

# Fetal Alcohol Spectrum Disorders in Finland: Clinical Delineation of 77 Older Children and Adolescents

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The adverse effects of alcohol on the developing human comprise a spectrum of structural anomalies and behavioral and neurocognitive disabilities, most accurately termed fetal alcohol spectrum disorders (FASD). We previously have proposed revisions to the 1996 Institute of Medicine Diagnostic Criteria for diagnoses in the FASD continuum [fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (PFAS), alcohol related birth defects (ARBD), and alcohol related neurodevelopmental disorder (ARND)], allowing for more reproducible and accurate FASD diagnosis in a clinical setting [Hoyme et al., 2005]. The NIAAA recently has coordinated and funded an international consortium of projects aimed at more complete characterization of the teratogenic spectrum of alcohol. One of the projects sites is in Finland. The aims of this project are: (1) to completely clinically characterize the structural and learning/behavioral phenotypes of a large cohort of older children and adolescents with moderate to severe disability within the FASD continuum; (2) to correlate FASD dysmorphology and behavioral phenotypes with CNS structure and function (i.e., MRS, MRI correlations); (3) to compare the phenotype of a genetically homogeneous population of Finnish children with FASD to that observed in other populations. We have recently completed dysmorphology examination and parent/guardian interviews of the 77 children in the Finnish cohort. The purpose of this report is to present historical and morphometric data on these patients, thereby more completely delineating the clinical spectrum of FASD in older children and adolescents, contrasting the phenotype with that described in other populations and examining whether a weighted dysmorphology score could be used as a clinical

and research adjunct when fetal alcohol exposure is being suspected. All children were previously diagnosed with FASD by an experienced pediatric specialist in Finland, and all were exposed to significant maternal alcohol abuse prenatally. The sex ratio of the cohort was 0.38 (male: female) and ages ranged from 8 to 20 years, with a mean of 13 years. After application of the Revised IOM Diagnostic Criteria, 53% of the subjects were diagnosed as having FAS, 30% PFAS, 12% ARND, and 5% other diagnoses. Of note, although a family history of mental retardation or birth defects was rare, 43% of the children had one or more sibling who also carried a diagnosis of FAS. Eighty-nine percent of the mothers smoked cigarettes during gestation; other teratogenic exposures were rare. Almost none had undergone genetics evaluation in the past. Almost all of the subjects had resided in multiple foster placements since early childhood and had been followed regularly by pediatric specialists. Although 11% were born prematurely, 70% demonstrated prenatal growth deficiency, and 45% were microcephalic. Other than growth deficits and the cardinal facial features, the most common major and minor anomalies noted were: camptodactyly (55%), “hockey stick” or other altered palmar creases (51%), refractive errors (40%), strabismus (38%), dental crowding (43%), nail hypoplasia (38%), GU anomalies (22%), and congenital heart defects (18%), “Railroad track” ears were not observed in this population.

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**Key words:** fetal alcohol syndrome; fetal alcohol spectrum disorders; dysmorphic features; diagnostic criteria

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## INTRODUCTION

Heavy drinking and repeated binge drinking during pregnancy are associated with a wide spectrum of adverse fetal outcomes ranging from mild to severe. The most severe end of this spectrum was defined by Jones and Smith [1973], who termed the disorder fetal alcohol syndrome (FAS). The subsequent discovery that prenatal alcohol exposure results in a continuum of harmful effects on the fetus has led to often confusing terminology with little clinical applicability [Aase et al., 1995]. Most recently the spectrum of disability associated with prenatal alcohol exposure has been accurately termed fetal alcohol spectrum disorders (FASD) [Barr and Streissguth, 2001]. A number of researchers have attempted to define diagnostic criteria for diagnoses within FASD [Astley, 2004; Centers for Disease Control and Prevention NCoBDaDD, National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effects, 2004; Chudley et al., 2005]. Those set forth by the Institute of Medicine in 1996 define the spectrum most broadly; however, the specific clinical norms necessary for making these diagnoses were left undefined [Stratton et al., 1996]. The IOM criteria have recently been revised [Hoyme et al., 2005] with the aim of providing a practical guide that can be easily applied in clinical practice, thereby improving care for affected children and leading to enhanced precision of clinical and population-based research in FASD (Table I). These revised criteria are currently being used in a large multicenter study on FASD.

