Challenges and Options for Estimating the Prevalence of Autism in Population Surveys

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1. What are autism spectrum disorders?

Autism spectrum disorders (ASDs) are complex neurodevelopmental disorders characterized by impairments in social communication and reciprocity and the presence of repetitive behaviors and restricted interests. Individuals diagnosed with an ASD experience significant social, communicative, and behavioral challenges beginning in early childhood. Although much effort has been focused on early detection of ASDs, ASD can be diagnosed in individuals at any age, including through adulthood. ASD also affects individuals from all racial, ethnic, and socioeconomic groups. Males are about 4 to 5 times more likely to be diagnosed with an ASD than females; the gender ratio is even higher (≈ 9:1) among those with IQ ≥ 80 (Hill, Zuckerman, & Fombonne, 2014; 2015). ASDs are highly heritable disorders with a strong genetic basis (Colvert et al., 2015; Huguet, Ey, & Bourgeron, 2013). Some environmental risk factors have been tentatively identified such as advanced paternal and maternal age and prenatal exposure to various neurotoxicants, although many of these associations have yet to be replicated (Mandy & Lai, 2016). Currently, there are no universal biological markers of ASDs and the etiology appears to be heterogeneous.

Although individuals with ASDs share common core symptoms, the ASD phenotype is characterized by a broad constellation of behavioral symptoms. No two individuals with an ASD are likely to present with identical symptoms. Even within the same child, symptoms can vary dramatically over time (Gotham, Pickles, & Lord, 2012; Lord, Bishop, & Anderson, 2015; Richler, Huerta, Bishop, & Lord, 2010; Szatmari et al., 2015). Because of this phenotypic heterogeneity and the lack of a medical, genetic, or biological test, diagnosis of an ASD is challenging. Diagnosis is typically made based on an individual's developmental history and direct observation of his/her behaviors (Baird, Douglas, & Murphy, 2011). A child can reliably be diagnosed with an ASD as early as two years of age, and early diagnoses tend to remain stable across childhood (Lord et al., 2006).

For children and adolescents suspected of having an ASD, instruments exist that help to standardize the diagnostic process for clinicians, both for eliciting parental reports of developmental history (i.e., the Autism Diagnostic Interview-Revised [ADI-R] (Lord, Rutter, & Couteur, 1994)) and for structuring the observation of children's behaviors (i.e., the Autism Diagnostic Observation Schedule [ADOS-2] (Gotham, Risi, Pickles, & Lord, 2007)). These instruments have been well-validated in supporting a clinical diagnosis of ASDs; however, these tools require significant training and time to administer. Though commonly used, no specific tools are required in order to diagnose a child with an

ASD. Even when standardized instruments have been used in an ASD assessment, best-estimate diagnosis by expert clinicians is the gold standard (Lord et al., 2012). Options for diagnostic instruments are more limited for adult populations, as informants (such as parents or other caregivers) who can report on early childhood development may not be available.

According to a recent report by the US Centers for Disease Control and Prevention (CDC), the median age of diagnosis of an ASD in the US is 50 months (Centers for Disease Control & Prevention, 2016). However, research has shown that the onset of symptoms occurs within the first 24 months of life (De Giacomo & Fombonne, 1998). Thus, diagnosis tends to lag months and even years behind the actual symptom onset. The developmental course of ASDs are generally marked by substantial improvements occurring as a function of both biological maturation and educational/behavioral interventions. Yet, even with the best outcomes, social difficulties and isolation persist throughout the lifespan (Howlin, Goode, Hutton, & Rutter, 2004). ASDs are lifelong disorders, and are associated with substantial financial and psychological costs for the individual, the family, and society (Buescher, Cidav, Knapp, & Mandell, 2014).

2. What have been challenges to estimating prevalence of ASDs historically?

The first epidemiological study of ASD was carried out in England (Lotter, 1966). At the time, the definition of ASD conformed to the severe syndrome described by Kanner (1943), the definition solely relied on a clinical (expert) opinion and children were exclusively identified through medical or educational services then catering to their condition. In this and other studies that followed in the 1970s, the prevalence was low (4 to 6/10,000). In the late 1970s, epidemiological surveys improved in two major ways. First, the case identification methodology included attempts to screen for ASD populations of children not formally diagnosed with ASD but presenting with symptoms and developmental profiles conceptually similar to the central Kanner description (Wing & Gould, 1979; Wing, Yeates, Brierley, & Gould, 1976). Second, the assessment of 'caseness' in the survey incorporated, for the first time, the use of a standardized diagnostic interview, the Health and Behavior Schedule (Wing et al., 1976). As a result, the 'triad of impairments' described by Wing and Gould (1979) allowed to capture specific autistic profiles seen in children with mental retardation that had been overlooked in the past. In parallel, the first descriptions of ASD occurring in children with good language levels and normal intelligence started to emerge in the clinical literature. The syndrome described (and forgotten) by Asperger (1944) became known to the medical community through English translations of his work

(Wing, 1981), and a new set of epidemiological surveys were conducted that investigated autism specifically occurring in populations of children with IQ levels greater than 70, referred to either as high-functioning autism or Asperger. As a result, rates of ASD started to increase substantially in the 1980s (Fombonne, 1999). As the concept of ASD had now extended to populations with a range of intellectual abilities, corresponding changes in the nosography occurred with the adoption of the terminology of pervasive developmental disorder (PDD; American Psychiatric Association, 1980; 1987), a symptom-oriented approach to the diagnosis of PDD/ASD, and the development of diagnostic algorithms that achieved a much needed higher level of inter-diagnostician reliability, in both clinical and epidemiological settings. In the 1990s, further changes occurred in nosographies with the advent of ICD-10 (World Health Organization, 1992) and DSM-IV (American Psychiatric Association, 1994) that capitalized on prior empirical field testing of competing definitions and algorithms (Volkmar et al., 1994) and on an attempt to harmonize the two diagnostic schemes. A specific category for Asperger was introduced. Diagnostic accuracy of the algorithms increased although levels of sensitivity and specificity of these algorithms rarely surpassed 80-85%. To accommodate this, 'Not Otherwise Specified' categories were created that had no specific algorithms and became overinclusive and of uncertain validity. In all nosographies, diagnostic criteria and algorithms were calibrated against expert clinical judgement as the gold standard.

In line with an increasing dimensionalization of the phenotype, new instruments were created for diagnostic assessments that were adopted in most clinical settings and, soon after, in epidemiological surveys as tools employed to confirm caseness. In line with measurement progress achieved in general psychiatric epidemiology, these evaluation techniques relied on a combination of methods and informants: parental interviews were combined with direct observation of the child, and sometimes supplemented by medical record review and teacher assessment. Important characteristics of now currently used diagnostic tools such as the ADI-R and the ADOS-2 are that they: a) necessitate specific training for their administration; b) are semi-structured schedules allowing flexibility in the administration and infusion of clinical judgement; c) are standardized in coverage, timeframes, definitions of symptoms and scoring procedures; d) consistently generate information that matches the information content of diagnostic criteria within nosographies; e) are applicable across the life span and with subjects with different developmental levels; and f) allow for some (partial) assessment of severity. None of these tools can in isolation generate a diagnostic conclusion; rather, it remains the

task of the experienced clinician to integrate their results across informants and data sources, alongside other tools used for evaluations. Of note, some standardized diagnostic tools are more structured that generally require less interviewer training, do not allow much flexibility in administration and scoring, and do not require clinical knowledge from the lay interviewer. These tools have been devised for large scale studies that require hundreds of interviews and must rely on lay (rather than clinically-trained) interviewers. As a complement to diagnostic interviews, several questionnaires have been developed for use by parents, teachers, other caregivers and sometimes professionals that consist of symptom checklists mapping the developmental domains associated with ASD (communication, social interaction, imagination/behavioral rigidity) and designed to evaluate dimensionally symptom severity and/or screen clinical and general populations to detect ASD. While they are easy and inexpensive to use, there is much less consistency in their coverage and content, their use is often limited to specific groups defined by age, level of functioning or clinical status, and with few exceptions, normative data are not available to assist in the interpretation of scores at an individual level. Likewise, their properties as screening instruments for epidemiological studies have rarely been systematically investigated. Although cut-offs are usually available to group individuals in separate categories, these instruments are not and should not be used alone for diagnostic approximations.

The design of epidemiological surveys has benefitted from these advances in the measurement of ASD both for screening children attending normal schools or referred to clinics for a range of behavioral and emotional problems, and for performing diagnostic confirmation as part of study protocols. Yet, as explained below, there is still no standardized survey methodology and each study has thus far relied on unique combinations of screening and diagnostic methods and tools that do not facilitate direct comparisons across investigations.

3. What are the current challenges to estimating prevalence of ASDs?

Estimating the prevalence of ASDs and monitoring prevalence over time is important to accurately plan for services, measure the efficacy of early detection and intervention programs, and detect possible causal factors associated with trends in prevalence that could be modifiable. However, because ASDs are behaviorally defined disorders, determining prevalence is more challenging than for a disorder where clear biological markers exist. How data are gathered, analyzed, and interpreted impacts the conclusions made regarding the prevalence of ASDs. Likewise, the interpretation of prevalence trends depends on maintaining data capture systems constant over time, which is hard both

to achieve and to demonstrate. Changes in societal awareness and the public health response also have an impact on prevalence estimates. For example, in the U.S., increases in public awareness about ASD, access to services, and improved identification of ASDs in primary healthcare have all contributed to the increase in prevalence and may also account for regional variations in estimates. Thus, prevalence estimates from any epidemiological survey should always be regarded in the context of the specific methodology employed in all survey phases.

