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Prevalence and Epidemiologic Characteristics of FASD from Various Research Methods with an Emphasis on Recent In-School Studies

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Researching the epidemiology and estimating the prevalence of fetal alcohol syndrome (FAS) and other fetal alcohol spectrum disorders (FASD) for mainstream populations anywhere in the world has presented a challenge to researchers. Three major approaches have been used in the past: surveillance and record review systems, clinic-based studies, and active case ascertainment methods. The literature on each of these methods is reviewed citing the strengths, weaknesses, prevalence results, and other practical considerations for each method. Previous conclusions about the prevalence of FAS and total FASD in the United States (US) population are summarized. Active approaches which provide clinical outreach, recruitment, and diagnostic services in specific populations have been demonstrated to produce the highest prevalence estimates. We then describe and review studies utilizing in-school screening and diagnosis, a special type of active case ascertainment. Selected results from a number of in-school studies in South Africa, Italy, and the US are highlighted. The particular focus of the review is on the nature of the data produced from in-school methods and the specific prevalence rates of FAS and total FASD which have emanated from them. We conclude that FAS and other FASD are more prevalent in school populations, and therefore the general population, than previously estimated. We believe that the prevalence of FAS in typical, mixed-racial, and mixed-socioeconomic populations of the US is at least 2 to 7 per 1,000. Regarding all levels of FASD, we estimate that the current prevalence of FASD in populations of younger school children may be as high as 2–5% in the US and some Western European countries.
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Key Words: fetal alcohol syndrome (FAS); fetal alcohol spectrum disorders (FASD); partial fetal alcohol syndrome (PFAS); epidemiology; prevalence

The teratogenic effects of alcohol on the developing fetus represent a continuum of disabilities, currently referred to as fetal alcohol spectrum disorders (FASD) [Barr and Streissguth, 2001]. Establishing the population-based prevalence and other epidemiological characteristics of the most severe form of this spectrum, fetal alcohol syndrome (FAS), and of other FASD has been a challenge. Both before [Sullivan, 1899; Abel, 1998a; Armstrong, 2003] and after Jones and colleagues defined and described the specific clinical components of FAS in the medical literature [Jones and Smith, 1973; Jones et al., 1973; Stratton et al., 1996], researchers have struggled with issues of diagnostic criteria, case finding, sampling, and coordination of interdisciplinary activities in epidemiological studies of FASD. Although key diagnostic features of FAS are generally well established, the specific assessment techniques and statistical measurements used to make the definitive diagnosis of FAS and other FASD are still debated [Aase 1994; Aase et al., 1995; Stratton et al., 1996; Astley and Clarren, 2000; Hymbaugh et al., 2002; Chudley et al., 2005; Hoyme et al., 2005; Astley, 2006; Clarren and Lutke, 2008]. Studies that have attempted to determine the prevalence of FAS, let alone other less severe diagnoses within the continuum of FASD, are limited in number, vary in their methodology, and suffer from incomplete data and also from a lack of

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accurate, routine screening in prenatal clinics. Therefore, many children with FASD remain undetected. The result has left scholars puzzled or unclear about the pattern and prevalence of FASD at any age in the US and in most every mainstream population. This is largely due to questions of assessment and major difficulties associated with access to children with FASD and their mothers.

Recent writings attest to the dearth of knowledge about FAS and total FASD prevalence. The following are some pertinent quotations from the literature. "So, the question, what the "true" occurrence of FAS/FASD may be in the Western world has been difficult to answer" [Eriksson, 2007]. "The true prevalence of fetal alcohol syndrome and fetal alcohol spectrum disorder is not established . . . in Canada nor anywhere else in the world. The difficulty of establishing the true prevalence for FAS/FASD is more complicated than for most conditions" [Clarren and Lutke, 2008]. One difficulty is the interdisciplinary nature of assessing FASD. "The determination and delineation of this complex form of brain dysfunction usually requires a team of investigators . . . each doing tests that are unique to their [sic] training" [Clarren and Lutke, 2008]. Many authors have referred to FASD as problems that frequently go undetected, yet prenatal alcohol damage affects children and adults across many areas of life. "This is a hidden epidemic, since the clinical capacity to recognize and diagnose these conditions is simply not present" [Clarren and Lutke, 2008].

For practical public health and educational reasons, and also for more esoteric and basic scientific purposes, it is important to identify children with an FASD and to know the prevalence of FAS and all FASD. For scientific purposes it provides accurately diagnosed cases of an FASD from which we can establish a more complete etiological understanding. Early identification can lead to the development of effective protocols for intervention and assisting children with developmental problems associated with an FASD. As presented in this article, elementary school children are old enough that an accurate diagnosis of various FASD is possible because most physical features, behavioral, and neuropsychological signs are evident, detectable, and testable by this age. Physical examinations and neurobehavioral testing are efficient for making an accurate diagnosis within the FASD continuum at ages 6–7 years. While it is most desirable to diagnose children with FASD and other developmental disabilities at the earliest age possible, diagnosis of an FASD for 1st graders can still lead to interventions that benefit most children and assist them in leading relatively normal lives [Carmichael-Olson et al., 1992; Streissguth et al., 1996; O'Connor and Kasari, 2000; Kalberg and Buckley, 2006; Kalberg et al., 2006; O'Connor and Paley, 2006; O'Connor et al., 2006; Adnams et al., 2007; Kable et al., 2007].

Fetal Alcohol Spectrum Disorders (FASD) and the Institute of Medicine (IOM) Diagnostic Categories

The Institute of Medicine has defined four diagnostic categories within the continuum of FASD (see below) [Stratton et al., 1996]. Components of the IOM categories describe FASD, from severe to mild [Stratton et al., 1996; Hoyme et al., 2005]. The specific diagnoses, from most severe to less severe are: fetal alcohol syndrome (FAS), partial FAS (PFAS), alcohol-related neurodevelopmental disorders (ARND), and alcohol-related birth defects (ARBD). Even though there are competing diagnostic systems which use slightly different criteria for the diagnoses, different thresholds for particular criteria, and different terms for many of the lesser effects of alcohol on humans [Astley and Clarren, 2000; Chudley et al., 2005; CDC, 2008], none dispute that there is a spectrum of damage, from severe to mild, which requires differential diagnosis. Recent diagnostic clarification and operationalization of these categories stress the importance of specific minor anomalies of the face in assigning diagnoses within FASD [Hoyme et al., 2005]. These specific, dysmorphic, craniofacial features include: microcephaly, short palpebral fissures, and a hypoplastic midface (smooth philtrum and thin vermilion border of the upper lip [Jones and Smith, 1973; Clarren and Smith, 1978]. IOM criteria clearly lay out names and theoretical and general clinical criteria for the specific diagnoses within the spectrum.

The two most severe diagnoses of an FASD, FAS, and PFAS, are currently most readily recognized and diagnosed by knowledgeable and experienced clinicians [May et al., 2000, 2006a, 2007a; Viljoen et al., 2005]. According to the revised IOM criteria [Hoyme et al., 2005], for the diagnosis of FAS a child must have: (1) evidence of a characteristic pattern of minor facial anomalies including at least two or more of the key facial features of FAS (palpebral fissures $\leq$10th centile, thin vermilion border, or smooth philtrum), (2) evidence of prenatal and/or postnatal growth retardation (height or weight $\leq$10th centile), (3) evidence of deficient brain growth (structural brain anomalies or occiptofrontal head circumference (OFC) $\leq$10th centile), and if possible, (4) confirmation of maternal alcohol consumption directly from the mother or a knowledgeable collateral source. For a diagnosis of partial FAS (PFAS), a child must have: (1) evidence of a characteristic pattern of facial anomalies including two or more of the three mentioned above, (2) one or more other characteristics, such as prenatal or postnatal growth retardation ($\leq$10th centile) in height or weight), (3) small OFC ($\leq$10th centile), and/or evidence of a complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level and unexplainable by genetic composition, family background, or environment alone, and if possible, (4) confirmation of maternal alcohol consumption directly from the mother or a collateral source. A checklist has been developed over the past 25 years to aid in the diagnostic process [Hoyme et al., 2005]. All physical growth and dysmorphology features significant in the IOM criteria are recorded on this weighted checklist. Dysmorphology scores range from 0 to 37. Specific, key features of FASD must be present resulting in a high dysmorphology score for a positive diagnosis of one of the more severe FASD. Furthermore, other similar birth defects and patterns of disabilities (e.g., Williams, Down, de Lange, and fragile X syndromes) must be excluded/ruled out by either a medical geneticist through clinical exam or through genetic testing in highly equivocal cases.

For a diagnosis of alcohol-related neurodevelopmental disorders (ARND), a child must have documented prenatal alcohol exposure, display neurological, or structural brain abnormalities (e.g., microcephaly), or manifest evidence of a characteristic, complex pattern of behavioral, or cognitive abnormalities inconsistent with developmental level not explained by genetic predisposition, family background, or environment alone. For a diagnosis of alcohol-related birth defects (ARBD), a child must

have confirmed prenatal alcohol exposure, evidence of a characteristic pattern of minor facial anomalies, including two or more of the following: short palpebral fissures, thin vermilion, and/or smooth philtrum, as well as either major malformations or a pattern of minor malformations [Hoyme et al., 2005].