Historically, the IOM diagnostic categories [FAS, partial FAS (PFAS), alcohol-related birth defects (ARBD), and alcohol-related neurodevelopmental

disorder (ARND)] have not been easy diagnoses to make—the more subtle the signs the more difficult they are for an inexperienced examiner to recognize [Astley and Clarren, 2000]. Although a child with full-blown FAS is easy for an experienced pediatric clinician to recognize, other malformation syndromes representing full or partial phenocopies must be excluded (e.g., Williams syndrome, Dubowitz syndrome, fetal anticonvulsant syndrome, toluene embryopathy, Cornelia de Lange syndrome, velocardiofacial syndrome, and others) [Jones, 1997; Chudley et al., 2005; Hoyme et al., 2005]. Diagnoses within the FASD continuum must be seen as etiologic diagnoses—not diagnoses that specify each child's individual needs. For clinical purposes it is thus necessary to have diagnostic criteria that are both easy to use but yet sensitive and specific enough to correctly affirm the etiology of each affected child's difficulties.

In Finland a prospective study on pregnancy outcome in women with problematic drinking was instituted in 1983 [Halmesmäki, 1988]. The diagnostic criteria used during in this prospective study were first based on Rosett [1980] and later on Finnish revisions to the IOM criteria [Stratton et al., 1996; Autti-Rämö, 2000]. The continuum of adverse fetal outcome was termed fetal alcohol effects (FAE), and the term FAE was implemented into Finnish clinical practice. Though ARND was clearly recognized in the prospective study [Autti-Rämö, 2000], this diagnostic subgroup heretofore has been poorly adopted in Finland.

The present study is part of an international collaborative study, the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD). The Finnish

TABLE I. Revised IOM Criteria for Diagnosis Within the FASD Continuum [Hoyme et al., 2005]

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**Diagnostic criteria for FAS or PFAS (with or without confirmed maternal alcohol exposure):** (FAS requires all features A–C; PFAS requires A and B or C or evidence of a complex pattern of behavior or cognitive abnormalities inconsistent with developmental level and that cannot be explained by genetic predisposition, family background, or environment alone [see ARND]).

A. Evidence of a characteristic pattern of minor facial anomalies, including at least two of the following:

- Short palpebral fissures (less than or equal to the 10<sup>th</sup> centile)
- Thin vermilion border of the upper lip (score 4 or 5 on the lip/philtrum guide; Fig. 1)
- Smooth philtrum (score 4 or 5 on the lip/philtrum guide)

B. Evidence of prenatal and/or postnatal growth retardation: height or weight less than or equal to the 10th centile

C. Evidence of deficient brain growth or abnormal morphogenesis, including one or more of the following:

- Structural brain abnormalities
- Head circumference less than or equal to the 10th centile

**Diagnostic criteria for alcohol-related effects (ARBD and ARND):** (A diagnosis in these categories requires a confirmed history of prenatal alcohol exposure)

- ARBD requires the characteristic facies as above plus specific congenital structural defects (including malformations and dysplasias) in at least one organ system (if the patient displays minor anomalies only, at least two must be present). This category assumes the subject to have normal growth and intellectual/behavioral characteristics
- ARND assumes the subject to have normal growth and structure and at least one of the following (A or B):

A. Evidence of deficient brain growth or abnormal morphogenesis, including one or more of the following:

- Structural brain abnormalities
- Head circumference less than or equal to the 10th centile

B. Evidence of a complex pattern of behavior or cognitive abnormalities inconsistent with developmental level and that cannot be explained by genetic predisposition, family background, or environment alone

- This pattern includes: marked impairment in the performance of complex tasks (complex problem solving, planning, judgment, abstraction, metacognition, and arithmetic tasks); higher-level receptive and expressive language deficits; and disordered behavior (difficulties in personal manner, emotional lability, motor dysfunction, poor academic performance, and deficient social interaction)

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project includes neuropsychological and morphological assessments as well as neuroimaging of affected children. The aims of the present study were to examine a genetically homogeneous cohort of Finnish children and adolescents with FASD on morphological, societal, cognitive, and educational levels, to compare the data to those previously published and to examine the utility of a weighted dysmorphology score as a potential adjunct in clinical practice and research when an FASD diagnosis is suspected.