In designing a prevalence study, three major features are critical for the planning and logistics of the study as well as for the interpretation of its results: case definition, case finding, and case evaluation methods. The unique combination of strengths and limitations for each set of methods chosen in a given survey can lead to biases in prevalence estimates in both directions, leading to estimates that are always guaranteed to be imperfect (Newschaffer, 2015).

3.1. Case definition: how will individuals with an ASD be counted?

The case definition is the standard set of criteria for deciding whether an individual should be classified as having ASD. This is a challenge in surveying ASD as the case definition should aim to be specific enough to identify true cases, yet sensitive enough to detect the full spectrum of ASDs present in the population. Common case definitions rely on the diagnostic criteria for autism, which have progressively broadened over time. Starting with Kanner's definition of autism (1943), case definitions have progressively broadened to include criteria proposed by Rutter (1970), and subsequently the International Classification of Diseases, ninth revision (ICD-9; World Health Organization, 1977); the Diagnostic and Statistical Manual of Mental Disorders, third edition and revision (DSM-III; American Psychiatric Association, 1980; DSM-III-R; 1987) and fourth edition and text revision (DSM-IV; American Psychiatric Association, 1994; DSM-IV-TR; 2000). The two most widely used nosographies in the past 20 years are the ICD-10 (World Health Organization, 1992) and DSM-IV (American Psychiatric Association, 2013), both of which agreed in their broad definition of PDDs, with some minor differences.

Early diagnostic criteria reflected the more qualitatively severe behavioral phenotypes, usually associated with severe delays in language and cognitive skills. In the 1980s, as explained above, less severe forms of autism were recognized, either as a qualifier for autism occurring without intellectual disability (i.e., high-functioning autism), or as separate diagnostic categories (e.g. Pervasive Developmental Disorders Not Otherwise Specified [PDD-NOS] or Autism Spectrum Disorders [ASD]).

Asperger's disorder appeared in nosographies in the 1990s, with unclear validity, particularly with respect to its differentiation from high-functioning autism. Some ASD subtypes that were described in DSM-III subsequently disappeared (e.g., Autism-Residual State); however, other nomenclatures have since added new diagnostic categories, such as "atypical autism" and "PDD unspecified" (ICD-10).

Most US prevalence surveys since 2000 have used DSM-IV-TR criteria (American Psychiatric Association, 2000) as the case definition for ASD. Recently, these criteria were substantially revised with the publication of DSM-5 (DSM-5; American Psychiatric Association, 2013), which includes a single new category of ASDs that is conceptually equivalent to the previous diagnostic class of PDDs. In DSM-5, fewer diagnostic criteria have been retained, and are combined in two clusters: social communication deficits and restricted patterns of behaviors and interests. The removal of the loosely defined PDD-NOS that was in DSM-IV-TR will likely increase the specificity of the ASD diagnostic category, and the removal of Asperger Disorder as a separate category is consistent with research that has generally failed to provide evidence for the discriminant validity of this diagnostic concept vis-à-vis forms of autistic disorder not associated with severe language impairments or intellectual deficits.

The impact of DSM-5 changes remains to be fully assessed in the context of epidemiological surveys. Two recent large-scale surveys have addressed this issue. In a re-analysis of data from the Centers for Disease Control and Prevention Autism and Developmental Disabilities Monitoring (ADDM) Network 2008 survey year (Maenner et al., 2014), 81.2% of children with ASD according to DSM-IV-TR also met DSM-5 criteria, resulting in a DSM-5 based prevalence of 10/1,000 compared to the reported estimate of 11.3/1,000 based on DSM-IV-TR criteria, a reduction of 9.1%. In a similar re-analysis, Kim and colleagues (2014) reported that 92% of children with ASD according to DSM-IV-TR also met DSM-5 criteria. Thus, estimated prevalence based on DSM-5 was 22/1,000 compared to the DSM-IV-TR based estimate of 26.4/1,000, a reduction of 16.6%. However, when DSM-5 ASD and Social Communication Disorder (SCD; a new diagnostic category in DSM-5) were considered together, 26.4/1,000 were identified, meaning that there was no significant change in the prevalence estimate (Kim et al., 2014). It is important to note that new diagnostic information required in DSM-5 (e.g., presence of sensory processing deficits) was generally not available in prior studies like these, making it difficult to classify DSM-5 ASD cases based on existing records due to the lack of documentation available. Additionally, previous studies were constrained in sampling children with a DSM-IV PDD

diagnosis and could not therefore estimate the proportion of children who did not meet criteria for DSM-IV yet would have met those for DSM-5.

3.2. Case finding: how will individuals meeting the case definition be systematically found?

Once an ASD case definition is set, efforts should be made to find individuals meeting case criteria in a well-described population. Surveys vary in the intensity and comprehensiveness of case finding methods, which range from identifying subjects already diagnosed to surveying larger clinical samples or non-clinical populations in order to detect undiagnosed, misdiagnosed or milder forms of the ASD phenotype. The sensitivity of proactive case finding is dependent on aspects of the study context that generally cannot be measured or controlled by investigators, including level of service development, awareness among professionals and the lay public, and participation rate and research engagement of segments of the population. In general, methods for drawing the sample from the population can be either non-random (or non-probability based) or random, with random samples being preferable for achieving samples with high representativeness to the target population.

3.2.1.Non-random samples

Surveys of ASDs based on non-random samples have the common limitation of relying on a sample population that was readily accessible through existing records from national registers or health, education, or other service provider databases. As a result, individuals meeting the ASD case definition who are not documented in current records will not be included as cases, leading to an underestimation of prevalence. This is particularly a concern when surveying younger children and adults, as both may lack documentation in such records and therefore may go unrecognized (Brugha et al., 2011; Yeargin-Allsopp et al., 2003). Below, we discuss some common data sources that have been used to estimate ASD prevalence with non-random samples.

3.2.1.1. National registries. Some countries have established national registries that record every health diagnosis for all registrants, including diagnoses like ASD. For example, numerous prevalence surveys have been conducted with various birth cohorts in Denmark (Atladottir et al., 2014; Ellefsen, Kampmann, Billstedt, Gillberg, & Gillberg, 2007; Kočovská et al., 2012; Lauritsen, Pedersen, & Mortensen, 2004; Parner et al., 2011), Sweden (Barnevik-Olsson, Gillberg, & Fernell, 2010; Fernell & Gillberg, 2010; Gillberg, Cederlund, Lamberg, & Zeijlon, 2006; Idring et al., 2012), Finland (Atladottir et al., 2014; Kielinen, Linna, & Moilanen, 2000), and Western Australia (Atladottir et al., 2014; Leonard et al., 2011; Nassar et al., 2009; Parner et al., 2011). Registration of all diagnoses in the Danish, Swedish

and Finnish registries is mandatory, with few exceptions (Atladottir et al., 2014). National registries seem to be most successful in countries that have a single health care system and are relatively small in area, permitting a limited number of centralized diagnostic centers. Using national registries to find ASD cases has a number of benefits because the sample population is usually quite large, well-defined, and can be considered to include all cases in a birth cohort in the area of interest. However, ASD diagnoses in registries reflect the current diagnostic criteria and practices by local physicians at any given time, which are of unknown validity and vulnerable to change over time. In most cases, validation studies have been performed with a subsample of registrants to evaluate the concordance between a registry diagnosis and in-depth diagnostic assessment, but these subsamples are usually small and circumscribed in time and place, thereby reducing their generalizability to the entire registry (Lampi et al., 2010; Lauritsen et al., 2009). In other studies, investigators have taken a rigorous approach to case evaluation, such as direct evaluation of individuals with a recorded ASD diagnosis and in-person interviews of family members in subsequent phases of the survey (Kočovská et al., 2012; Saemundsen, Magnusson, Georgsdóttir, Egilsson, & Rafnsson, 2013). However, national registers require an infrastructure not currently in place in the U.S.

3.2.1.2. Educational records. Some studies have taken advantage of the fact that ASD is a mandatory reporting category under the US Individuals with Disabilities Education Act, and thus has been reported by all states to the US Department of Education since 1990 (Gurney et al., 2003; Maenner & Durkin, 2010; Shattuck, 2006). A major benefit of using educational data is that it is universally reported, and because annual data are available, time trends in prevalence can be estimated. Additionally, because of compulsory education laws in the U.S. that require school attendance, coverage of the child population is likely to be quite high (although the age ranges and number of years required vary by state). However, there are several limitations to using special education categories to identify individuals with ASD. First, states vary widely in ASD eligibility criteria requirement, as well as in assessment practices and the ASD-specific expertise of special education assessment teams (Barton et al., 2015; Brock, Huber, Carter, Juarez, & Warren, 2014). Currently, only two states (Maine and West Virginia) specifically refer to the use of DSM criteria during autism eligibility assessments for special education (Barton et al., 2015). Second, ASD determinations are made in the educational setting for service use purposes. Thus, if a child who meets the ASD case definition is not known in the educational system (i.e., those who are home-schooled), or is not using any services (or discontinued

service use), he/she might not be counted, resulting in underestimation of prevalence. In addition, often only the primary disability category is reported; if a child had multiple disabilities (e.g., Down Syndrome and ASD), he/she might not be counted as having ASD. Conversely, there is also concern about over-ascertainment of ASD in educational service use data. Though the Department of Education uses a similar case definition to current DSM criteria, it is somewhat more broad. As a result, an educational determination is not equivalent to a medical diagnosis (Shattuck, 2006), and might be assigned to provide supportive education services even though a child does not meet standard diagnostic criteria. Again, as with other recorded diagnoses, the validity of an ASD special education designation against expert clinical judgement is unknown.