Epidemiological Studies and Capture of Highly Dysmorphic Versus Less Dysmorphic Children

Only children diagnosed with the two most severe manifestations of FASD, FAS, and PFAS, are the focus of most studies of the prevalence of FASD. The less severe categories of FASD (ARND and ARBD) are the least likely to be diagnosed in any study, and children with these disorders are rarely presented to the specialized medical practitioners who are capable of making the diagnoses. Even outreach, population-based studies such as in-school studies that are highlighted in this article are not likely to identify large numbers of children with ARND because: (a) dysmorphology is rarely assessed on children with mild mental retardation, (b) a specific battery of neuropsychological tests that are highly definitive for diagnosing the intelligence and behavioral traits of children with ARND have not yet been settled upon, and (c) population-based case finding methodology has been keyed by physical growth, physical development, and dysmorphology. Therefore, major epidemiological studies are most likely to identify children with the more severe forms of FASD, as the dysmorphology of the severe forms is much better established at this stage of understanding. However, in recent in-school studies in Italy, a surveillance study in Australia [Elliott et al., 2008] and pilot, in-school studies in the US, many more cases of PFAS have been identified than FAS, and increasing numbers of cases of ARND are diagnosed as the popular battery of neurobehavioral tests applied to children with a FASD becomes more sensitive and specific [Kodituwakku et al., 2001, 2006b; Aragón et al., 2008a,b]. Also, in very high risk populations such as South Africa, where many extensive population-based studies have been carried out, more severe cases have been encountered because of extremely high levels of maternal risk factors among the low SES, binge-drinking population (binge drinking has been defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and many studies as consuming five or more drinks per occasion, or sitting, for a male, and three or four drinks per occasion for a female). Furthermore, because the maternal risk factors are less extreme in more developed countries, major epidemiological studies have not been pursued to date in US and European populations. Therefore, higher SES populations, and populations with lower proportions of binge drinkers produce more PFAS as a ratio to FAS and other less severe cases when fetal exposure to alcohol occurs [Bingol et al., 1987; Abel and Hannigan, 1995; Abel, 1998a; May et al., 2006a,b, 2007a, 2008].

Researchers have used three main approaches to study the prevalence, characteristics, and patterns of occurrence of various FASD. The approaches are: (1) surveillance and record review systems, (2) clinic-based studies, and (3) active case ascertainment approaches. In-school studies are a special type of active case ascertainment, and the results from such studies in three countries are highlighted.

Review of Previous Studies and Methods Used for the Epidemiological Study of FASD

Researchers have used three main approaches to study the prevalence, characteristics, and patterns of occurrence of various FASD. The approaches are: (1) surveillance and record review systems, (2) clinic-based studies, and (3) active case ascertainment approaches [May and Gossage, 2001a]. Of these approaches, clinic-based studies have been the most common, followed by passive systems, and active case ascertainment. Passive surveillance systems are the least expensive, followed by clinic-based studies. Active case ascertainment is the most costly and time intensive [Stratton et al., 2006]. We review previous studies using the first three approaches to assess the prevalence of FASD and summarize their findings, highlighting biases, strengths, weaknesses, and key findings. Then we provide more detailed description and findings of in-school studies. Such studies may be the most complete and accurate way of determining the epidemiological characteristics of FASD within a population and will come closest to determine the true prevalence and far-reaching effects of FASD in human populations.

Surveillance Systems: Passive and Record Review Systems

Surveillance systems collect data in a particular geographical catchment area (e.g., a town or state) via registration systems or by utilizing existing records and registries. Researchers must first establish the diagnostic criteria of FASD. Then a team of reviewers look for documented or probable cases of children with particular symptoms of an FASD, or children actually diagnosed with an FASD, in a defined time period. Three types of records are generally collected and reviewed: birth certificates, special registries for children with developmental disabilities or birth defects, and/or medical records.

The Centers for Disease Control and Prevention (CDC) maintains the Birth Defect Monitoring Program (BDMP) in hospitals throughout the US, tracking most major birth anomalies, including FAS [Chavez et al., 1988]. The BDMP is a passive surveillance system, as it depends on the diagnosis if an FASD is made at birth by clinicians working in selected hospitals. Many surveillance studies have used more active surveillance where multiple types of records are searched to identify as many cases of alcohol-related anomalies as possible, since a case of a particular FASD can be documented in more than one place (e.g., birth certificates, physician records, registries, and school records over time) [Bower et al., 2000]. These multiple-record approaches are referred to as capture–recapture methods [Egeland et al., 1998].

The major advantage of surveillance methods is an efficient utilization of existing health care systems and

records. This makes them relatively inexpensive and easily implemented. But major disadvantages exist. Some birth defects, such as severe spina bifida and Down syndrome, are easy to recognize and diagnose because the anatomical or genetic markers are obvious at birth and well known. FAS, and especially less severely dysmorphic forms of FASD, however, are complex, involving multiple indicators of physiology, development, and behavior, many of which are neither obvious nor easily identified at birth [Little et al., 1990; Aase, 1994; Clarren et al., 2001]. Therefore, surveillance systems, which generally depend on the efforts and diagnoses of hundreds of nonspecialist physicians and other service providers, lack rigor and consistency. Furthermore, these passive systems suffer from dependence on the quality and completeness of a variety of registries for complete and consistent record compilation.

The CDC has published three estimates of FAS rates in the US, based on passive surveillance, via the BDMP which use hospital discharge data from 10 to 30% (depending on the year) of all births. The estimated rate of FAS at birth was 0.2 per 1,000 births from 1979 to 1992 [CDC, 1993]. Increased rates of 0.37 and 0.67 per 1,000 were reported in 1992 and 1993 [CDC, 1995]. CDC authors have questioned, however, whether this increase reflected a true increase in FAS births or better reporting. A third report from the BDMP estimated FAS rates by ethnic group from 1981 to 1986: 0.6 per 1,000 for African–Americans, 0.08 for Hispanics, 2.9 for American Indians, 0.03 for Asians, and 0.09 for whites [Chavez et al., 1988]. All of the above rates are much lower than those produced by any other method (see Table 1).

Local studies using passive surveillance methods (e.g., the Metropolitan Atlanta Congenital Defects Program) have also produced low estimates of FAS prevalence. Researchers [CDC, 1997] reported FAS among newborns as 0.1 per 1,000. Including partial FAS, the rate was 0.25.

In Alaska, a more active capture–recapture study used multiple sources including: data from hospitals, pediatricians, birth certificates, Alaska Native Health Service records, and genetics, disabilities, and education programs. Researchers reported the FAS rate for 1977–1992 for the non-Native population as 0.2–0.3 per 1,000, and the rate for the Native population (where active case ascertainment methods were also used during this period) as 3.0–5.2 per 1,000 [Egeland et al., 1998]. In North Dakota, Burd et al. [1996] reported rates of 1.1–2.0 per 1,000 from the state's birth registry system. In a passive method study from New Zealand, pediatricians were asked to complete a postal survey on children with alcohol-related birth defects. In 1993, the FAS rate among children <10 years of age was 0.11 per 1,000 [Leversha and Marks, 1995].

The last two surveillance studies in Table 1 further illustrate the low rate of FASD case identification with relatively passive record-based methods. Surveillance research studies in Wisconsin and New York, the later as part of the CDC-funded FASSNet, yielded rates of FAS below 1 per 1,000. The highest rate was in one of two similar counties in New York. The authors attributed the significantly higher rate to one dedicated dysmorphologist who participated in the registry program by regularly diagnosing and reporting cases of FASD [Druschel and Fox, 2007].

Surveillance methods using extensive searches of multiple records have applications other than prevalence studies. Kvigne et al. have successfully used hospital records of the Indian Health Service to report on alcohol use factors among fathers and mothers of children with FASD, maternal risk factors for FASD, physical characteristics of children with FASD, paternal traits of children with FASD, characteristics of grandmothers of children with FASD, and injuries and alcohol use among mothers of children with FASD in three successive pregnancies [Kvigne et al., 1998, 2003, 2004, 2006, 2008a,b].

Good records yield a variety of useful data which can be mined for valuable information on maternal risk and related matters. But, unfortunately few good records exist with accurate and detailed information on alcohol use and FASD. Therefore, surveillance systems clearly report very low rates of FAS and all FASD. A recent CDC-sponsored conference of experts in Atlanta concluded: that "sensitivity is much lower for passive methods of case finding" (p 11); "both the general population and special populations need to be accessed more aggressively"; ages 0–7 is the optimal age range for surveillance (p 12), and in-school screening in the earliest years is a promising setting for research on the prevalence of FASD (p 11) [CDC, 2008]. While earlier screening is desirable for therapeutic reasons, first grade is the first age in most US settings and other countries where all children in a population can be accessed and efficiently and accurately diagnosed in an institution of learning.