## METHODS

### Patients

Until 1999, all Finnish speaking children with permanent signs of CNS dysfunction and living in the Helsinki area were diagnosed and followed at one of three hospitals: Aurora District Hospital, Children's Castle Hospital, or the Helsinki University Hospital. In 1999 the hospitals merged, and since that time all children with signs of CNS dysfunction have been diagnosed and treated at the Hospital for Children and Adolescents, University of Helsinki. Swedish speaking children are referred to the Folkhälsan Rehabilitation Center for follow-up. All children diagnosed as having FASD born between the years 1984 and 1996 were identified from the records of the three hospitals. One hundred four children were ascertained. Heavy maternal alcohol consumption during pregnancy was confirmed for all cases by review of patient records or other reliable collateral sources, including interview of biological parents and/or guardians. The parents or guardians of these children were contacted and 77 agreed to participate in the study.

### Dysmorphology Assessment

All subjects and/or their parents, or guardians underwent a standard interview regarding family, medical, and developmental histories. All dysmorphology examinations and diagnostic assessments were performed by a single experienced dysmorphologist (HEH) during a 3 month period during the summer of 2004. The parent or guardian of the child, a nurse, and a research psychologist were present during the interviews and examinations, and helped with the translation when needed. Anthropometric measurements were recorded. Height, weight, and head circumference were transformed into age and sex specific centiles according to Finnish norms [Sorva et al., 1990a,b]. Palpebral fissure measurements were obtained using a rigid ruler, marked in millimeters, with the examiner directly seated in front of the subject, recording the distance from the medial canthus to the lateral canthus. American norms [Thomas et al., 1987] were used for palpebral fissure length. The morphology of each subject's upper lip

and philtrum was scored utilizing the lip philtrum guide [Astley et al., 2000], as presented by Hoyme et al. [2005]. A physical examination was performed to assess major and minor anomalies. All children were assigned a dysmorphology score, a weighted quantitative measure of associated major, and/or minor anomalies according to the method of Hoyme et al. [2005] (Table II). Finally, the children were assigned diagnoses according to the revised IOM criteria for FASD [Hoyme et al., 2005].

### Ethics Approval

The Ethics Committee of the Hospital for Children and Adolescents, the Joint Ethics Committee of the Helsinki University Hospital (required for studies receiving funding from abroad), and the Institutional Review Boards of San Diego State University and Stanford University School of Medicine reviewed and approved this study.

### Statistical Analysis

The data were recorded and analyzed utilizing an SPSS<sup>®</sup> for Windows<sup>®</sup> software package.

TABLE II. Dysmorphology Scoring System [Hoyme et al., 2005]\*

Feature	Points
Height <10%	1
Weight <10%	2
Occipitofrontal circumference <10%	3
Inner canthal distance <10%	0
Palpebral fissure length <10%	3
Attention deficit/hyperactivity	1
Fine motor dysfunction	1
Midfacial hypoplasia	2
"Railroad Track" ears	1
Strabismus	0
Ptosis	2
Epicanthal folds (non-racial)	1
Flat nasal bridge	1
Anteverted nares	2
Long philtrum	2
Smooth philtrum	3
Thin vermilion border of upper lip	3
Prognathism	0
Cardiac murmur	1
Cardiac malformation (confirmed)	1
Hypoplastic nails	0
Decreased pronation/supination of elbow	2
Clinodactyly of fifth fingers	1
Camptodactyly	1
"Hockey Stick" palmar creases	1
Hirsutism	1
Total possible dysmorphology score	36

\*The dysmorphology score is a weighted calculation based on assigning points to clinical findings characteristic of FASD (the highest point values are assigned to the cardinal findings of FAS, that is, growth deficiency, microcephaly, short palpebral fissures, smooth philtrum, and a thin upper lip). The score is an objective method of quantifying dysmorphology, but is *not* used in assigning clinical diagnoses in the FASD continuum.

## RESULTS

### Demographic Characteristics

The sex ratio of the cohort was 0.38 (male: female) and the ages of the subjects ranged from 8 to 20 years, with a mean of 13 years. In terms of current living situation, 64% lived with a foster family or had been adopted, 16% resided in a children's home, 16% resided with a biological parent, and 4% lived independently. Ninety-six percent were currently or had previously been in a special education program, and 46% had received multiple therapeutic interventions (speech, occupational, and/or physical therapy).

### Family History

Ninety-five percent of the subjects were racially Finnish; no consanguinity was reported. A family history of genetic disorders, birth defects, or mental retardation was rare. However, 42% reported first degree relatives with learning disabilities and/or attention deficit hyperactivity disorder (unrelated to prenatal alcohol exposure). Finally, 43% reported a sibling who also had been diagnosed with FASD.