3.2.1.3. Health records. Many ASD surveys have relied on existing health records to identify individuals currently carrying a medical diagnosis of ASD in a given community (Chien, Lin, Chou, & Chou, 2011; Croen, Grether, Hoogstrate, & Selvin, 2002; Davidovitch, Hemo, Manning-Courtney, & Fombonne, 2013; Lingam et al., 2003; Taylor, Jick, & MacLaughlin, 2013; Taylor et al., 1999; Wong & Hui, 2007). Surveys of ASD capitalizing on existing diagnoses in health records (e.g., ICD-9 or 10 codes) rely on specific diagnostic codes for counting ASD cases (Lingam et al., 2003; Taylor et al., 1999; 2013). The benefit of this approach is that these codes are uniform across health systems and payers, so a consistent case definition based on standard diagnostic categories is used. However, the disadvantage is that little data about the quality of the ASD diagnosis are available. This is particularly of concern for ASD, since the standard of care for diagnosis requires comprehensive testing by a multidisciplinary team (Johnson, Myers, and the Council on Children With Disabilities, 2007). Thus, as in a national registry, the mere presence of an ICD, DSM, or current procedural technology code indicating an ASD diagnosis does not guarantee that the standard of care was applied, and the validity of such codes against expert clinical judgement is unknown. As a result, it is possible that a diagnostic code for ASD may be recorded when a provider has a concern for ASD risk, when a parent reports a diagnosis from elsewhere, when no comprehensive diagnostic evaluation has been performed, or when the quality of the diagnostic assessment is poor, which might lead to upward bias in prevalence estimates due to the presence of false positives. Conversely, some individuals with ASD may have had limited contact with the health care system, and therefore may not have any records documenting the presence of an ASD diagnosis, which might bias prevalence estimates lower due to the presence of false negatives. Thus,

misclassification bias is a substantial limitation of studies that use health records as the only data source.

3.2.1.4. Service provider records. Some ASD surveys rely on existing service provider databases to identify cases in a given geographical area. In the US, a study by Croen and colleagues (2002) used data from the California Department of Developmental Services (DDS) to find ASD cases with a diagnosis of "full syndrome" autism as defined by the DDS. As with other convenience samples, similar concerns apply here about the validity of the diagnoses in the databases and nonrepresentativeness of the sample to the population of individuals with ASD as a whole (Fombonne, 2001). Furthermore, eligibility to autism services in California has fluctuated as a function of budget constraints, adding another source of variability in reporting of ASD in the DDS database. Trends over time based on service access data are additionally confounded by many factors such as referral patterns, availability of services, heightened public awareness, decreasing age at diagnosis, and changes over time in diagnostic concepts and practices, all factors that have been described with various degree in studies relying on this source (King & Bearman, 2009; Schechter & Grether, 2008; Van Meter et al., 2010).

3.2.2.Random sampling

If random sampling is an option, several approaches to case-finding are possible. Some national surveys in the US rely on selecting a random sample of households (Blumberg, Bramlett, Kogan, Schieve, & Lu, 2013; Zablotsky, Black, Maenner, Schieve, & Blumberg, 2015), although these surveys have identified ASD cases based on parent report alone without independent validation of cases by professionals at a later case evaluation phase. Concerns about this approach are similar to insurance claims case-finding methods; e.g., the diagnosis may be reported by parents when the child does not meet diagnostic criteria, or else a child who meets the ASD case definition may not actually have a formal ASD diagnosis. Moreover, such surveys typically cannot define ASD caseness based on standard diagnostic criteria, as individuals are unable to be evaluated. However, it should be noted that surveys using this approach to case finding have yielded similar prevalence estimates to those using more rigorous approaches in the U.S. (Blumberg et al., 2013).

A more robust way to estimate ASD prevalence is to use probabilistic random sampling in the context of a multiphase survey. Multiphase sampling designs have a long history in epidemiology (Neyman, 1938), particularly when case evaluation is difficult or expensive to do (Pickles, Dunn, &

Vazquez-Barquero, 1995). In multiphase surveys, the initial screening phase serves the purpose of casting a wide net to identify individuals possibly affected with an ASD, with the final diagnostic status determined in a subsequent case evaluation phase for a subset of individuals.

Multiphase designs have been adopted in several ASD surveys with mixed success. A number of unique challenges are presented in each phase of such a design in the context of an ASD survey. For example, the sensitivity of the screening method is important (with ASD, none have perfect sensitivity) and, even with validated instruments, is unknown in any one survey sample. Typically, investigators must make assumptions about the number of individuals with ASD who are missed in the screening phase (false negative screens), and this number is often arbitrarily assumed to be zero (Pantelis & Kennedy, 2015). Because false negatives remain unknown to investigators, it is not possible to adjust for the insensitivity of the screening phase, leading to underestimation of ASD prevalence. One approach is to randomly sample screened negative individuals to include in the case evaluation phase in order to estimate the proportion of false negatives and adjust estimates accordingly. This additional step is not typically undertaken, likely due to lack of resources combined with a lack of access to individual respondents. Also, in both phases, non-response bias can dramatically impact prevalence estimates, yet is difficult to assess (Newschaffer, 2015; Pantelis & Kennedy, 2015). Again, investigators typically assume that individuals with and without ASD are equally likely to participate in both the screening and evaluation phases, although this may not be a valid assumption. For example, Posserud, Lundervold, Lie, & Gillberg (2010) reported an ASD prevalence of 72/10,000 in their identified sample and estimated a prevalence of 128/10,000 in the group of nonresponders (based on teacher ratings during the screening phase), indicating increased refusal rates among individuals with more ASD symptoms and thus underestimation of prevalence based on the identified sample. On the other hand, Webb et al. (2003) reported increased refusal rates among individuals with fewer ASD symptoms leading to possible overestimation of prevalence. Thus, uneven participation rates, either due to participant non-response or to lack of documentation in existing health or education records, provides another source of variation in multiphase surveys.

3.2.2.1. Multi-source records-review surveillance. Several large surveys in the U.S. and elsewhere have relied on case finding by accessing records from multiple sources including medical, educational, and/or service records to identify potential ASD cases (Centers for Disease Control & Prevention, 2016; Idring et al., 2012; Kim et al., 2011; Windham et al., 2011). These methods differ from

those discussed above in that case finding is followed by a case evaluation phase, typically conducted by clinician reviewers with specific expertise and training related to ASDs. For example, the CDC ADDM has developed a two-phase methodology that relies solely on access to existing records, without any contact with the family or child. The case finding phase involves systematic screening of multi-source records by trained record abstractors. Records are first reviewed for the presence of either a confirmed or suspected ASD diagnosis, as well as any ASD "triggers" such as poor eye contact, limited interest in other children, being oblivious to others, or persistent focus on sensory input, among others (Avchen et al., 2010; Rice et al., 2007). In the presence of any such indicators, the child is identified as a possible ASD case and his/her records are abstracted if he/she is age 8 and meets the study residency requirement (Centers for Disease Control & Prevention, 2016). One strength of this approach is that a documented ASD diagnosis is not necessary for a child to meet the ASD case definition. In the 2012 survey year, approximately 9% of identified ASD cases had suspicion but not diagnosis of ASD noted in an evaluation and 9% had no mention of ASD in any record (Centers for Disease Control & Prevention, 2016).

This type of approach is labor-intensive: in the 2012 survey year, 48,304 records were reviewed and 9,629 were abstracted (Centers for Disease Control & Prevention, 2016). The CDC has estimated that abstractors spend as much as 55 hours to review/abstract 100 records (Van Naarden Braun et al., 2007). Aside from resource constraints, the major limitation to this type of approach is "documentation bias" (Newschaffer, 2015). That is, factors unrelated to the child's behavior likely influence how much and what type of information gets documented in the existing records (Mandell & Lecavalier, 2014). These include the availability and quality of services (which may vary by state/county/geographical regions), heightened public and professional awareness (also may vary by community), and changes in diagnostic criteria and practices over time (Hill et al., 2014). Documentation bias is also inherent in any case-finding methods that use non-random samples derived from patient registers or administrative datasets.

Another significant drawback to the CDC approach is that it does not estimate the false negative rate, as children without records are not identified in the case finding phase. This is particularly a concern in states with recognized limitations in available services for families (such as Alabama), and for participants who may have more limited access to services such as those from certain immigrant groups, racial/ethnic minorities, or families living in poverty.