Clinic-Based Studies

Clinic-based studies have provided considerable knowledge of the characteristics of FASD in humans but fall short when determining the prevalence in a population [Abel and Sokol, 1987, 1991; Stratton et al., 1996; Abel, 1995, 1998a]. They are studies of treated prevalence rather than a population-based prevalence. Research in prenatal clinics lends itself to consistent design and rigorous methodology that can eliminate some problems inherent with passive methods, as data can be efficiently collected from mothers as they progress in their pregnancies. Researchers use standard screening, interview instruments, and specimen samples to gather information from pregnant women about: diets, jobs, social interactions, psychological health, and the use of alcohol and other drugs. Control groups are relatively easy to obtain from consenting women in the clinics, and one-half to 85% [Floyd et al., 1999] of women report abstinence from alcohol, providing a large comparison group. Because of the prospective nature of these designs, researchers are generally able to examine the infants at birth or in infancy to match maternal behaviors with the pregnancy outcomes. But it is virtually impossible to diagnose most FASD cases in the first 6 weeks of life, and only the most severe cases are obvious and diagnosable even throughout the infant period to approximately age 3.

Clinic-based studies have many advantages: the opportunity to gather maternal history data; the opportunity to study a large number of pregnancies with various levels of alcohol and other drug exposure; health services are provided, which are incentives for participants; and the prospective design provides greater control and rigor in measuring many important variables. However, there are also disadvantages. First, participants are self-selected. The women at highest risk for having a child with FASD are less likely to attend prenatal clinics early in pregnancy, regularly, and/or at all, making consistent and meaningful access to the highest risk cases difficult or impossible. Second, there is extreme variability in the reporting of alcohol use and abuse in various clinics stemming from: the

Table 1. Prevalence of FAS (and Total FASD) in Various Studies by Method

Method and Source Type	Years	Location/ Population	Ages	Rate of FAS per 1,000	Rate of FASD per 1,000	Source
Surveillance/record review methods						
Surveillance and registry based	1979–1992	US General	Newborn(nb)	0.20		CDC, 1993
Registry (BMDP)	1992	US General	nb	0.37		CDC, 1995
Registry (BMDP)	1993	US General	nb	0.67		CDC, 1995
Registry (BMDP)	1981–1986	US: Asian/Hispanic	nb	0.03/0.08		
		White/African American		0.07/0.60		Chavez et al., 1998
		American Indian		2.90		
Registry (BMDP)	1992	US General	nb	0.52		Cordero, 1994
Local surveillances-registry	1981–1989	Atlanta	nb	0.10		CDC, 1997
Surveillances and capture-recapture	1977–1992	Alaska	3–18 years	0.20–0.30 and 3.00–5.00		Egeland et al., 1998
Birth Certificates	1991–1994	North Dakota	nb	1.10–2.00		Burd et al., 1996
Multiple source: Surveillance	1989–1992	Atlanta	nb – 1 year	0.23–0.33		Cordero, 1994
Surveillance form: Pediatricians	2001–2004	Australia	6–14 years	0.06		Elliot et al., 2008
Pediatrician forms	1993	New Zealand	nb–10 years	0.11		Leversha and Marks, 1995
Multiple sources	1998–1999	Wisconsin	nb	0.23		Weiss et al., 2004
Multiple sources	1995–1999	Two Counties in NY	nb	0.90 Country A 0.21 Country B		Druschel and Fox, 2007
Totals				Md = 0.265, $\overline{X}$ = 0.845		Median and mean
Clinic-based studies						
Various studies (avg.)	1976–1987	Western World	nb/infants	1.90 [avg.]		Abel and Sokol, 1987
Various studies (avg.)	1976–1987	US and Canada	nb/infants	2.20 [avg.]		Abel and Sokol, 1987
Prospective studies only	1976–1990	US	nb/infants	0.33 [avg.]		Abel and Sokol, 1991
Prospective and Retrospective: Multiple Sources	1976–1994	Western World	nb/infants	0.97 [avg.]		Abel, 1995
		US Only	nb/infants	1.95 [avg.]		Abel, 1995
		African American	nb/infants	2.29 [avg.]		Abel, 1995
		White	nb/infants	0.26 [avg.]		Abel, 1995
Prospective Screening	Late 1970's	Cleveland	Infants	3.0		Sokol et al., 1986
Prospective Screening	1974–1975	Seattle	Infants	2.8	9.1	Sampson et al., 1997
Prospective Screening	Early 1990's	Detroit	Infants	3.9		Sokol et al., 1993
	1977–1979	Roubaix, France	Infants	1.4	4.7	Dehaene et al., 1981
	1986–1990	Roubaix, France	Infants	1.2	4.8	Dehaene et al., 1991
Prospective Screening	1977	Gothenberg, Sweden	nb	1.6		Olegard et al., 1979
Totals				Md = 1.9, $\overline{X}$ = 1.83	Md = 4.8, $\overline{X}$ = 6.2	Median and mean
Active case ascertainment[a]						
Active recruitment to referral clinics	1969–1982	American Indians:	0–14 years			May et al., 1983
		SW Plains		10.7	19.5	
		Navajo		1.6	2.5	
		Pueblo		2.2	2.7	
		Overall avg.		2.0	3.1	
Active recruitment to referral clinics	1982–1989	American Indians: Plains and Plateau	0–18 years	9.0 (multi-tribe avg.)		May et al., 2002
Active recruitment to referral clinics	1985	Plateau Indians	0–18 years	9.2	18.4	Quaid et al., 1993
Active outreach in centralized health care system	1985	Western BC, Yukon	0–18 years	10 24	25.0 46.0	Asante and Nelms-Matzke, 1985
Active for screening of all children and adolescents	1985	Native–Entire Community in BC, Canada	0–21 years	120	189	Robinson et al., 1987
Active outreach in centralized health care system	1990–1992	Plains Indians in SD	<14 years	3.9–8.5		Duimstra et al., 1993
Active outreach in diagnosis training to pediatricians	1997–2005	Norway (1 County)	<16 years	0.3 before outreach dx training: 1.5 after		Elgen et al., 2007
Totals				Md = 8.5, $\overline{X}$ = 15.61	Md = 19.0, $\overline{X}$ = 38.2	Median and mean

[a]In-school, Active Case Ascertainment Studies covered in Table 2.

way that alcohol questions are asked, the busy nature of many clinics which detracts from the time devoted to the interview, and the stigmas associated with alcohol questions in the prenatal setting [Viljoen et al., 2002; Whaley and O'Conner, 2003; Hannigan et al., in press]. Many of the clinic-based studies conducted in the US have been carried out in publicly-funded hospitals and clinics where disadvantaged populations predominate; therefore, clinic-based studies may accurately or even over-represent the prevalence of FAS in minority populations, while under-representing mainstream middle-class populations [Abel, 1998b]. Third, since FAS is not easily diagnosed at birth, these studies generally underestimate the prevalence of FAS and all FASD [Aase 1994; Stratton et al., 1996; Clarren et al., 2001].

The clinic-based approach has been the most common method used to estimate the prevalence of FASD and define maternal risk factors. Abel and Sokol's [1987] review of 18 clinic-based studies reported an average rate of FAS for the western world of 1.9 per 1,000 and 2.2 per 1,000 births for North America. Abel and Sokol [1991] later reviewed 20 prospective, clinic-based studies (including many of the studies reviewed in 1987), and reported a lower rate of 0.33 per 1,000 for the Western world. By 1994 [Abel, 1995] a total of 35 prospective, clinic-based studies had been conducted in at least 40 sites in the Western world including: the US (12), United Kingdom (15), Australia (4), Spain (3), and Canada, Denmark, France, Italy, Netherlands, Portugal, Sweden, and Switzerland (15 combined). Many of the studies performed outside of the US contained a majority of subjects who were middle class and Caucasian and only a few of these studies reported any FAS cases at all, the total being four cases. This provides a very low average rate, and median and modal rates were 0.0 FAS per study. Abel [1995] concluded that FAS occurred "considerably more often" at some sites than at others, estimating the rate for the Western world at 0.97 per 1,000 and the rate for the US at 1.95 per 1,000. This is a fascinating finding, as the proportion of the population that drinks alcohol in other parts of the Western world, and the per capita consumption of alcohol in much of the Western world is higher than in the US. This has been referred to as the "American Paradox" since it is likely linked to the fact that the US has more abstainers, but also more heavy drinkers when compared with France and other populations of the Western world [Abel, 1998a,b]. Abel concludes that it is not the prevalence of drinkers or the amounts consumed over time in European countries, but rather the proportion which consumes high quantities of alcohol in short periods of time (e.g., binge drinkers) that elevates the frequency of severe symptoms of FASD. Not mentioned by Abel is that European populations and health providers are quite unlikely to: believe that FASD exist or are common, be critical of normative drinking practices (as are health care providers in the US), or to diagnose cases of FASD.

All but four of the US studies (67%) reviewed by Abel [1995] were carried out in general obstetric clinic settings, mostly among African–Americans from inner cities of low socioeconomic status (SES). He concluded that in US sites where the study population was predominantly low SES, the FAS rate was 2.29 per 1,000, 10 times higher than reported for White middle to upper class sites (0.26 per 1,000) (see Table 1). In two of the studies of inner city, low SES populations, the rates of FAS were 3 and 3.9 per 1,000. Therefore, Abel's review concluded that FAS was linked to low SES more than to race [Abel, 1998]. Calculations from another aggregation of these 28 studies indicated that FAS occurred in 4.3% of the births to heavy drinkers [Abel, 1995], and no estimate was given for other diagnoses of FASD.