### Prenatal/Birth History

Eleven percent of the subjects were born prematurely (less than 36 weeks gestation). Seventy percent demonstrated prenatal growth deficiency and 45% were microcephalic at birth. Although other potentially teratogenic exposures were rare, 89% of women (from whom prenatal data were available) smoked cigarettes throughout pregnancy.

### Revised IOM Diagnostic Category Assignment

Of the 77 subjects evaluated, 73 (95%) had an FASD diagnosis, whereas 4 (5%) had features of other unrecognizable multiple malformation syndromes inconsistent with the teratogenic effects of alcohol. These four subjects were excluded from the clinical analysis. Fifty three percent of subjects were assigned a diagnosis of FAS, 30% a diagnosis of PFAS, 12% a diagnosis of ARND, and 5% a diagnosis of other

malformation syndrome. No subjects were diagnosed as having ARBD. The revised IOM diagnostic categories of the study cohort and comparison with previous diagnoses assigned by Finnish clinicians are set forth in Table III.

### Major and Minor Anomalies

The dysmorphic features observed in the FASD cohort are listed by order of frequency in Table IV. The weighted dysmorphology scores for the study cohort are depicted in Figure 2. The mean dysmorphology score for the entire cohort was 16 (range 2–29). The mean dysmorphology score for children with FAS was 19.7 (range 12–29), PFAS 12.4 (range 5–19), and ARND 5.3 (range 2–10),  $P < 0.001$ . Except for one child, the children with unknown multiple malformation syndromes scored within the range of children with FAS, the mean being 17.2 (range 7–21). Morbidity by organ system is set forth in Table V. Of the 14 patients who reported congenital heart defects, 10 had a VSD, 5 had an ASD, 1 reported coarctation of the aorta, 1 had a history of a hemodynamically significant PDA, and 1 reported a hypoplastic aortic arch (some of the subjects had more than one defect).

## DISCUSSION

The present study comprises one of the largest cohorts of fully clinically characterized children with FASD described in the medical literature. Although the subjects herein described represent a significant number of Finnish children with FASD, during this ongoing study it has become clear that not all children in Finland with diagnoses within the FASD continuum are ascertained for various reasons. In Finland social support and health care are not diagnosis dependent, but rather are based on the burden of the disease and the medical and social needs of each individual child. Since FASD diagnoses are not informative about the specific needs of affected children, some rehabilitation teams still prefer to use descriptive diagnoses that specify each child's developmental problems rather than assigning etiologic diagnoses (e.g., attention deficit hyper-

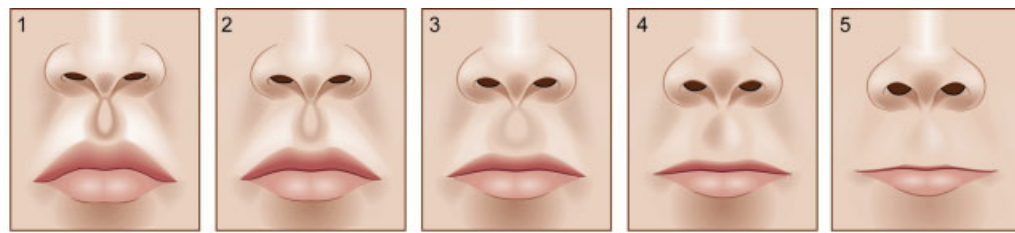


FIG. 1. The lip/philtrum guide [derived from Astley and Clarren [2000]; printed with permission from M. Muenke, the National Human Genome Research Institute]. Scores of 4 or 5 are compatible with the adverse effects of alcohol on fetal development.

TABLE III. Comparison of Initial Diagnosis and Revised IOM Diagnosis

Original diagnosis	N	Revised IOM diagnosis			
		FAS	PFAS	ARND	Other
FAS	32	23	7	2	0
FAE	23	5	14	3	1
FAS/FAE	22	13	2	2	3
ARND	2	0	0	2	0
TOTAL	77	41	23	9	4

activity disorder with arithmetic difficulties). The confirmation of heavy alcohol exposure during pregnancy may also be difficult, since not all mothers are willing to accept the relationship between their child's problems and their alcohol consumption. Some biological and adoptive parents are also reluctant to have alcohol-related diagnoses assigned to their children, since they regard them as negative labels. For these reasons, we were not able to trace all children with FASD living in the Helsinki district area. We consider, however, that the clinical characteristics of our cohort of children with FASD represent well the spectrum of this disorder in the Finnish population. This study cannot, however, be used to estimate the prevalence of FASD in Finland.