3.2.2.2. Multiphase total population surveillance. Instead of relying on existing records or in combination with it, some surveys include screening a random sample of individuals from the target population to identify potential ASD cases (Fombonne et al., 2016; Isaksen, Diseth, Schjølberg, & Skjeldal, 2012; Kim et al., 2011; Kočovská et al., 2012; Nygren et al., 2012). This process often involves reaching out to schools, healthcare providers, and other professionals in a given geographic area to help to identify individuals in the community who may meet the case definition. Then, a screening instrument (such as a brief questionnaire, checklist, or phone-based interview) is administered (phase 1), and individuals who screen positive are invited to return for a diagnostic evaluation (phase 2). In some surveys, a fraction of individuals who screen negative are also evaluated in order to estimate sensitivity of the initial screening.

When designing a multiphase survey to identify ASD cases, there are several key decisions to consider. First, the geographic area to be screened needs to be determined. Since most multiphase approaches are resource intensive at the case evaluation phase, important trade-offs exist between the size of the geographic area surveyed and the quality of the case finding/evaluation methods. Large geographic areas present a number of challenges in the context of a multiphase survey. Specifically, the larger the area surveyed, the greater the number of site-specific teams needed, and thus the greater the between-site variation in estimated prevalence. Ultimately, such surveys typically report an average estimated ASD prevalence across sites, which should not mask the extreme variation in such estimates across sites within the same study using the same case finding and evaluation methods.

Sample size is another important consideration in survey design. Current estimates of ASD prevalence are around 1-2% (Hill et al., 2015). If a survey seeks to conduct meaningful analysis among individuals with ASD, a large sample will need to be screened in order to identify sufficient cases. For instance, conservatively anticipating an ASD prevalence of 1%, it would be necessary to screen about 100,000 to obtain a sample size of 1,000 individuals with ASD. Such efforts require considerable resources.

Careful consideration should also be made about what age range is studied. Age-specific prevalence estimates of ASD are often lower at both ends of the age spectrum (Brugha et al., 2011; Rice et al., 2007). A primary reason for this is that such individuals tend to lack documentation in both health and education records. For example, in the preliminary studies by the CDC, prevalence estimates varied widely from ages 3 to 10, ranging from 1.9/1,000 at age 3 to 4.7/1,000 at age 8, with the

latter reflecting peak prevalence across the eight one-year age bins (Rice et al., 2007). For younger children, the lack of documentation likely reflects the fact that a number of young children with ASD have not yet come to the attention of professionals (Yeargin-Allsopp et al., 2003), signaling the need for more intensive case finding methods to identify young children with ASD. Likewise, older adults with ASD are also likely to lack documentation due to an age bias in ASD diagnosis, as well as changes in public and professional awareness of ASD symptoms, which again signals the need for different and more intensive methods for case finding within an older population. For these reasons, case finding is likely to be most sensitive and valid when concentrated on the population of school-age children.

It is also important to consider which individuals should be excluded from the survey. For example, a disproportionate number of young adults with ASD live in residential settings (Anderson, Shattuck, Cooper, Roux, & Wagner, 2014). Some evidence also suggests that ASD is also over-represented in the U.S. incarcerated population (King & Murphy, 2014). As a result, household-based surveys may significantly under-count people with ASD, particularly those with greater functional impairments. Finally, ASD often exists in concert with other known genetic disorders (e.g. Rett Syndrome, Down Syndrome). Current CDC ADDM protocols exclude children with known Rett Syndrome or childhood disintegrative disorder from ASD surveys (Rice et al., 2007). Thus, when designing an ASD survey, investigators may wish to consider whether individuals with other disorders or who are likely to be missed by sampling households are in the population of interest.

The quality of screening instruments used in multiphase surveys varies widely, ranging from forms with a few clinical descriptors of autism-related symptoms or diagnostic checklists rephrased in nontechnical terms, to more systematic screening strategies based on questionnaires or rating scales of known reliability and validity (Fombonne et al., 2016; Kim et al., 2011). When possible, screening instruments specifically focused on ASD symptomology with basic psychometric properties should be used, and ideally one instrument would be chosen that is appropriate for the full age range in the target population. Instruments with versions intended for different kinds of informants (e.g., both parents and teachers) are also preferred, as well as those with translations available, particularly in Spanish to accommodate respondents with limited English proficiency. For example, the 2nd edition of the Social Responsiveness Scale (SRS; Constantino & Gruber, 2012) is a 20-minute questionnaire with 65 items scored on a Likert scale. Versions are available for parents and teachers to rate individuals between the ages of 2.5 to 18 years. The Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003)

contains 40 yes-or-no questions (taking approximately 10 minutes to complete) designed for parents to answer for children ages 4 and older. These two screening questionnaires are the most widely-used and have the strongest validity, although a range of alternative screening instruments are available, some of which have been developed and used mainly in relatively small regional surveys. A complete review of the psychometric properties of the available ASD screening measures is beyond the scope here, but several reviews are available (Charman & Gotham, 2013; Charman et al., 2007; Johnson, Myers, and the Council on Children With Disabilities, 2007; Lai, Lombardo, & Baron-Cohen, 2014; Norris & Lecavalier, 2010). We note that the majority of screeners have been validated in referred samples, and positive predictive values will be lower in a population sample (Charman & Gotham, 2013).

3.3. Case evaluation: how will you evaluate whether an individual meets the case definition?

Once individuals in the target population have been found, the next step is to evaluate whether or not they meet the ASD case definition. Methods used to evaluate case status vary from passive recording of an administrative diagnostic code to a very intensive diagnostic work-up involving direct testing of a child and a comprehensive evaluation of developmental history arising from multiple data sources. Case evaluation for ASD usually involves a combination of data from multiple informants (parents, teachers, pediatricians, other health professionals, etc.) and multiple sources (medical records, educational sources, direct observation), with a direct assessment of the individual with autism being offered in some but not all studies. A common limitation of all multiphase surveys is that unbiased participation in the case evaluation phase is often assumed; that is, that ASD and non-ASD cases are equally likely to participate. Differential participation could occur in direct evaluations because those with ASD may be more motivated to participate in research about the topic, or in clinical records evaluation because individuals with ASD are more likely to have medical and educational records. Complex survey design, including sampling weights, can be used to adjust for non-participation at both the screening and confirmation phases of research.

3.3.1.1. Direct individual evaluation. When individuals suspected for ASD are directly evaluated, assessments typically use various diagnostic instruments, ranging from an unstructured examination by a clinical expert (but without demonstrated psychometric properties) to the use of standardized ASD assessment tools by trained research staff. As mentioned above, instruments such as the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) have been increasingly used in many recent surveys. Such evaluations require specialized training and specific materials to administer.

For example, the ADOS is a semi-structured autism diagnostic observation for children and adults with demonstrated test-retest reliability, internal consistency, and predictive validity against best estimate clinical diagnosis (Gotham et al., 2007). It is conducted by trained examiners, and an individual evaluation lasts about 45-60 minutes.

Although direct evaluation using instruments like the ADOS is one of the gold standards for detecting and diagnosing ASD (Johnson, Myers, and the Council on Children With Disabilities, 2007; Jones & Lord, 2013), there are significant challenges to implementing this approach across multiple sites (Lord et al., 2012). First, many screening questionnaires for ASD have a high false positive rate. In the context of clinical care, this can be seen as a benefit in order to minimize the risk of a false negative screen. In a multiphase survey, however, this means that large numbers of non-cases will need to evaluated, necessitating considerable resources. Second, because of the time-consuming nature of direct evaluations requiring both parent and child attendance, some families may not have the resources (time, transportation, childcare for other siblings, etc.) to participate in the evaluation phase, potentially limiting representativeness of the ASD individuals whose diagnosis is able to be confirmed. Third, a direct evaluation approach must maintain reliability of procedures and scoring across all staff across all sites (Lord et al., 2012), which poses real challenges in the context of a nationally representative survey with multiple sites spanning large geographical areas.

3.3.1.2. Informant-based evaluation. Another option for case evaluation is to rely on interviews of informants knowledgeable about the child's early development and current behaviors. Several standardized parent/caregiver interviews have been developed that gather information specific to ASDs from knowledgeable informants including the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994), the Diagnostic Interview for Social and Communication Disorders (Leekam, Libby, Wing, Gould, & Taylor, 2002; DISCO; Wing, Leekam, Libby, Gould, & Larcombe, 2002), and the Developmental, Dimensional, and Diagnostic Interview (3di; Skuse et al., 2004). Like direct evaluation instruments, these interviews require significant training to administer, and last approximately 2-3 hours. Similarly, the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS; Kaufman et al., 1997) is a semi-structured clinical diagnostic interview that comprehensively covers most child and adolescent psychopathology, including autism. The K-SADS interview for parents is concise and generates information on core symptoms of ASD. The combination of direct evaluation and informant-based methods is associated with higher sensitivity and specificity compared

to when a single instrument is used (Risi et al., 2006), and several ASD surveys have taken this comprehensive approach to case evaluation (Fombonne et al., 2016; Isaksen et al., 2012; Kim et al., 2011; Mattila et al., 2011; Nygren et al., 2012). However, their use is recommended jointly with other structured observational methods or they may necessitate direct observations of the target child by the interviewer.