From Europe, Olegard et al. [1979] and Dehaene et al., [1981, 1991] have reported relatively higher rates of FAS than some other studies of mainstream populations, probably due to the intense nature of the scrutiny exerted by the researchers and the circumscribed nature of these particular health systems and clinics. From infant and young child studies, FAS was reported as 1.6 per 1,000 in Göteberg, Sweden and 1.4 and 1.2 in Roubaix, France, in two different time periods. In France, other levels of FASD that roughly correspond to the IOM classification of PFAS and ARND were combined with the FAS cases for an FASD rate of 4.7 and 4.8 per 1,000 [Dehaene et al., 1981, 1991].

Other clinic-based studies have documented various levels of FASD severity present in cohorts of children born to mothers recruited when receiving prenatal care. At study sites in Seattle, [Streissguth et al., 1991, 1994], Detroit [Jacobson et al., 1993, 1994], and Pittsburgh [Day et al., 1991, 1999], researchers have followed large cohorts of children born to women with various levels of drinking and compared them over time, on physical and psychological growth and development and dysmorphology. By grouping the data in various ways to describe the effects of prenatal alcohol exposure and documenting the link between FASD symptoms and alcohol exposure, these researchers estimate the prevalence of FASD. One longitudinal study from this body of literature [Sampson et al., 1997] estimated the combined rate of FAS and ARND at 9.1 per 1,000 live births (1%) in the general Seattle obstetric population, which is the most quoted estimate for FASD.

Some studies in other parts of the Western world, including former European colonies, have found a similar pattern of FASD symptoms as that found in American studies. For example, French researchers [Rostand et al., 1990] reported that craniofacial morphology was "a sensitive indicator of alcohol exposure in utero" and that "alcoholic" consumption was associated with negative effects on infant weight, length, and head circumference. On the other hand, a study in Australia by Walpole et al. [1989] failed to show any significant relationship between low to moderate maternal alcohol intake and fetal outcome. Therefore, in spite of the similar pattern of anomalies associated with low and moderate levels of alcohol consumed during pregnancy, studies outside the US continue to illustrate the "American Paradox" described by Abel [1998a], where low to moderate use of alcohol (defined liberally as <21 drinks per week by Rostand et al. [1990]) does not cause alarm or result in FAS or features as severe as reported in US studies.

Active Case Ascertainment Methods

Active case ascertainment methods which aggressively search for children with FASD in select populations and provide specialized clinical diagnosis, were first used for the study of FAS in American Indian, Alaskan, and Canadian Native communities [May and Hymbaugh, 1982; May et al., 1983, 2002]. Until 1997, active case ascertainment methods had been used exclusively among American Indians.

Active case ascertainment generally yields the highest rates of FASD. Although the same clinical, diagnostic

criteria are used as in clinic-based studies, differential prevalence rates relate to the selection of children presented to clinicians for diagnosis and the age at which clinical contact is made. Many children who have an FASD are never seen in clinics where the proper diagnosis of an FASD can be made, or at a time when it can be made. For example, Clarren et al. [2001] reported that six of seven first-graders who were diagnosed with FAS in their in-school pilot study had never before received an FAS diagnosis. Similarly, Little et al. [1990] reported that of 40 newborns in a large hospital in Texas who were strong candidates for an FAS diagnosis (i.e., they were born to heavy drinking mothers and had most of the physical features of FAS), 100% left the hospital without an FAS diagnosis and most never received a diagnosis even though follow-up exams estimated that as many as 17 were possible FAS. These studies further emphasize that age at examination is a critical consideration in establishing the prevalence of all FASD; and all FASD are very difficult to diagnose in the newborn period and in the first 3 years of life except in very severe cases [Little et al. 1990; Ernhardt et al., 1995; Stoler and Holmes, 2004].

The active case ascertainment studies conducted among American Indians are generally in very high-risk communities characterized by low SES and a significant proportion of heavy, episodic drinking [May et al., 2002]. Studies of American Indian communities have yielded variable, but generally high, FAS rates. Among Plains and Plateau culture tribes, prevalence rates vary by community: average FAS rates are 9 per 1,000, ages 1–14 [May and Gossage, 2001b]. Among tribes of the southwestern US, rates vary: over time, between tribes, and by cultural group [May et al., 1983]. The average rates (per 1,000) of FAS in 1969–1982 (children, 0–14 years.) ranged from 0.0 to 26.7 from one community to the next. Tribal averages (see Table 1) ranged from 1.6 to 2.2 to 10.7 by major cultural group (Navajo, Pueblo, and southwestern Plains). One active case ascertainment study in Canada examined every child (a total of 102) in a Native village characterized by a concentration of heavy drinkers. The FAS rate reported was 120 per 1,000 children [Robinson et al., 1987]. Findings in such small and unique communities cannot be compared to other populations unless there is evidence that similar social, cultural, economic, behavioral, nutritional, and health conditions exist.

Active case ascertainment methods have at least three advantages. One, the primary focus is aggressive recruitment and case finding of children with an FASD at appropriate ages for accurate diagnosis made by clinical specialists. Two, aggressive outreach into a population or catchment setting is likely to uncover children with an FASD and high-risk alcohol-abusing mothers. Three, by studying entire populations, active methods may eliminate much selectivity and provide more generally applicable findings [Stratton et al., 1996].

There are also disadvantages of active case ascertainment approaches. First, outreach is labor intensive, time consuming, and costly [Stratton et al., 1996]. The outreach process involves: gaining trust, credibility, and permission to access a community or population; training people to recognize symptoms and refer children who may be involved; locating and securing consent for children and maternal subjects is required; and hiring specialists for the clinical assessments who carry out special "developmental clinics" or screening. Furthermore, the complete diagnostic process involving medical evaluation, child assessment, and maternal interviews requires multiple hours of work by a multidisciplinary team. Second, studies of this type require cooperation from many nonresearchers (e.g., community, political, health and education officials, parents, etc.). If one or more vital community constituencies do not support a study, case finding may be incomplete or selective. High levels of cooperation with research on stigmatized topics such as FASD and maternal drinking are often difficult to achieve. Third, access to particular populations may be selective, and in the early years of FASD research, only high risk, heavy drinking populations were studied. If such selective high or low-risk populations are studied and findings projected to the general population, then the prevalence of FAS will be over or underestimated.

A Summary of Previous Studies, Methods, and Rates of FASD

Estimates of the prevalence of FAS and total FASD vary greatly: from population to population, by method utilized, and by specific study. Some of this variation is a valid reflection of actual differences in FASD rates between populations. But variance in rates is often a function of how aggressive their methods are. As displayed clearly in Table 1, the lowest rates of FASD are found with passive surveillance and the highest rates with clinic-based and active case ascertainment methods. Surveillance studies that have produced rates somewhat comparable to studies using other methods either used hybrid methods or studied very high-risk populations. For example, the study by Egeland et al. [1998] used multiple sources of records and benefited from clinic-based data from the government health care system and an active case ascertainment project carried out among Alaska Natives during the period studied.

Considering the strengths and limitations of the various methods reviewed, and the various prevalence findings produced by each method, a simple average of the results does not produce accurate estimates of the magnitude of FAS and FASD in a population. Abel et al. have demonstrated this clearly in their publications [Abel, 1987, 1991, 1998a,b]. The passive surveillance methods produce, by far, the lowest number of cases and lowest rates of prevalence: a median of 0.265 and a mean of 0.85 per 1,000. Rates produced by the clinic-based studies, which reported any cases of FAS at all, are on average higher than the passive systems: the median is 1.9 and the mean is 1.8 per 1,000 births. But rates produced by clinic studies are lower than those for active case ascertainment methods, and Abel pointed out that the median and modal rates produced by clinic-based studies he reviewed were zero [Abel, 1995]. Based on the active case ascertainment studies in Table 1, the average of FAS rates is a median of 8.5 and a mean of 15.6 per 1,000. Keeping in mind that active case ascertainment studies have generally involved high-risk groups, as did many clinic-based studies, an estimate from these studies may be biased on the high side.

Also in Table 1 are the few rates of FASD (usually reported as FAE or ARND) produced by any of the above methods. For the clinic-based studies the average rates of FASD are: median of 4.8 and a mean of 6.2 per 1,000. For the active case ascertainment methods, the FASD averages are: median 19.0 and mean of 38.2 per 1,000.

Therefore, the conclusion from previous literature reviews and this review are that most studies of prevalence have under-identified cases of FAS and total FASD in mainstream or general populations. Population-based

studies using active outreach and case-identification are needed.

Population-Based Studies Provide a Different View of the Symptoms of FASD—Likely a More Complete Prevalence of Most Categories of FASD

Our experience with in-school research in two other countries and pilot data in US schools indicate that not only is the prevalence of FASD underestimated, but also the characteristics of the children as described in clinic-based studies is substantially different from that which exists in the general population. For example, cleft lip and palate, [Shaw and Lamer, 1999], optic nerve hypoplasia [Stromland, 2004], hemangiomas [Ferraro and Dehaene, 1996], ear malformations [Aase 1994], and other physical traits frequently cited as commonly associated features of FAS and other FASD in clinic-based studies, occur less frequently in FAS and PFAS children in population-based studies. Conversely, some subtle features (e.g., 5th finger clinodactly, insufficient pronation and supination of elbows, and unique palmar creases) are more frequently recorded in the population-based studies. Particularly odd, unique, and rather uncommon but obviously dysmorphic physical features make referral of an FASD child to specialist physicians (who diagnose FASD) more likely and therefore may skew the data on the frequency of these features in FASD children. Similarly, the more subtle signs, symptoms, and co-occurring features of FASD are not detected, referred for diagnosis, and therefore these children may go undetected. Therefore, passive or clinic-based studies will not reflect either the true catalogue of symptoms with their true frequency or the accurate number of children with an FASD.