With respect to the demographic characteristics of our cohort, significantly more girls than boys were assigned an FASD diagnosis. Most previous studies have identified affected boys more frequently than girls [Clarren and Astley, 1997; May et al., 2000; Burd et al., 2003]. However, Kvigne et al. [2004] noted no sex difference among subjects in their study of Native American children with FASD. The explanation for the sex differences in FASD prevalence recorded in these various studies is unknown, but may reflect statistical sampling differences rather than real variation in teratogenic susceptibility between the sexes. As in previous studies, a minority of our

TABLE IV. Dysmorphic Features by Order of Frequency

Dysmorphic feature	Percent
Vermilion score 4 or 5	87
Short palpebral fissures (<10%)	78
Philtrum score 4 or 5	77
Epicantal folds	68
Anteverted nares	56
Camptodactyly	55
Long philtrum	47
Midface hypoplasia	45
Dental crowding	43
Nail hypoplasia	38
Hockey stick palmar crease(s)	30
Altered palmar crease(s) (other)	21
Limitation in radioulnar rotation	16
Ptosis	14
Clinodactyly	12
Flat nasal bridge	10
Railroad track ear	5

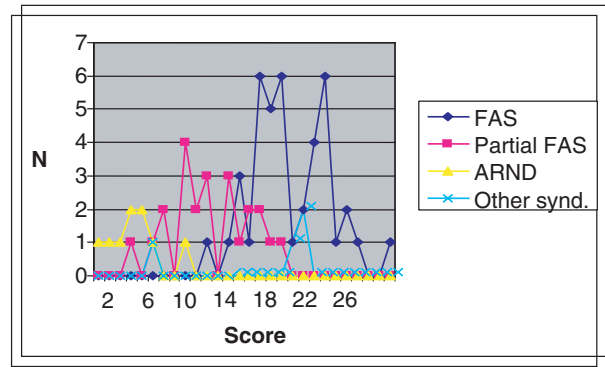


FIG. 2. Dysmorphology score by diagnosis.

subjects lived with their biological parent(s), and the majority had received or were receiving special educational and other therapeutic services [Aronson, 1997; Clarren and Astley, 1997; Kvigne et al., 2004]. Ninety-five percent of our patient population self-reported their ethnic background as Finnish, thereby discounting the possibility that our observations could be accounted for by racial or ethnic differences among the subjects.

The family histories of our subjects were remarkable for a high rate of learning and behavior problems among first-degree relatives of the probands (50%). This was unrelated to alcohol exposure. This suggests that at least some of the behaviors observed in our population may have a genetic basis. In addition, nearly half of subjects identified a sibling who had also been assigned an FASD diagnosis, a finding previously documented in a retrospective review of the medical literature on FAS [Abel, 1988]. The high prevalence of FASD in siblings of affected probands is particularly important in terms of prevention, since identifying women who have had one child affected with FASD and focusing efforts on treating their alcoholism and/or improving their birth control practices (if they continue to drink) may potentially have a huge impact on the occurrence and recurrence of this disorder in a given population.

There is no consensus as to the number and type of minor physical anomalies that should be assessed in a structured dysmorphology checklist. Studies in

TABLE V. Morbidity by Organ System

Organ system	Percent with malformation
Cardiac	18
Genitourinary	22
Skeletal	21
Gastrointestinal	26
Pulmonary	14
Vision <i>Strabismus</i>	38
<i>Refractive errors</i>	40
Hearing <i>impairment</i>	16

children with fetal alcohol exposure have used varying, often self constructed scales [Majewski, 1978; Tennes and Blackard, 1980; Vitez et al., 1984; Day et al., 1991; Autti-Rämö et al., 1992]. For this study we used a weighted dysmorphology score first developed by Dr. Jon Aase of the University of New Mexico [Hoyme et al., 2005]. In this scale, particular weight is given to those features which are most prevalent in children with FASD (i.e., the three cardinal facial features, head circumference, height, and weight). The timing and pattern of alcohol consumption may also have a large role in the development of specific malformations. It was not possible to obtain exact information on the pattern of alcohol consumption during pregnancy for the children included in the study, and thus we are not able to analyze time and pattern specific malformations. However, since the structural morphogenesis that can be assessed on a dysmorphology examination is largely complete by the end of the first trimester of pregnancy, children with significant first trimester exposure would be expected to have the highest scores.