A comprehensive diagnostic evaluation may not be feasible when the geographical area for a survey is quite large. Likewise, although "gold standard" informant interviews may be preferable to direct evaluation for logistical reasons, it also may not be possible to conduct 2-3 hour interviews with all screen positive families. One compromise is to instead use a briefer structured interview tool such as the Development and Well-being Assessment (DAWBA; Goodman, Ford, Richards, Gatward, & Meltzer, 2000), which gathers ICD/DSM-relevant information but takes only 20 minutes to administer. The DAWBA is designed to capture information about most common psychiatric disorders, and has been used in several previous ASD population surveys (Fombonne, Simmons, Ford, Meltzer, & Goodman, 2001; Heiervang et al., 2007; Mullick & Goodman, 2005). The DAWBA now has a separate module for ASD, which has been shown to have acceptable sensitivity and specificity (McEwen et al., 2016; Posserud et al., 2010). The DAWBA is administered by trained nonclinician interviewers who interview parents about psychiatric symptoms and their functional impact. Skip rules and screening questions allow for a reduction of administration time. Positive symptoms are followed up by open-ended questions and supplementary prompts, and parental descriptions are entered verbatim (but not rated) by the interviewer into a computer. One drawback to the DAWBA is that the validity of the algorithm against best estimate clinical judgement of an ASD diagnosis is not known. In one study, the DAWBA was not positive for ASD for any of 938 screen negative children, and of the 87 screen positive children, DAWBA classification for ASD was in 100% agreement with ASD classification based on the DISCO interview conducted in a third phase (8 out of 10 identified by the DAWBA, 2 did not complete the DISCO). However, an additional 5 children out of 14 interviewed with the DISCO were identified with ASD who were missed by the DAWBA (Posserud et al., 2010). The investigators noted that 4 out of the 5 children missed by the DAWBA had IQ-levels of 70, and suggested that the DAWBA may be more sensitive among children with lower ranges of intellectual ability (Posserud et al., 2010). The researchers who developed the ADI-R (S. Bishop and C. Lord) are also reportedly developing and

validating a 20 minute telephone screener, the Autism Screening Interview (ASI), which may become available and prove useful in epidemiological surveys (Charman & Gotham, 2013).

Although a common limitation of all informant-based methods in the absence of direct evaluation is the lack of contact with the individual suspected of having ASD, such methods have the benefit of being relatively less resource-intensive, and may be less vulnerable to documentation bias (compared to records-based evaluation) and differential participation bias (compared to direct evaluation). As well, unlike the ADI-R and similar instruments, interviews like the DAWBA or ASI do not require interviewers to have clinical training, often only requiring a brief training to administer the interview. Instruments like these could be paired with clinical review of medical/education records to improve the sensitivity and validity of case evaluation.

3.3.1.3. Clinical records evaluation. Surveys of large populations, such as those conducted in the United States' CDC ADDM Network (2007; 2009; 2007; 2012) or in European national registers (Idring et al., 2012), rarely include direct or informant-based evaluations. For example, the CDC ADDM network gathers the records abstracted during the earlier case finding phase, and evaluates them in a separate, independent process, again without contact with the child or family. In the second phase, trained clinicians review each abstracted record and apply a standardized coding scheme (regardless of whether a formal diagnosis is present). A standardized case algorithm based on DSM-IV-TR diagnostic criteria is then used to identify ASD cases, and a second and sometimes third independent review is conducted should the first clinician reviewer disagree with the algorithm classification (Avchen et al., 2010). Specifically, an ASD case had to have at least 1 social and either 1 communication or 1 behavioral criterion for autism clearly documented (Yeargin-Allsopp et al., 2003). A recent validation study on a small sample indicated a low sensitivity (0.60) for the record-review procedure when compared to an in-depth clinical evaluation (Avchen et al., 2010). Furthermore, substantial misclassification occurred with 21% of record-review cases not confirmed with ASD by clinical evaluation, and 9% of non-cases by record review being determined to be ASD cases by the clinical method. As a result, potential underestimation of prevalence by a factor of 32% could have occurred (Avchen et al., 2010). In addition, although this case evaluation methodology is more efficient than direct evaluations, it is still rather resource-intensive and would be expensive to conduct on a large, nationally-representative sample.

4. What estimates do we currently have for ASD prevalence in the US?

4.1. Center for Disease Control & Prevention

Since 2000, the CDC has conducted active ASD surveillance of children age 8 using the same methodology across defined sites in two-year cycles. These surveys are currently the only in the US that could be considered to be approximately nationally representative; however, it must be stressed that a systematic population-based survey of the country was not done. Participating states are not chosen at random, but rather through a competitive funding process. Within selected states, survey areas are also selected for convenience. The case definition across all survey years and sites has been based on DSM-IV-TR diagnostic criteria. As already described, the case-finding method is multi-source records review surveillance, followed by a case evaluation phase conducted by expert clinical reviewers. The most recent results based on the 2012 survey year (2004 birth cohort) indicate that 1 in 68 children aged 8 in the US meet surveillance criteria for ASD (Centers for Disease Control & Prevention, 2016). The CDC has also recently developed the Early ADDM Network, which is a subset of sites from the larger ADDM Network that survey children age 4 using the same methods (Christensen et al., 2016). In the first Early ADDM report based on the 2010 survey year, 1 in 75 children aged 4 met ASD criteria (Christensen et al., 2016). Of note, one of the biggest sources of variability across sites within the ADDM Network is records access. For example, average ASD prevalence among children aged 8 was 17.1 per 1000 for ADDM sites with access to both health and education records in 2012, compared to 10.7 per 1000 for sites with primarily access to health records (Centers for Disease Control & Prevention, 2016). Similarly, in the Early ADDM, ASD prevalence among sites with access to both health and education records was nearly double that for sites with access to health records only (Christensen et al., 2016). In general, ASD prevalence estimates from the CDC ADDM demonstrate high state-to-state variability (see Figures 1 and 2). These differences likely reflect ascertainment variability across sites in a study that was otherwise performed with the same methods, at the same time, on children of the same age, and within the same country.

4.2. National Health Interview Survey

The National Health Interview Survey is an annual household interview survey of the civilian, non-institutionalized US population funded by National Center for Health Statistics (NCHS), which is part of the CDC. The survey has a multiphase area probability design that permits the representative sampling of US households. The survey itself collects data via self report for those ≥ 17 years old, and via a "parent or knowledgeable adult" for children between 2-17 years. The response rate for the NHIS Child Core survey is approximately 70%. Multiple survey years can be combined to increase the

sample size; however, the wording as well as the placement of the autism item in the Child Core Survey has varied over the years, and changes in this item have been shown to affect reported prevalence rates (Zablotsky et al., 2015). The NHIS does not include confirmation of parent-reported diagnoses either through health/educational records or direct evaluation. From 1997 through 2013, parents were provided a 10-condition checklist, asked to read through the list, and instructed to indicate whether a doctor or other health professional had ever told them that the child had any of the conditions listed; in 2004-2011, the condition was worded used the name the condition was "autism" whereas in 2011-2013 the wording was modified to "autism/autism spectrum disorder" (Zablotsky et al., 2015). In 2014, the NHIS included a stand-alone question about the presence of ASD for children age 2-17 only, using the language "Has a doctor or health professional ever told you that [child] had Autism, Asperger's disorder, pervasive developmental disorder, or autism spectrum disorder?" Notably, in 2014, this question was asked before asking parents about whether their child had any other developmental delay- which is opposite of the order presented to parents in previous years (Zablotsky et al., 2015). In 2014, the survey sample size for ASD was 243. The most recent prevalence data from the NHIS was 2.24% based on 2014, which is somewhat higher than most other recent estimates (Hill et al., 2015) and than earlier NHIS surveys, which investigators posited might signal that previous estimates were biased downwards because parents of children with ASD said "yes" to the first question about developmental delays first before being asked about ASD (Zablotsky et al., 2015). Alternatively, it is possible that parents report a diagnosis that may have been considered but not confirmed.

4.3. National Survey of Children's Health

The National Survey of Children's Health is a periodic telephone survey of the non-institutionalized population of US children aged 0-17 years. The goal of the survey is to produce national and state-based estimates on the health and well-being of children, their families, and their communities. The National Survey of Children with Special Health Care Needs (NS-CSHCN) is a similar telephone survey whose goal is to assess the prevalence and impact of special health care need among US children aged 0-17 years. Both surveys are funded by the National Center for Health Statistics via the CDC, and are sponsored by the Maternal Child Health Bureau of the Health Resources and Services Administration. Data from the NSCH were collected in 2003, 2007, and 2011-12, and data from the NS-CSHCN were collected in 2001, 2005-6, 2009-10. Both surveys produce valid estimates of

parent-reported disease prevalence on a state level. Data from prior surveys were collected via parent telephone interview and used the National Immunization Survey sampling frame. Since 2012, the Maternal Child Health Bureau has been planning a survey redesign, and the next NSCH and NS-CSHCN will be a combined survey that is fielded annually by the Census Bureau, using an address-based sampling frame with primarily mail/web modes of administration. In both surveys, and in the planned redesign, the case definition for ASD is based on parent report, using the item, "Has a doctor or other health care provider ever told you that [child] has Autism, Asperger's Disorder, pervasive developmental disorder, or other autism spectrum disorder?" Parents who answer affirmatively are asked "Does [child] still have autism or autism spectrum disorder?" Age of ASD diagnosis is also obtained. Children were classified as an ASD case if their parent answered yes to both questions. However, there is no confirmation of parent-reported diagnoses through health/educational records or direct evaluation. The sample size for ASD in the 2011-12 NSCH is 1,624. The sample size in the 2009-10 NS-CSHCN is 3,055. The estimated prevalence of ASD in the National Survey of Children's Health in 2011 was 2.00%, which is similar to the NHIS estimate (Blumberg et al., 2013).

