DJ, Parlier M, Daniels JL, Piven J. When father doesn't know best: selective disagreement between self-report and informant report of the broad autism phenotype in parents of a child with autism. Autism Res. 2014;7(6):731-9. doi: 10.1002/aur.1425. PubMed PMID: 25339495.

252. Insel T. The NIMH Research Domain Criteria (RDoC) Project: Precision Medicine for Psychiatry. Am J Psychiatry. 2014;171(4):395-7. doi: 10.1176/appi.ajp.2014.14020138.