Similarly, regarding intelligence and behavioral measures for diagnosing FASD, mild to severe mental retardation, and severe behavioral problems have been described as close to universal in the FASD cases referred for clinical assessment. Yet our studies of in-school populations in three different countries indicate that many children with an FASD are not as impaired behaviorally or intellectually as those in clinic-based studies. In fact many are functioning within the normal or low normal range and go unnoticed and undiagnosed unless their morphology or behavior is highly outstanding from the norms. It is therefore likely that only the children with the most obvious physical and behavioral signs and symptoms have been studied and described in clinic-based, passive studies and even in the active ascertainment studies if they rely on referrals from schools, health care providers, or other sources. Severe anomalies and behaviors associated with FASD are likely to be less common among all children with an FASD in the general population. In other words, children who meet criteria for FAS, PFAS, and ARND overall may have higher intelligence and may function well enough to avoid detection and referral. In fact, the severe physical, behavioral, and intellectual abnormalities and deficits are most often examined in clinics that lead to diagnosis, and children with less obvious or severe physical deformities or behavior go undiagnosed even though they are affected.

Many cases of FASD may only be detected in the broader population when expert diagnosticians examine them in the field. Nevertheless, undiagnosed FASD children may have substantially limiting learning disabilities, inappropriate of challenging behavior, or suffer from diminished functioning in a number of academic areas. Unless diagnosed (preferably early in their life) and placed in the proper curricula and activities in school, they may not pass or succeed in their studies, may be labeled as "bad" or incapable, drop out, or otherwise not reach their full potential. Diagnosis of all children with an FASD has implications for both their long-term development and for the attributions that others make of them.

In-School Studies: The Methodology and the Prevalence of FASD

In-school studies are a special type of active case ascertainment. Rare until recently, researching the epidemiology of FASD in schools increases efficiency of case identification and logistics, reduces costs, provides needed services, and theoretically solves many of the problems of selectivity. First, school children are representative of entire local populations. Second, identification of many more cases is achieved and complications of logistics are reduced, as the clinicians go to the children in the schools. Third, intellectual testing services are provided early in life which is a bonus to the students, their families, and the schools. Fourth, the credibility of the educational system and services that they provide locally, lend confidence to reluctant parents and provide needed evaluative and remedial services that might otherwise be unavailable. Not only children with suspected FASD, but normal controls are involved in these studies. The children receive benefits from the special testing, which makes the impact even broader. Also the control methodology decreases stigma that would otherwise affect the quality of the research, particularly the maternal reports of maternal risk.

In one of the counties in Washington studied by Clarren et al., [2001], the Board of Education required active consent from guardians, and less than 25% of the students were allowed to participate. Therefore, no useable results were produced in that county. In the other county, passive consent was allowed (a child participated unless the guardian specifically requested exclusion) and participation was much higher, although the specific percentage is not provided in the article. In this second county the estimated rate of FAS was 3.1 per 1,000 [Clarren et al. 2001]. The researchers did not describe in detail the specific social conditions in this county or what behavioral testing (if any) and maternal risk factor information was used for diagnosis. But this FAS rate is high for a mainstream population, especially when compared with rates produced by other methods. Virtually all active case ascertainment studies carried out in schools have reported higher rates of FAS and other FASD than those produced by other methods, and likely access to a broad cross section of the population at an optimal age for diagnosis by expert clinicians. Clarren et al. [2001] identified seven cases of FAS, only one of which had been previously diagnosed.

One community study in Sweden using active case ascertainment methods in younger children was conducted and described in the literature [Hagberg et al., 1981a,b]. Examining the causes of mild mental retardation (MMR) in Gothenberg schools, 8% of all MMR cases (intelligence quotient (IQ) 50–70), and also cases of children with IQ's of 71–75, were attributed to prenatal alcohol consumption. Translating this to a rate, 0.45 per 1,000 children were found to have FAS. These data are also quoted by Olegard et al., [1979].

South Africa

The most extensive and complete series of in-school studies has been carried out in South Africa in the Western Cape Province. Four studies have been initiated among first graders [May et al.,

2000, 2007a; Viljoen et al., 2005]. These studies of FAS and later PFAS as well were among a population of mixed race (colored) people generally low SES living in rural and small town settings. Most people labor on the farms and in small industries there and a regular weekend pattern of heavy drinking is practiced by many people. The rates of FAS are the highest reported to date in the world, 41–46 per 1,000, 65–74 per 1,000, and 51–67 per 1,000 for the in-school, first grade population (ages 5–7) for the three waves [May et al., 2000, 2007a; Viljoen et al., 2005]. Furthermore, when the cases of PFAS were added to the FAS cases in the third cohort, the rate of FAS and PFAS combined was 68–89 per 1,000 (6.8–8.9%) in this population. This region of South Africa has a long history of wine production, workers were formerly paid a portion of their wages in wine, people currently have relatively easy access to inexpensive commercial alcoholic beverages, and drinking heavily is practiced by a substantial proportion of colored laborers as a major form of recreation on weekends [May et al., 2008]. Viljoen et al., and Urban et al. have carried out similar in-school studies in two cities in the Northern Cape Province of South Africa [Urban et al., 2008]. Very high rates of FAS and FASD were also reported: 67.2 per 1,000 for FAS and 88.0 for FASD (FAS and PFAS only).

Italy

Two in-school studies have been completed in the Lazio region in the Province of Rome, Italy [May et al., 2006a,b; Kodituwakku, 2006b; Aragón et al., 2008a]. Carried out in conditions more similar to those in the US pilot studies reported below, the populations are generally well educated, middle class people, the majority of whom practice moderate drinking of one-half to two glasses of wine with meals, and less binge drinking than reported in most other populations studied with active case ascertainment. Nevertheless, the rates of FASD identified in Italy have been higher than were predicted by the scant literature on FAS in Italy [May et al., 2006a,b] and other mainstream Western European populations. The proportion of PFAS cases far exceeds those of FAS in Italy. The rates of FAS reported from the Italian studies ranged from 3.7 to 9.2 per 1,000, PFAS from 15.7 to 43.8 per 1,000, and the prevalence of total FASD is estimated as 2–5.5% in the first grade children.

US pilots

In addition to the Washington State study, two additional in-school studies have recently been completed in the US. Carried out in first grade classrooms, these studies have identified children with an FASD who would not otherwise have been recognized in other settings at other ages. Many would likely not be recognized at birth or referred into clinical settings where the diagnosis is likely. These two in-school studies were short term, low budget pilot studies completed by the same research team that completed studies in South Africa and Italy. Both were carried out in a smaller city in the Western United States where they were requested by public health and public school officials. Participation has been good (55 and 56%) utilizing only one mail out of consent forms with minimal explanation of the study. Therefore the outreach was active, but not nearly as intense as desirable. The FAS rate for the first pilot wave was 1.4–2.5 per 1,000 and a total FASD rate was 9.5–17.4 per 1,000 (1–1.7%). In the second pilot wave (2008) the rate of FAS was 6.4–11.3 per 1,000 and of all FASD (FAS and PFAS combined) were 14.1–24.8 per 1,000 or 1.4–2.5%. The variance in rates in the two different years may be accounted for by variations in maternal drinking by cohort, selectivity in consent to participate, and small samples generally experience greater variation in annual rates. Nevertheless, these pilot studies demonstrate the need for more extensive studies of this type in US schools with larger samples over time.

In the Western US city and in Italy, it has been more difficult to obtain participation rates much higher than half of the enrolled children (see Table 2), for both studies at both sites were underfunded and completed within a very short time frame; less than 1 year per wave and in each wave of study 15–25 schools were involved at each site. However in a third pilot currently underway in this same US city, minimal efforts at simpler and clearer information in the first letter sent out, community comfort is growing, enhanced attention to, and recruitment by, administrators has resulted in an increased consent rate, over 60%. In the future, other techniques of active recruitment could potentially raise the consent percentage even further. Unlike the predominance of the one problematic drinking style that is common among the studied colored population of South Africa, in US mainstream communities there is a greater variation in drinking styles. This variation and the mix of risk and protective maternal factors (e.g., adequate nutrition), variable SES, and various prenatal behaviors produce a variety of diagnoses within the continuum of FASD. In the pilot US studies and in Italy there are more moderate drinkers and fewer drinking in a binge manner. Therefore as in Italy, the number of PFAS cases is far greater than the cases of FAS. Local officials believed that in-school screening was a natural route to take for identifying more cases of children with an FASD who were in need of early identification. Officials were aware that in-school screening had been efficacious in South Africa and Italy.