4.4. Other large-scale U.S. surveys

While other studies have not attempted to make nationally-representative assessments, they have assessed autism prevalence in defined US geographic areas. All US prevalence studies with clear case definitions and sample sizes > 5,000 are shown in Tables 1 and 2.

5. What are the characteristics of an "ideal" ASD survey in the US?

In the US, there is currently no active ASD surveillance based on a nationally representative sample obtained with probabilistic sampling methods. An ideal survey for providing such an estimate for the US would have: (a) a well-defined *case definition* based on standard diagnostic criteria allowing comparisons with other surveys; (b) a *case finding* method that involves systematic random sampling from the target population in concert with a robust, consistent screening method that does not rely solely on either parent reported diagnoses or on the existence of a formal ASD diagnosis; and (c) a *case evaluation* phase that involves independent validation of caseness by a professional. As noted previously, the larger the geographic area to be surveyed, the more expensive and time-consuming the process will be for case finding. If the goal is to design a nationally representative survey, then the geographic area to be surveyed is quite large, and will limit the case evaluation options available.

6. What kind of survey is feasible under realistic circumstances?

6.1. Case definition

For prevalence estimates to be reliable and comparable, case definitions for ASD should follow the diagnostic criteria set forth by the DSM, which is the standard diagnostic nosography in the US. However, this is somewhat challenging given the unknown impact of DSM-5 on prevalence estimates. For this reason, it might be beneficial to design a survey which can estimate ASD prevalence simultaneously based on DSM-IV-TR and DSM-5 criteria. The benefit to including DSM-IV-TR criteria is to keep the ability to compare ASD prevalence estimates to others obtained in US surveys. In addition, ICD is used for discharge diagnoses and claims in several information systems and depending on the expected use of the data, incorporating an ICD-based definition might be wise (the ICD-10 does not differ much from DSM-IV-TR; the relation between DSM-5, ICD-10 and the future ICD-11 is not known).

6.2. Case finding

After selecting the geographic area to be surveyed, the next decision is to select the age of the survey sample. If a whole population prevalence estimate is desired, then the survey would need to include individuals between the ages of 5 to 89 years. Surveying autism in adults is likely to be much harder than with children due to the lack of tools and informants, underdiagnosis in older birth cohorts, and potential age bias resulting from the fact that many adults with ASD will lack documentation in available records. In a recent study of adults with ASD (ages 18-52), self-reported ASD symptoms were uncorrelated with maternal reported symptoms, and only 44% of individuals met the screening questionnaire "cut-off" (Bishop & Seltzer, 2012), indicating that self-report may not be a reliable case-finding method for an adult population. The benefits of sampling younger children are that parents can be queried retrospectively about their child's developmental history, and there are tools that are validated for structuring these types of interviews. As well, even if parents either did not notice symptoms early on or they have been unable to act on their concerns, children will often have encountered other adults by school-age such as teachers who can corroborate parents' reporting of early symptoms. If the goal of the survey is to track trends over time, a school-age population is probably the best, with a target age range between 6 or 7 to 15 years.

Once the geographic area and age have been set, the final key decision to make is the sample size needed. The sample size needed depends on the age of the target population to be sampled. To get

an accurate prevalence estimate, we would want to conservatively plan to identify 50-100 children with ASD in *each* one-year age bin. For example, if the population of school-age children (6-15 years) in the U.S. were determined to be the target population, we would plan to identify 1,000 children with ASD: 100 across each of the 10 one-year age bins. Conservatively estimating an ASD prevalence rate of 1%, we would need to survey a total population size of 100,000 children between the ages of 6 and 15. If instead the goal is to build on current National Survey on Drug Use and Health (NSDUH; Center for Behavioral Health Statistics and Quality, 2015) efforts, which survey children ages 12 and older, another possibility is to enrich the number of 12-18 year-olds included in the sample. In this scenario, we would plan to identify 700 children with ASD: 100 across each of the 7 one-year age bins. Again, conservatively assuming a 1% prevalence, we would need to survey a total population size of 70,000 children between 12 to 18 years of age. One difficulty with sampling from this age range is that older children may be more likely to reside outside of the home, which introduces a potential source of bias due to lack of coverage of individuals residing in residential settings (Mandell, 2008). It also may be beneficial to consider oversampling children aged 8 if one goal is to generate precise prevalence estimates that could be compared to those obtained in the CDC ADDM surveys.

Household surveys like the NSDUH offer a unique opportunity to estimate ASD prevalence. However, if the age range included adults, some adult populations are likely to be missed in a household survey, such as individuals from certain immigrant groups (undocumented, migrant or seasonal, or recently arrived), as well as those who are incarcerated, homeless, or in the military. Sampling from populations in these types of settings could supplement a household survey in order to provide representative population-based estimates. Also, in order to ensure that there are enough members of certain minority groups to provide reliable estimates for different racial/ethnic groups such as Native Americans, Alaskans, and Hawaiian/Pacific Islanders, investigators may wish to oversample by selecting more people from these groups considering that response rates can be lower in these groups.

How could a good ASD case-finding strategy work in the context of a nationally representative sample? Currently, the NSDUH involves professional interviewers who personally visit selected homes based on a random sample of households across the US. The interviewers who conduct the in-home visits could be trained to conduct brief semi-structured interviews with parents to query about their children's development, but would not need to have any clinical training or background. During the

visit, the trained interviewer could begin with a brief screening interview with one or more of a child's parents and/or primary caregivers. This screening interview would include 3-6 key questions such as: (1) whether the child has ever been evaluated for ASD, (2) whether the child has a diagnosis of ASD (and at what age), (3) whether the child has an individualized education plan at school that indicates ASD or social/communication problems, (4) whether anyone (such as a healthcare provider, educator, or other professional) has ever suggested that the child has ASD, (5) whether parents ever had any developmental concerns about the child's language, social, or communication abilities before age 3, and (6) how the child's current behaviors impact his/her daily living skills such as learning and functioning at school, peer relationships and friendships, family life, and leisure activities. Based on this screening interview, an algorithm could be developed that would allow the trained examiner to determine in real time whether or not the target child has "screened positive." This algorithm would likely be similar to that used by the CDC ADDM in the decision to abstract a child's record (Rice et al., 2007). This screening interview would need to be validated in a separate sample of parents with children in the same age range as the target population who either are diagnosed with ASD or who are typically-developing or presenting with non-ASD behavioral/emotional problems. The validity of the screener would need to be determined prior to implementation, choosing the combination of questions based on sensitivity to ASD diagnosis. For example, it may be that any answer of "yes" should be considered a positive screen, or that "yes" responses to more than one question should be considered positive.

In the case of a positive screen, the interviewer would begin a second, more in-depth interview focused on gathering information specific to ASD, for example, based on the DAWBA that is specific to ASD (McEwen et al., 2016). This second interview would take an additional 20 minutes to complete. To screen for false negatives, this second interview should be conducted on 1 out of every 5 or 1 out of every 10 screen negatives as well. Interviewer training should emphasize the need to obtain respondents' descriptions of any problems and concerns in their own words, facilitating this with open-ended prompts. Interview materials may need to be adapted to particular circumstances such as for children with ASD who are orphans or have been adopted. It may also be beneficial to ask caregivers for consent to audio record such an interview, allowing for a later second reviewer to independently code responses for a subset of respondents (15-20%) to estimate agreement.

At the end of the interview, parents could be asked to nominate a teacher who knows their child well; a teacher version of a questionnaire such as the SRS or the Strengths and Difficulties

Questionnaire (Goodman, 2001) would then be mailed to this teacher. Reminder letters could be sent to teachers who do not respond. Parents could also be asked to sign a consent form to access medical records for the child in question. While requests for additional information from health or education sources might not be made available for many respondents, including such requests even for a small subsample of respondents would be useful to validate the survey core definition with more comprehensive data sources.

6.3. Case evaluation

Clinical expert review could then be conducted based on all the information gathered. Some individuals who screen positive will only have information gathered by the interviewer (initial + DAWBA or alternative measure); a subset of families will complete the full inventory of measures including the teacher questionnaire and medical records. Others may consent to the request for some but not all documents. A process for following up with families to retrieve as complete information records as possible could be implemented. Interviews like the DAWBA have an algorithm that, based on the answers entered, classifies children as meeting criteria for ASD or not. Clinical reviewers would have expertise specific to ASD, and would review all available documents alongside the DAWBA output. A consensus review process could be called upon in cases where reviewers disagree with the algorithm classification. Although incomplete records would be a limitation, analyses could be conducted to estimate the effect of missing data on prevalence estimation.