In this study we were also interested in evaluating whether genetic differences exist in terms of the prevalence of certain minor anomalies among children with FASD by comparing our findings in Finnish children with those from other racial and ethnic groups. The methodology set forth in this study has also been applied in the dysmorphology assessment of children with FASD in Native American and Cape colored communities in the Upper Great Plains of the United States and the Western Cape Province of South Africa, respectively [May et al., 2000; Hoyme et al., 2005]. The weighted dysmorphology scores were higher in Finnish children in every diagnostic subgroup than in those previously reported in Native Americans and South Africans [Hoyme et al., 2005]. The validity of this score has now been evaluated and confirmed in three different racial and genetic backgrounds. A significant difference in the weighted dysmorphology scores among the diagnostic subgroups in FASD could also be observed. Although the present study did not include a control group, an earlier study of 60 dysmorphic features in Finnish children with prenatal alcohol exposure [Autti-Rämö et al., 1992] showed that multiple minor anomalies are very rare in non-alcohol exposed Finnish children. The results of the current study and those previously reported in the literature indicate that the weighted dysmorphology score is a useful adjunctive tool in the clinical and/or research assessment, or subjects when fetal alcohol exposure is suspected. Although the dysmorphology score is a useful tool for quantifying major and minor anomalies, it should not be used in assigning clinical diagnoses in the FASD continuum. Further research is needed to evaluate its specificity in the Finnish population.

The presence of cardinal facial features was very high in this Finnish cohort of children and adolescents with FASD. The lip/philtrum guide [Astley and Clarren, 2000] was highly sensitive in Finnish children: 77% of all children had philtrum scores of 4 or 5 and 87% had vermilion scores of 4 or 5. Our results strongly support the use of the lip/philtrum guide in the clinical assessment of children for FAS and PFAS. Midfacial hypoplasia, long philtrum, and anteverted nares are also useful features, observed in nearly half of the children. Epicanthal folds were the most frequently observed dysmorphic feature in non-alcohol exposed children in an earlier study of Finnish children [Autti-Rämö et al., 1992], and although present in nearly 70% of exposed children in this study, its significant prevalence in normal Finnish children suggests that it is not useful as a sign of FASD in this population. A "railroad track" configuration of the ear, reported to be a common minor anomaly in children with FASD in other populations [Hoyme et al., 2005], was a rarity in Finnish children, but minor anomalies of the extremities (camptodactyly, nail hypoplasia, altered palmar creases (including the "hockey stick" crease) and clinodactyly) were observed frequently in Finnish children.

## CONCLUSIONS

Drinking among women of reproductive age has increased in Finland. Only one in ten such women is abstinent, and binge drinking has increased especially among young women [STAKES, Helsinki, 2004]. A similar study from Sweden suggests a significant and increasing problem with drinking during pregnancy [Göransson et al., 2003]. With the advent of new European Union legislation, the excise duty on alcohol and alcoholic beverages was reduced by an average of 33% in 2004. As a consequence aggregate consumption, calculated in pure alcohol, increased by 9.6% in comparison with the previous year (from 9.4–10.3 L per inhabitant) [Ministry of Finance, Research and studies, Helsinki, Finland, 2005]. To be able to accurately assess the outcomes of these drinking practices during pregnancy, it is essential that an accurate and population-tested diagnostic methodology for FASD be employed.

In this study of 77 Finnish children and adolescents with confirmed heavy prenatal alcohol exposure the revised IOM criteria for FASD were tested and found to be a reliable tool to differentiate among the various diagnostic groups within the FASD continuum. The adoption of these criteria requires, however, a change in current practice and national education will be required to reduce confusion among pediatric providers. Data from our study cohort indicate that the lip/philtrum guide should be used for screening FAS/PFAS in Finnish children. In addition, because of their particular prevalence in children with FASD in

the Finnish population, special emphasis should be given to identifying minor anomalies of the extremities, since these signs are easy to recognize. Our study also indicates that the weighted dysmorphology score may be a valuable tool in clinical assessment and research in children with prenatal alcohol exposure. Finally, the recognition of children with ARND remains a significant clinical challenge, one that will require the concerted efforts of clinicians and researchers around the world to delineate more accurately and completely.

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