Child Physical Growth and Development and Dysmorphology Data from In-School Studies

In Table 3 a summary is presented of selected data on children examined and diagnosed in some of our in-school projects in South Africa, Italy, and the Western City of the United States. Generally, the case control samples drawn by in-school methods of FASD case selection, using low physical growth and development to efficiently intensify case identification and random methods for picking controls, do not produce any significant differences in the age and sex of children in the FASD groups versus controls. But other features and variables which are integral to the diagnosis of FASD consistently distinguish children with FASD from controls selected from the same schools and grade. We have highlighted only some of the variables that are used to compare and distinguish between FASD and normal children. And in the case of the South Africa data, we have presented comparisons of FAS and PFAS as well. Considerably more detail of the children's physical features, including key indicators of facial and limb dysmorphology, is found in publications [May et al., 2000, 2006a, 2007a; Viljoen et al., 2005]. Briefly, children with FAS and PFAS are shorter, weigh less, and have smaller heads (low OFC or microcephaly) than do their peers. They have short palprebral fissures, large inner canthal distances, long and smooth philtrums, thin vermilion borders to the upper lip, epicanthic folds, ptosis, and more frequent heart murmurs (see Table 3).

The purpose of Table 3 is to highlight how the physical component of the diagnosis is made and showcase

Table 2. Sampling and Prevalence Findings from In-School Studies of Various Populations

Study	Setting	Nature of Sampling	Participation Rate and Type of Consent	Population	Socioeconomic Status (SES)	FAS (PFAS) and total FASD per 1,000
Hagberg et al., 1981a,b	Gothenberg, Sweden	91 school children (8–12 y.o.) w/mild MR (IQ 50–70) studied for cause. Eight children w/MMR and 3 w/ IQ 71–75 were classified as fetal alcohol exposure	100% Consent: unknown	White	Middle SES	0.45
May et al., 2000	Western Cape, South Africa	Children ≤10% on OFC or hgt. and wgt. From all 1st graders in 12 schools (rural and urban) in one town	99% Active Consent	Mixed race (coloured) 85% and white	• Coloured population Low and Middle SES • White Population Middle and Upper SES	40.5 – 46.4
Clarren et al., 2001	Washington State, USA 2 counties	Passive consent of all 1st grade children w/ nurse screening and <10% hgt. and/or wgt. Or teacher referral or file info on prenatal exposure	County A = 95% Passive Consent County B <25% Active Consent	Mixed ethnic	Middle SES	3.1
Viljoen et al., 2005	Western Cape, South Africa	Children ≤10% on OFC or hgt. and wgt. from all 1st graders in 12 schools (rural and urban) in one town	94% Active Consent	Mixed race (coloured) 85% and white	• Coloured population Low and Middle SES • White Population Middle and Upper SES	65.2 – 74.2
May et al., 2006a	Lazio Region, Italy	Children ≤10% on OFC or hgt. and wgt. From all 1st graders in 25 randomly-selected schools of subregion – (rural, suburban and urban)	50% Active Consent	Mixed race Italian Mostly white	Middle SES	3.7 – 7.4 (15.7 – 31.3) 20.3 – 40.5
May et al., 2007a,b,c	Western Cape, South Africa	Children ≤10% on OFC or hgt. and wgt. From all 1st graders in 12 schools (rural and urban) in one town	81% Active Consent	Mixed race (coloured) 85% and white	• Coloured population Low and Middle SES • White Population Middle and Upper SES	51.3 – 67.2 (16.8 – 22.0) 68.0 – 89.2
May et al., 2007a poster	Lazio Region, Italy	Children ≤10% on OFC or hgt. and wgt. From all 1st graders in 25 randomly-selected schools of subregion – (rural, suburban and urban)	49% Active Consent	Mixed race Italian Mostly white	Middle SES	4.4 – 9.2 (21.0 – 43.8) 26.6 – 55.4
Urban et al., 2008	Northern Cape, South Africa	Children ≤% on OFC, or hgt.and wgt. 1st grade schools in 2 cities	Not reported Active Consent	Mixed ethnic/race 64% Coloured 36% Black	Low and Middles SES	6.4 – 11.3 (7.7 – 13.5) 14.1 – 24.8
May et al., unpublished	Western City, USA	Children ≤25% on OFC or hgt. or wgt. From 1st grades in all 15 public schools in school district, urban, and suburban	55% Active Consent	Mixed race about 75% white 25% American Indian Black and Asian	Middle SES with full range from low to upper	1.4 – 2.5 (8.1 – 14.9) 9.5 – 17.4
May et al., unpublished	Western City, USA	Children ≤25% on OFC or hgt. or wgt. From 1st grades in all 17 public and private schools in school district, urban, and suburban	56% Active Consent	Mixed race about 75% white 25% American Indian Black and Asian	Middle SES with full range from low to upper	6.4 – 11.3 (7.7 – 13.5) 14.1 – 24.8

some of the range of data collected and analyzed. Also, by providing data on several populations, we are highlighting the fact that these features will vary slightly from one child to the next and from one ethnic or racial population to the next; but in general, similar variables cut across populations. As many of these features are slight variations on normal, a clinical team must understand ethnic and racial relativity in clinical assessments and may establish slightly different statistical parameters for each race and culture based on comparisons with an adequate number of controls in each population.

Child Intelligence, Developmental, and Behavioral Characteristics from In-school Studies

In Table 4 we have provided a sampling of the types of data that are used for the behavioral domain of the diagnosis for the in-school studies. A focus on children in the first grade per-

Table 3. Child Characteristics for Selected In-School Studies

	South Africa[a] (2002) (n = 218)			Italy[b] (2005) (n = 89)		Western City, USA[c] (2007) (n = 57)		Western City, USA[d] (2008) (n = 71)	
Trait	FAS	PFAS	Control	FASD	Control	FASD	Control	FASD	Control
Sex (% male)	58.2	61.1	47.6	50.0	44.8	42.9	62.0	45.5	60.0
Age (years)	7.8★★★	7.6	7.3	6.7	6.7	7.5	7.1	6.9★	6.5
Height (cm)	114★★★	115	119	116★★★	121	118★	124	119.5★★★	125.1
Weight (kg)	18.3★★★	19.3	21.8	22.0★★	25.5	22.3	25.9	23.5★	27.5
BMI (mean)	13.9★★★	14.6	15.3	16.2	17.3	15.7	16.9	16.3★★	17.6
Head circumference (OFC) (cm)	48.3★★★	48.5	50.9	50.7★★★	51.9	50.3★★★	52.4	50.9★★★	52.9
Palpebral fissure length (PFL) (cm)	2.3★★★	2.3	2.5	2.4★★	2.5	2.3★★★	2.5	2.4★	2.5
Philtrum length (PL) (cm)	1.4	1.4	1.4	1.4★★	1.5	1.3	1.4	1.5	1.4
Ptosis (%)	18.2★★	5.6	2.1	13.6★★	0.0	0.0	0.0	0.0	1.7
Epicanthal folds (%)	61.8	55.6	48.7	40.9★	14.9	42.9	12.0	18.2	23.3
Heart murmur (%)	10.9★★	22.2	3.4	0.0	1.5	0.0	0.0	9.1	1.7
Hypoplastic nails (%)	10.7★★	0.0	1.4	0.0	0.0	0.0	0.0	0.0	1.7
Limited elbow supination (%)	3.6★	11.1	0.7	13.6	3.0	0.0	0.0	0.0	1.7
Clinodactyly (%)	50.9	61.1	43.8	31.8	26.9	57.1	36.0	36.4	36.7
Camptodactyly (%)	36.4★★	27.8	8.3	22.7★★	7.5	0.0	8.0	27.3★	6.7
Altered palmar crease (%)	43.6★	38.9	26.2	45.5★	19.4	57.1	20.0	27.3	28.3
Total dysmorphology score (mean)	18.4★★★	17.8	8.1	12.5★★★	3.3	12.4★★★	4.1	12.5★★★	4.4
Adoptive/foster placement (%)	20.4★★★	33.3	5.3	–	–	–	–	–	–

[a]May et al., 2007a.
[b]May et al., 2006a.
[c]May et al. (as of October 1, 2008) unpublished pilot study data.
[d]May et al. (as of April 20, 2009) unpublished pilot study data.
★$P < 0.05$.
★★$P \leq .01$.
★★★$P \leq 0.001$.

mits testing to properly measure differential ability. At this age, tests exist that can readily distinguish between children who are doing well and those who are not, and children with an FASD perform less well than controls in a variety of areas. It is important that children with FASD are compared with their normal peers from the same culture and the same schools to define local population norms, and compare them fairly to determine differences resulting from prenatal alcohol exposure.

In Table 4, children with an FASD score lower in verbal and nonverbal intelligence in each comparison, have more behavioral problems, and perform more poorly on a variety of specific tasks such as coding, reading, numerical manipulation, making choices, and discriminating between options (e.g., executive functioning). They may be deficient in many skills, especially more complex cognitive skills, required for successful daily living [Kodituwakku et al., 2006a,b; Aragon et al., 2008a,b]. At the bottom of Table 4, diagnoses are associated with total dysmorphology scores and generally with particular drinking levels reported by the mother, especially drinks per drinking day (among those who drink), a key measure of heavy drinking. While variation on these selected tests is found across populations, relatively poor performance is consistently linked to particular patterns of maternal alcohol use and to relative levels of FASD-linked dysmorphology.