Again, as with any epidemiological survey of ASD, the prevalence estimates obtained would be imperfect. One limitation would be the absence of direct assessment of individual children. However, conducting direct assessments of children have their own pitfalls. One way to address this limitation is to subsample from those children that screen positive on the household visit and invite them for a diagnostic evaluation, in which an ADOS for example could be conducted. Another possibility is to include a calibration sample, in which the interview phase is tested with a sample of children with a known diagnosis of ASD. However, the main drawback to both of these approaches is that the samples are not likely to be representative. Additionally, such surveys lack information on non-responders, which forces investigators to make several analytical assumptions that may or may not be tenable had more details been known about the non-responders.

6.3.1. What additional information should be collected?

Any national estimates of ASD should collect information on other factors that are known to affect ASD prevalence rates. This would not only be helpful for descriptive characterization of the study sample, but also would allow for statistical adjustment for complex sampling designs, or imputation of missing data.

6.3.1.1. Intellectual ability. Recent data has shown interesting time trends in the prevalence of comorbid intellectual disability and ASD: As the overall prevalence of ASD has increased, the prevalence of ASD without comorbid intellectual disability has also increased, and the most recent estimate from the ADDM survey showed that about 68% have reported IQs within the normal to borderline range (> 70). Correspondingly, the odds of being classified in the learning disability (odds ratio: OR = 0.98) and the mental retardation categories (OR = 0.97) have also decreased (Shattuck, 2006). Collecting information on intellectual disability can be challenging, since a direct measurement approach is time-consuming. However, this information is well captured in U.S. educational service use data. ASD estimates based on parent survey alone have also attempted to assess rates of comorbid intellectual disability by directly asking parents whether their child has intellectual disability. However, there is concern that parent-reported prevalence rates may be affected by confusion about the terms "intellectual disability," "mental retardation," and "developmental delay," particularly among young children.

6.3.1.2. Language level. A current estimate of language level (e.g., based on the four categories used in the ADI-R to assess overall verbal communication competence) would be useful to describe and analyze the sample.

6.3.1.3. Comorbid medical and psychiatric conditions. Comorbid psychiatric conditions, such as depression, anxiety and attention deficit hyperactivity disorder, are common in ASD (Lever & Geurts, 2016; Simonoff et al., 2008); thus; collecting data on the prevalence of these comorbid conditions would be of research interest. Rates of these conditions could be ascertained by parent/individual report. Brief, validated screening instruments are also available for depression and anxiety, which could be incorporated into a survey instrument for direct measurement. Information on current drug use may be added. In addition, the co-occurrence of sleep disturbances, GI problems, epilepsy, metabolic and genetic disorders would be useful alongside key health indicators such as height and weight (allowing calculation of BMI and tracking obesity rates).

6.3.1.4. Race/ethnicity. Multiple surveys suggest that ASD prevalence rates are lower in the US Hispanic and non-Hispanic Black population. As noted previously, this difference is thought to be mainly related to undercounting as a result of differential health care and educational service access and use. Obtaining adequate ASD counts in these populations may be particularly challenging since minority populations are less likely to participate in research; thus, oversampling of these populations may be necessary.

6.3.1.5. Socio-economic status. The reported prevalence of ASD in the U.S. is lower in families of lower socio-economic status (e.g., lower parental educational attainment, lower household income) (Bhasin & Schendel, 2007; Durkin et al., 2010). However, it is thought that much of this difference relates to lack of service use access instead of a true prevalence difference, since rates in other countries with more equitable health care access have shown no difference, or even have shown higher prevalence rates among families of low socio-economic status (Rai et al., 2012). In any case, measurement of components of socio-economic status alongside estimates of ASD prevalence provides important information about the population surveyed.

6.3.1.6. Affected siblings. Supporting the role of genetics in ASD is the fact that siblings of individuals diagnosed with ASD are at an elevated risk for being diagnosed with ASD themselves. The most comprehensive study to date on 664 infant siblings of children with ASD found that the sibling recurrence risk is 18.7%, with an even higher recurrence of about 26% among male infant siblings (Ozonoff et al., 2011). Knowledge about the number of children affected by ASD within families would be valuable to gain in the context of a household survey, and are a potential source of variability in current ASD prevalence estimates across surveys. Currently, other similar U.S. household surveys that query parents about ASD randomly select one child from each family to be the survey subject (Blumberg et al., 2013; Zablotsky et al., 2015), whereas CDC ADDM estimates do not randomly sample from families. There is strong current research interest in understanding the genetics of autism in children with and without a family history.

7. Leaner design options

The suggested design could be amended in several ways to reduce costs and increase feasibility. One possibility is to restrict the validation of the screening questions to a subsample (e.g. 1 in 2 positive) or to one survey area (which might allow to train only a fraction of survey interviewers

administering longer interviews); similarly, the in-depth interviewing of screen negatives could be restricted in the same manner.

Another option would be to simplify the in-depth validating interview (suggested above for all positive screens and a fraction of the negative screens) to a less open-ended, less semi-structured format. In essence, the simplification would collect data at a symptomatic level in a way that is consistent with existing diagnostic schemes; the questions would be read aloud to parents with minimal request by the interviewer to write down behavioral descriptions. Each question would map on the diagnostic criteria laid out in the DSM and questions on each diagnostic criterion could be illustrated by several indicators (symptoms) commonly observed by parents that tap the same underlying abnormality. Answers could be divided between the current period and prior developmental history to account for developmental changes in symptomatic expression. Interviewer training would thus be reduced and data could be scored during the interview, allowing the application of diagnostic algorithms to generate automated diagnoses at the analysis stage. Such a simplified structured diagnostic questionnaire could be derived from existing interviews (such as the DAWBA, the K-SADS, the DISCO, or the ADI-R) and questionnaires (SCQ, SRS, etc.) but would have to be validated within the survey and/or separately.

Finally, questions on correlates regarding affected siblings or medical/psychiatric comorbidity could be dropped. It is assumed the survey would generate data on certain demographic variables like socio-economic status and race/ethnicity. Maintaining a way to stratify ASD children by degree of severity as indexed by intellectual functioning and language level remains important.

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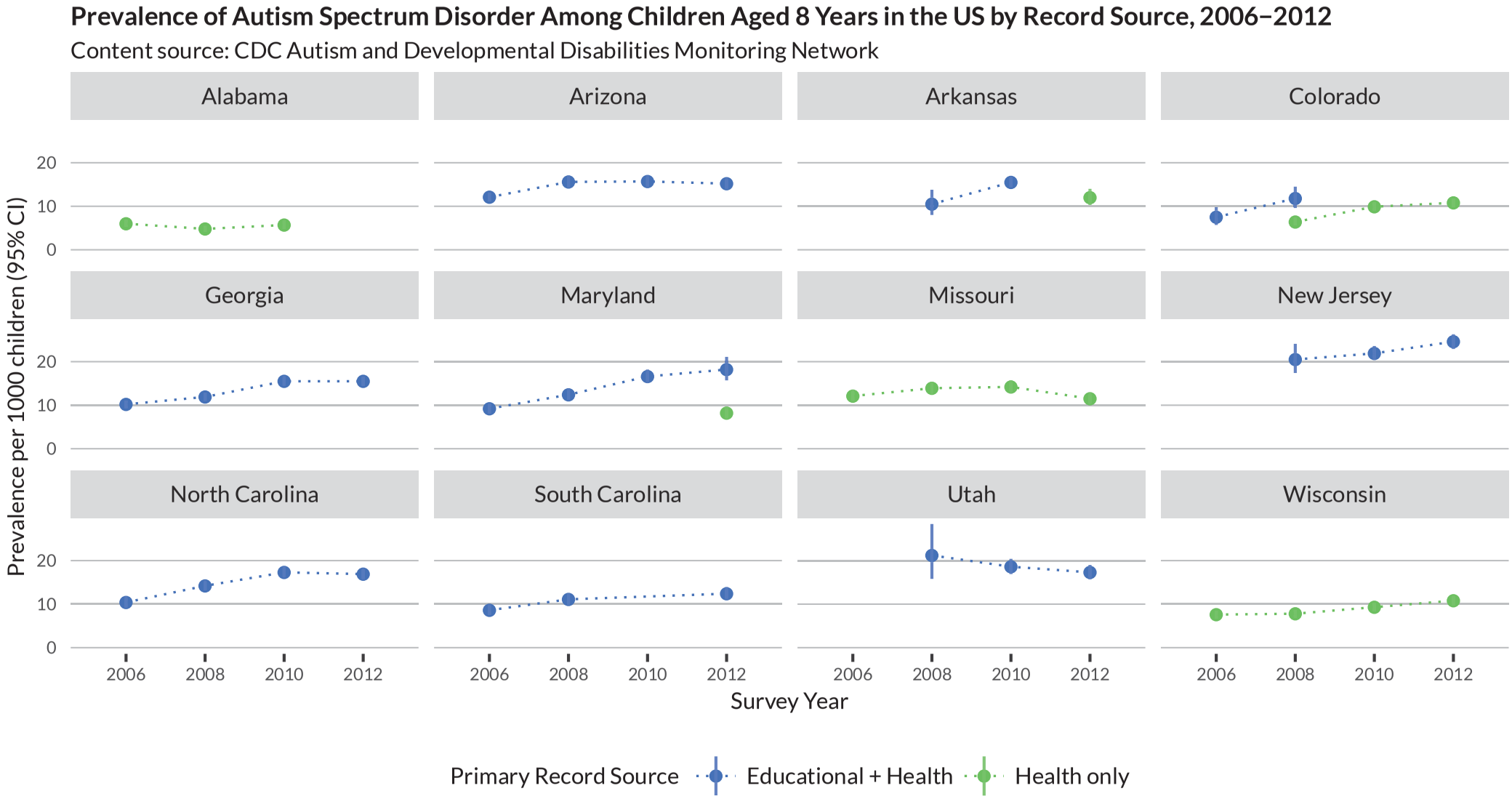
Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years in the US by Record Source, 2006–2012
Content source: CDC Autism and Developmental Disabilities Monitoring Network
Alabama
Arizona
Arkansas
Colorado
Georgia
Maryland
Missouri
New Jersey
North Carolina
South Carolina
Utah
Wisconsin
Prevalence per 1000 children (95% CI)
0
10
20
2006
2008
2010
2012
Survey Year
Primary Record Source
Educational + Health
Health only

Figure 1

Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years in the US by Race/Ethnicity, 2006–2012

Content source: CDC Autism and Developmental Disabilities Monitoring Network

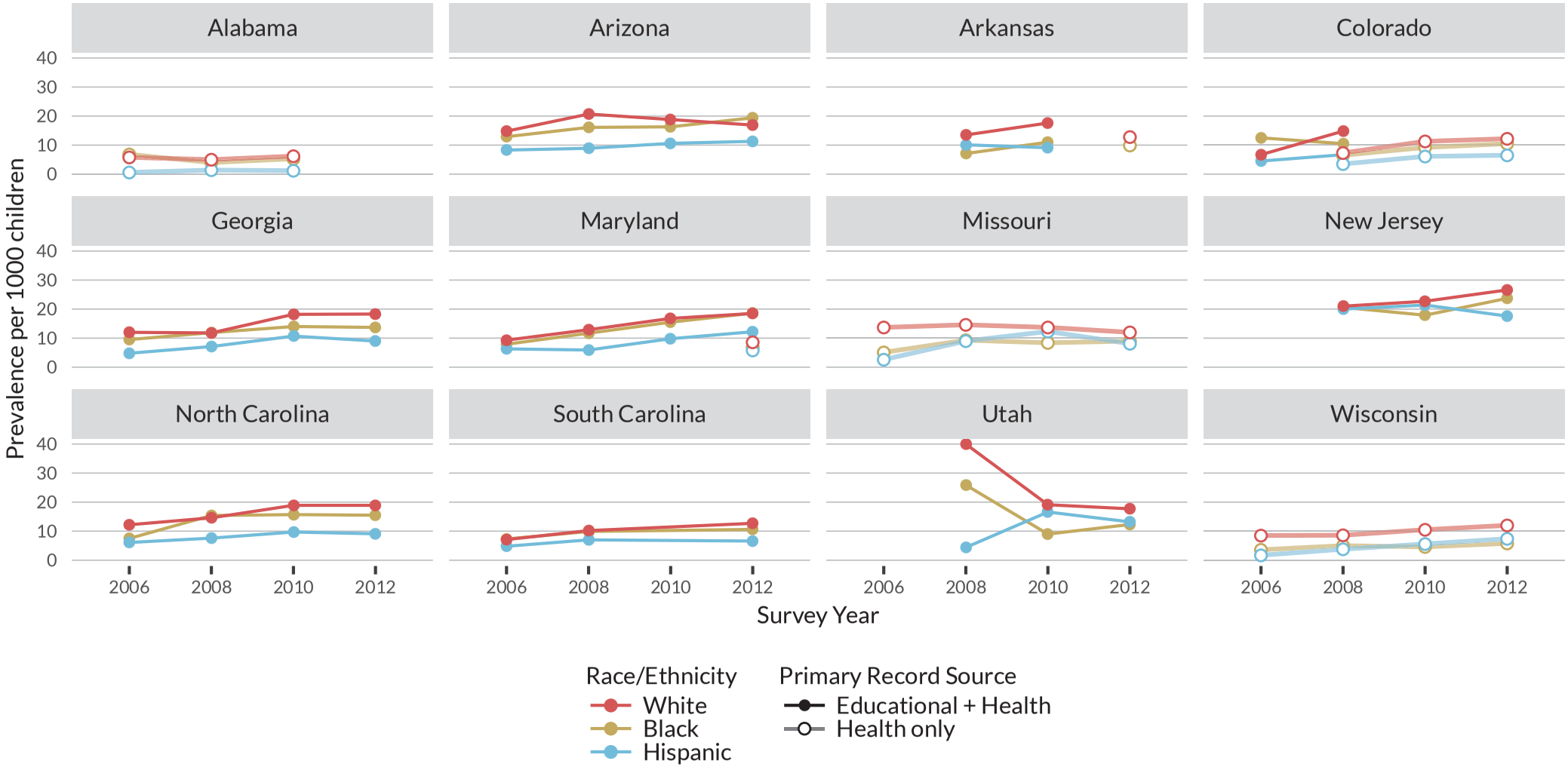

Figure 2

Table 1. US Prevalence surveys of Autistic Disorder (AD)

Year	*Authors*	*Area*	*Population*	*Age*	*Number affected*	*Diagnostic criteria*	*% with normal IQ*	*Gender ratio (M:F)*	*Prevalence Rate/10,000*	*95% CI*
1970	Treffert	Wisconsin	899,750	3-12	69	Kanner	---	3.06 (52:17)	0.7	0.6; 0.9
1987	Burd et al.	North Dakota	180,986	2-18	59	DSM-III	---	2.7 (43:16)	3.26	2.4; 4.1
1989	Ritvo et al.	Utah	769,620	3-27	241	DSM-III	34	3.73 (190:51)	2.47	2.1; 2.8
2001	Bertrand et al.	Brick Township, New Jersey	8,896	3-10	36	DSM-IV	36.7	2.2 (25:11)	40.5	28.0; 56.0
2002	Croen et al.	Northern California (DDS: 1987-1994)	4,950,333	5-12	5,038	"Full syndrome autism"- CA Dept. of Developmental Services	62.8[a]	4.47 (4116:921)	11.0	10.7; 11.3
2005	Barbaresi et al.	Olmstead County, Minnesota	37,726	0-21	112	DSM-IV	---	---	29.7	24.6; 35.7*
2011	Windham et al.[b]	San Francisco Bay Area (DDS: 1994, 1996)	162,402	0-8	477	"Full syndrome autism"- CA Dept. of Developmental Services	---	6.4 (493:77)	29	26.9; 32.1*

* Calculated by the authors.

[a] This proportion is likely to be overestimated and to reflect an underreporting of mental retardation in the CDER evaluations.

[b] Note that there is partial overlap between this sample and that reported by Croen et al. (2002); because of the minimal overlap between these two sample populations (birth year: 1994), both prevalence estimates are included in this table.

Table 2. US Prevalence surveys of ASDs since 2000

Year	*Authors*	*Area*	*Population*	*Age*	*Number Affected*	*Diagnostic Criteria*	*% with Normal IQ*	*Gender Ratio (M:F)*	*Prevalence Rate/10,000*	*95% CI*
2001	Bertrand et al.	New Jersey	8,896	3–10	60	*DSM-IV*	51	2.7 (44:16)	67.4	51.5; 86.7
2003	Yeargin-Allsopp et al.	Atlanta, GA	289,456	3–10	987	*DSM-IV*	31.8	4.0 (787:197)	34.0	32; 36
2003	Gurney et al.	Minnesota (2001–2002)	787,308	6–11	4094	Receipt of MN special education services	—	—	52.0	50.4; 53.6
2007	Croen et al.	Northern California (1995–1999)	132,844	5–10	593	*ICD-9-CM*	—	5.5 (501:92)	45	41.2; 48.4
2007	CDC	6 states	187,761	8	1,252	*DSM-IV-TR*	38 to 60	2.8 to 5.5	67.0	63.1; 70.5
2007	CDC	14 states	407,578	8	2,685	*DSM-IV-TR*	55.4	3.4 to 6.5	66.0	63; 68
2009	Nicholas et al.	South Carolina	8,156	4	65	*DSM-IV-TR*	44.2	4.7	80	61; 99
2009	CDC	11 states	308,038	8	2,757	*DSM-IV*	59	4.5	90	86; 93
2010	Maenner and Durkin	Wisconsin	428,030	Elementary school–aged	3831	*DSM-IV* like criteria for WI special education services (by school district)	—	—	90	86.7; 92.4
2011	Windham et al.	San Francisco Bay Area (1994,1996)	80,249	9	374	"Full syndrome autism"—CA Dept. of Developmental Services, receipt of CA special education services, *or DSM-IV*	—	6.2 (324:50)	47	42; 52
2012	CDC	14 states	337,093	8	3,820	*DSM-IV*	38	4.6	113	110; 117
2014	CDC	11 states	363,749	8	5,338	DSM-IV	69	4.5	147	142.9; 150.7
2016	CDC	11 states	346,978	8	5,063	DSM-IV-TR, ICD-9	68.4	4.5 (4.2:4.8)	146	142; 150
2016	Christensen et al. (CDC)	5 states	58,467	4	783	ICD-9-CM, DSM-IV-TR	54	3.3 (610:173)	134	125; 144