Maternal Risk and Protective Factors

Studies of school children allow initiation of successful and effective data collection of maternal risk factors. Most mothers of children suspected of an FASD are interviewed regarding maternal risk: demographic, childbearing, social, religious, nutrition, physical, alcohol and drug use, and genetics. Mothers of control children receive the same interview. We believe that retrospective collection of data is a strength because of time-line follow back techniques, careful sequencing of questions, a presumed lack of anxiety over viability of the children, calibrated drink (vessel) size measurement [Kaskutas and Graves, 2000, 2001; Kaskutas and Kerr, 2008], and the reduction of exposure anxiety on the part of the mothers 6- to 7-year postpartum [May, 1995; Viljoen et al., 2002; May et al., 2005, 2008]. In fact, some studies have found that retrospective assessments of prenatal drinking are more accurate than those gathered in prenatal clinics [Czarnecki et al., 1990; Robles and Day, 1990; Jacobson et al., 1993, 1994; Alvik et al., 2006]. In prenatal clinics stigma and threat of discovery are often supressors of accurate preporting of alcohol use data [Hannigan et al., in press].

As can be seen in Table 5, mothers of children with an FASD are generally older than comparison mothers, are more likely to live in impoverished or low SES areas (rural farms in our South African studies), have lower educational attainment and other low SES indicators, are less likely to married (except in Italy), have high gravidity and parity, are more frequently suffering from poor nutrition, and are smaller in height and weight, with a lower body mass (measured by Body Mass Index (BMI)). Other variables, not listed in Table 5, also discriminate between and within populations. In many populations it has been found that mothers of children with an FASD are significantly more likely to be: less regular in the practice of a religion, lower occupation status, lower income, more depressed, and in relationships with men with substantial drinking problems themselves [Viljoen et al., 2002; May et al., 2005, 2006, 2008].

Also in Table 5 some highlights are presented for drinking variables that distinguish the mothers of children with FASD from controls. Binge drinking variables are generally most discriminating, although the particular patterns and amounts of alcohol reported vary from

Table 4. Intelligence, Developmental, and Behavioral Characteristics of Children and Related Maternal Drinking Data from Previous In-School Studies of FASD: Selected Findings

	South Africa[a] (2002) (n = 151)			Italy[b] (2005) (n = 89)		Western City, USA[c] (2007) (n = 55)		Western City, USA[c] (2008) (n = 69)	
	FAS[(test)]	PFAS	Control	FASD[(test)]	Control	FASD[(test)]	Control	FASD[(test)]	Control
Test measure									
Full scale IQ						84.85[f]	108.60★★★	84.18	106.40★★★
Verbal IQ	10.9[d]	14.0	24.1★★★	3.4[e]	4.9★★	88.14[f]	110.62★★★	85.00	107.66★★★
NonVerbal IQ	9.4[e]	10.7	21.1★★★	102[g]	109★★	84.85[f]	104.62★★★	87.36	104.60★★★
Behavior	12.6[f]	12.2	6.5★★★	8.5[h]	3.9★★★	14.1[h]	5.9★★	16.5	6.4★★★
Coding				9.43[i]	11.71★	8.57[i]	11.22	11.40	10.88
Digit span	6.8[i]		10.05★★★	8.13[i]	10.23★	7.14[i]	10.31★	7.50	10.35★★
Mazes				9.78[i]	12.66★	8.14[i]	11.66	7.10	10.31★★
Reading						89.28[j]	110.3★	99.82	112.03★★
Adaptive measures									
Composite						81.86[k]	106.79★★★	93.55	110.02★★
Communication						79.71[k]	100.2★★★	90.09	109.57★★★
Daily living						83.00[k]	108.06★★★	95.91	109.50★★
Social						89.14[k]	105.02★	97.91	105.19
Maternal drinking data									
Total dysmorphology score	18.4	17.8	8.1★★★	12.4	3.3★★★	12.4	4.1★★★	12.5	4.4★★★
Drinkers only: Current drinks per week	7.5	6.3	8.9★★★★[l]	11.9	1.5★★	2.0	2.3	0.0★★★★	2.0
Current drinks per drinking day	3.5	1.8	0.8	2.1	0.8★	1.3	1.9	2.0	2.2

[a]May et al., 2007a and unpublished data.
[b]May et al., 2006a and unpublished data.
[c]May et al. (as of October 1, 2008) unpublished pilot data.
[d]Tests of Reception of Grammar (TROG)(std. score).
[e]Rustioni Qualitative Tests (# endorsed – higher = poorer).
[f]Personal Behaviors Checklist (PBCL)-36(# endorsed – higher = poorer).
[g]Raven Coloured Progressive Matrices(std. score).
[h]Wechsler Adaptive Scales of Intelligence (WASI)(std. score).
[i]Wechsler Intelligence Scales for Children (WISC)(std. score).
[j]Wide Range Achievement Test (WRAT-3)(std. score).
[k]Vineland Adaptive Behavior Scales (VABS)(std. score).
[l]The control group current average drinks per week exceeds that of FAS and PFAS mothers because: many FASD mothers seem to have cut down several years after the birth of the affected child; drinking is only one of a number of influential risk factors in S.A. (e.g., BMI, nutritional deficiencies, are others); only 27% of the control mothers drink at all, and as information increases over time in a population, mothers of children with an FASD child are more likely to under-report their consumption (see May et al., 2007a,b,c, 2008).
★$P < .05$.
★★$P \leq .01$.
★★★$P \leq 001$.

population to population. Obtaining accurate drinking data from women in developed countries, especially from those of middle to high education, is difficult, not because of recall, but because of a tendency to under-report [Czarnecki et al., 1990; Robles and Day, 1990; Jacobson et al., 1993, 1994; Alvik et al., 2006]. The interview format, sequence, and questions must be adapted to individual populations to ensure specificity and sensitivity to the local culture, norms, behaviors, and conditions.

Higher-Level Statistical Modeling from Larger In-School Studies

Because of the substantial sample sizes, and the greater number of FASD cases in South Africa, higher-level statistical techniques can be used to produce controlled models of the factors that are most highly associated with the physical and dysmorphological characteristics of children with FAS and PFAS [May et al., 2007c]. Generally the findings indicate that alcohol use variables such as a binge drinking pattern and large quantities drunk per occasion, especially during pregnancy, combine to produce the most significant factor that explains the severity of the dysmorphology including: head circumference, lip configuration, palprebral fissure size, height and weight, total dysmorphology score, and final diagnosis. Also significant are the mother's physical characteristics. For example, in both Italy and South Africa it has been documented that smaller mothers are more likely to bear a child with an FASD, presumably due to higher blood alcohol concentrations produced in the mother and therefore reaching the fetus [Khaole et al., 2004], Also significant in such models are the mother's social status and living conditions (e.g., low SES) which are highly influential on both drinking pattern [May et al., 2008] and in fetal outcome [Bingol et al., 1987].

The combination of the three major data sets (child growth and dysmorphology, child development and behavior, and maternal risk factors) collected via (South African) in-school studies, and the access to large numbers of children and mothers, permit modeling to address studies of associated, and possibly etiological, human factors relating to FASD. Some of the structural equation models of associations with physical features of FASD have explained over 60% of the variance in FASD physical features in the South African population [May et al., 2007c].

Similar multiple correlation analyses predicting behavioral characteristics (verbal and nonverbal IQ, specific executive functioning, and problem behavior) of children with FASD in South Africa, can also be used with large in-school studies elsewhere to define associations with the behavioral characteristics of children with FASD. Structural equation models of the differential behavior among South African children explain over 50% of the variance, even with a set of rather limited and imper-

Table 5. Maternal (Risk and Protective Factor) Characteristics from In-School Studies of FASD: Selected Findings

	South Africa[a] (2002) (*n*= 206)			Italy[b] (2005) (*n*= 81)		Western City, USA[c] (2007) (*n*= 57)		Western City, USA[d] (2008) (*n*= 38)	
	FAS	PFAS	Control	FASD	Control	FASD	Control	FASD	Control
Variable									
Age (mean) at interview	37.6	32.3	33.9***	37.9	36.6	35.9	33.1	34.4	33.5
Rural residence during pregnancy (%)	71.2	47.1	33.8***	29.4	20.6	–	–	–	–
Educational attainment (years)	4.6	6.5	8.0***	9.1	11.3*	H.S. or GED+ (%)		H.S. or GED+ (%)	
						75	100***	71	100**
Childbearing									
Gravidity	3.6	3.1	2.9**	2.9	2.2	4.1	2.8*	4.6	3.4
Parity	3.2	2.9	2.7*	2.5	1.9*	3.5	2.5*	3.9	2.8
Birth order of child	3.2	2.3	2.2***	2.0	1.5	2.5	1.9	2.7	1.7*
Age at birth of child	28.8	24.8	25.7**	31.8	29.7	26.5	29.3	26.7	26.6
Marital status (% married)	18.0	50.0	45.7***	82.4	82.5	50.0	76.3	57.1	71.0
Body mass index	22.5	23.5	27.4***	25.0	23.4	23.2	26.5	28.1	27.4
Alcohol/drug use									
Drinker at time of interview	65.9	46.7	26.7***	91.7	100.0*	[d]	[d]	[d]	[d]
Drank in 3 months before pregnancy (%)	96.0	80.0	25.4***	91.7	87.5	[d]	[d]	[d]	[d]
Drank during index pregnancy (%)	96.0	93.8	24.8***	69.2	64.6	[d]	[d]	[d]	[d]
Drank during 3rd trimester (%)	94.1	92.9	25.4***	50.0	33.3	[d]	[d]	[d]	[d]
Estimated peak BAC of drinkers in 3rd trimester (among those who drank)	0.191	0.102	0.076*	–	–	[d]	[d]	[d]	[d]
Smokers: cigarettes per week (#)	31.7	19.5	10.7**	56	66.5	[d]	[d]	[d]	[d]
Smoked during index pregnancy (%)	84.3	82.4	35.8***	40	37.5	37.5	14.5	28.6	16.7

[a]May et al., 2007a, 2008.
[b]May et al., 2006a,b and unpublished data.
[c]May et al. (as of) unpublished pilot data.
[d]Comparable data across populations do not exist in these individual studies, or maternal risk factor data have not yet been analyzed for these entire samples (for more detail see May et al., 2006a,b for Italy and May et al., 2008 for South Africa Wave III).
*$P < 0.05$
**$P < 0.01$
***$P < 0.001$.

fect measures of assessment as dependent variables [May et al., 2007b].

Summary of the In-School Prevalence of FASD

In Table 6, nine in-school studies from three countries are summarized. South African prevalence of FASD is the highest with an average of 72.3 per 1,000 or 7.2%. FAS rates are proportionally higher than PFAS in South Africa with 3.1 cases of FAS to each PFAS case [May et al., 2007a] and 3.2 to one PFAS case [Urban et al., 2008] in the two most recent studies published. However, these studies concentrated on screening for children ≤10th centile (on height, weight, and OFC) which may have reduced the number of taller and heavier affected children with PFAS entering the diagnostic tier of the study (see Table 2).

In Italy the rates of FASD are lower than South Africa, but higher than in the US Western City. Italy has an average FASD rate of 35.7 per 1,000 (3.6%) with a rate of FAS of 6.2 per 1,000 and PFAS rate of 27.9 per 1,000. This makes 0.22 cases of FAS to each case of PFAS; and the same size criteria were used for initial entry into the study as in South Africa (≤10th centile on height, weight, and OFC). Therefore, more severe damage is found in South Africa than in Italy.

Finally, the Western City Pilot Studies in the USA have produced an FASD rate of 16.5 per 1,000. The rate of FAS is 4.9 per 1,000 and 11.0 for PFAS. The ratio of FAS to PFAS is 0.44, which is more like Italy than the South African ratio. The inclusion criteria used in the Western City were more liberal (see Table 2) as children were included who were ≤25th centile on height, weight and OFC.

CONCLUSION: THE PREVALENCE OF FAS AND TOTAL FASD IN MAINSTREAM POPULATIONS IS LIKELY HIGHER THAN PREVIOUSLY ESTIMATED

The study of the prevalence and characteristics of FASD have generally progressed slowly since the 1970s, but progress has accelerated in the past decade. We believe that in-school studies advance the assessment and understanding of prevalence beyond that of other methods. The overall prevalence of FAS in the US was estimated in 1996 by the IOM Committee [Stratton et al., 1996] to be between 0.5 and 3.0 per 1,000 births. And in a previous review by two of the authors of this article, FAS was estimated to be between 0.5 and 2.0 per 1,000 births [May and Gossage, 2001a], an estimate made from the clinic-based studies and referral-based, population outreach studies in relatively small communities. Also, as cited above, the prevalence of all FASD combined is commonly believed to be at least 9.1 per 1,000, or 1% [Sampson et al., 1997].

In the past, our multidisciplinary team of researchers has examined the prevalence, specific characteristics, and targeted etiology of FAS and other FASD in humans in multiple settings: medical clinics, referral clinics, and school populations. This experience, and the data that we have presented here, have demonstrated that in-school studies are innovative, straight-forward, and a most promising method for establishing an accurate and complete epidemiology of FASD within a population, especially for the diagnoses of FAS and PFAS. Yet they are expensive, time-consuming, labor intensive, and involve

Table 6. Summary of the Prevalence of FASD from In-School Studies: Rates per 1,000 Children

Diagnosis	South Africa Western Cape (1997)[a,b]	South Africa Western Cape (1999)[b,c]	South Africa Western Cape (2002)[d]	South Africa Northern Cape (2008)[e]	South Africa Mean	Italy[f] (2005)	Italy[g] (2006)	Italy Mean	USA Washington State Pilot[h] (2001)	USA Western City Pilot[i] (2007)	USA Western City Pilot[j] (2008)	USA Mean
FAS	(*n* = 42) 40.0 – 42.3	(*n* = 37) 40.1 – 42.9	(*n* = 55) 51.2 – 67.2	(*n* = 123) 67.2	50.1	(*n* = 4) 3.7 – 7.4	(*n* = 4) 4.4 – 9.2	6.2	(*n* = 7) 3.1	(*n* = 1) 1.4 – 2.5	(*n* = 5) 6.4 – 11.3	4.9
PFAS	(*n* = 4) 3.8 – 4.0	(*n* = 29) 31.4 – 33.6	(*n* = 18) 16.8 – 22.0	(*n* = 38) 20.8	18.9	(*n* = 17) 15.7 – 31.3	(*n* = 19) 21.0 – 43.8	27.9	–	(*n* = 6) 8.1 – 14.8	(*n* = 6) 7.7 – 13.5	11.0
ARND	–	(*n* = 10) 10.9 – 11.6	–	–	11.3	(*n* = 1) 0.9 – 1.8	–	1.4	–	–	–	–
ARBD	–	–	–	–	–	–	(*n* = 1) 1.1 – 2.3	1.7	–	–	–	–
Total FASD	(*n* = 46) 43.8 – 46.4	(*n* = 76) 82.4 – 88.16	(*n* = 73) 68.0 – 89.2	(*n* = 161) 88.0	72.3	(*n* = 22) 20.3 – 40.5	(*n* = 24) 26.6 – 55.4	35.7	–	(*n* = 7) 9.5 – 17.4	(*n* = 11) 14.1 – 24.8	16.5

[a]May et al., 2000.
[b]Figures in this column differ slightly from published figures as the revised IOM criteria have been applied to the cases resulting in new cases of PFAS and ARND whereas all cases were FAS in publications.
[c]Viljoen et al., 2005.
[d]May et al., 2007a.
[e]Urban et al., 2008.
[f]May et al., 2006a.
[g]May et al., 2006b (poster).
[h]Clarren et al., 2001.
[i]May et al., unpublished.
[j]May et al., unpublished.

complicated interdisciplinary and interagency interactions. But the more formal, more adequately-funded, and longer term in-school studies that have been supported by NIAAA and conducted in two foreign countries, South Africa and Italy, have yielded rich and very valuable information. Yet in schools in the United States, only pilot studies with: very limited budgets and resources; limited, part-time field personnel; and short time frames have been conducted to date. Therefore, the population-based prevalence and characteristics of FASD in any US population are still relatively unknown. However, the methods, logistics, and analyses of in-school studies have developed nicely, have been refined in the foreign studies and US pilot studies, and could potentially yield accurate and meaningful results that will help move epidemiological studies of FASD forward to benefit both basic and clinical science. Such studies for the US and Western Europe are lacking and long overdue.

While the epidemiological context, extent, and impact of FASD in mainstream US populations remain relatively undefined, studies in Italy and pilots in the US indicate that the rate and impact of FASD in mainstream populations may be significantly greater than previously thought or estimated. Professionals need to continue population-based studies in search of: more accurate estimates of FASD in the mainstream US population, better assessments of the physical and behavioral characteristics of children with the various diagnoses within the continuum of FASD, and further define specific behavioral and medical risk factors for various levels of prenatal alcohol damage [Dehaene et al., 1991; Stratton et al., 1996; Hoyme et al., 2005]. The challenge is to employ better and more sophisticated diagnostic criteria in population-based studies assessing FASD in a representative cross section of the population.

With experience gained recently, we believe that the upper limit of the IOM report (3.0 FAS per 1,000) is a more realistic estimate of the prevalence of FAS, or even a bit low. Therefore, we believe that the prevalence of FAS in typical, mixed-racial, and mixed-SES populations the US is at least 2 to 7 per 1,000. Also, with employment of improved diagnostic procedures within school populations, our belief is that there is a higher prevalence of the lesser levels of FASD than previously believed. It is clear that there are many more

cases of PFAS and ARND than have been diagnosed in the past.

Regarding all levels of FASD, we currently estimate that the prevalence of FASD, using IOM recommended methodology in populations of younger school children, may be 2–5% in the US and many Western European countries. If this is true, then FASD present a larger public health problem than most researchers have estimated in the past. The problems of FASD require immediate attention and emphasis from the public health, obstetric, pediatric, and education communities. Clearly the US Surgeon General's warning of 1981, which was reissued in 2005, was accurate and sage advice. "The Surgeon General advises women who are pregnant (or considering pregnancy) not to drink alcoholic beverages and to be aware of the alcoholic content of food and drugs" [Koop, 1981; Carmona, 2005]. Epidemiological and clinical researchers must work diligently to improve the ability to access cases of FASD and produce evidence of, and insight into the far-reaching effects of alcohol on child growth and development. ■

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