Drug and Alcohol Dependence 145 (2014) 201–208

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Maternal risk factors for fetal alcohol spectrum disorders in a province in Italy☆

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ARTICLE INFO

Article history:
Received 21 May 2014
Received in revised form 14 October 2014
Accepted 17 October 2014
Available online 25 October 2014

Keywords:
Fetal alcohol spectrum disorders (FASD)
Fetal alcohol syndrome (FAS)
Maternal risk for FASD
Italy
Alcohol consumption

ABSTRACT

Background: Maternal risk factors for fetal alcohol spectrum disorders (FASD) in Italy and Mediterranean cultures need clarification, as there are few studies and most are plagued by inaccurate reporting of antenatal alcohol use.
Methods: Maternal interviews ($n = 905$) were carried out in a population-based study of the prevalence and characteristics of FASD in the Lazio region of Italy which provided data for multivariate case control comparisons and multiple correlation models.
Results: Case control findings from interviews seven years post-partum indicate that mothers of children with FASD are significantly more likely than randomly-selected controls or community mothers to: be shorter; have higher body mass indexes (BMI); be married to a man with legal problems; report more drinking three months pre-pregnancy; engage in more current drinking and drinking alone; and have alcohol problems in her family. Logistic regression analysis of multiple candidate predictors of a FASD diagnosis indicates that alcohol problems in the child's family is the most significant risk factor, making a diagnosis within the continuum of FASD 9 times more likely (95% C.I. = 1.6 to 50.7). Sequential multiple regression analysis of the child's neuropsychological performance also identifies alcohol problems in the child's family as the only significant maternal risk variable ($p < .001$) when controlling for other potential risk factors.
Conclusions: Underreporting of prenatal alcohol use has been demonstrated among Italian and other Mediterranean antenatal samples, and it was suspected in this sample. Nevertheless, several significant maternal risk factors for FASD have been identified.

1. Introduction

Maternal and child risk factors that influence the severity of fetal alcohol spectrum disorders (FASD) can be grouped into factors of: (1) the host (mother's health, age, diet, body mass index (BMI), nutrition, gravidity (No. of pregnancies), and parity (No. of viable births); (2) alcohol exposure to the fetus (by quantity, frequency, and timing of dose); (3) maternal antenatal environment (socio-economic status (SES), prenatal care, social norms; May and Gossage, 2011; May et al., 2014a); and (4) for neurodevelopment, the quality of child's postnatal environment (mother's education,

☆ Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:...

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http://dx.doi.org/10.1016/j.drugalcdep.2014.10.017
0376-8716/

cognitive/behavioral stimulation, and nutrition; Gibbs and Forste, 2014; Jacobson et al., 2014; May et al., 2013c). But much of the evidence for specific maternal risk for FASD originates from studies in lower SES subpopulations, and questions remain about maternal risk in middle and upper SES populations where low fertility and better living conditions reduce the above risks (Abel and Hannigan, 1995; Abel and Sokol, 1987; May et al., 2005, 2008a, 2011b, 2013a).

1.1. General maternal risk in Mediterranean studies

In Mediterranean cultures, regular social drinking, generally with meals, is the modal pattern of alcohol consumption among females; but drinking frequency and specific levels of fetal alcohol exposure are not adequately understood. While descriptions of fetal alcohol syndrome (FAS) existed in the Italian literature (Calvani et al., 1985; Moretti and Montali, 1982; Roccella and Testa, 2003; Scianaro et al., 1978; Scotto et al., 1993), early maternal risk studies found little relationship between maternal alcohol use and adverse outcomes (De Nigris et al., 1981; Parazzini et al., 1994, 1996; Primatesta et al., 1993). Prenatal alcohol use and smoking were linked with low birth weight (Lazzaroni et al., 1993); one-third of women delivering in Italian hospitals were daily drinkers, even after recognition of pregnancy (Bonati and Fellin, 1991); and "abusive" and binge drinking were occasionally linked to spontaneous abortion and low birth weight (Cavallo et al., 1995). In Milan, 9% of women reported risky average weekly alcohol use prior to pregnancy and 29% drank daily during pregnancy (Primatesta et al., 1993). These rates are higher than those reported in the United States (Floyd et al., 1999), and comparable to those in Norway (Alvik et al., 2006b). Therefore, recognition of problem prenatal alcohol exposure started slowly in Italy.

Recent studies in Italy and Spain provide further evidence of maternal risk for FASD. In Verona, a study linked small for gestational age babies to women who reported consuming ≥3 drinks per day in each trimester (Chiaffarino et al., 2006). In Rome, antenatal clinic data indicated that 17.7% of women use alcohol during pregnancy and linked use to being unmarried, having had a previous induced abortion, and low parity (De Santis et al., 2011). In Spain, smaller head circumference at birth was associated with alcohol, illegal drug, and tobacco use, and maternal alcohol use was linked to low maternal and paternal education level, net family income, and father's alcohol use (Ortega-Garcia et al., 2012).

1.2. Unreliability of self-reporting measured by biomarkers

Biomarkers provide new ways to assess prenatal drinking. Manich et al. (2012) compared self-reported prenatal alcohol use in Barcelona, Spain, to levels of fatty acid ethyl esters (FAEE) in the meconium of their offspring, and 16% of those reporting no alcohol use were indeed exposing their fetuses to alcohol in pregnancy. In another meconium analysis of FAEE in Barcelona, gestational alcohol use was found in 45% of women (Garcia-Algar et al., 2008). A similar study in seven Italian cities concluded that 7.9% of fetuses were alcohol-exposed, the highest was in Rome (29.4%), and low maternal education and younger age were associated with maternal drinking (Pichini et al., 2012). Using meconium FAEE in three Italian sites and Barcelona, Spain, 11.9% of mothers exposed their fetuses to alcohol. Again, Rome had the highest exposure (22.6%), and those most likely to cause fetal exposure had less education and low SES (Morini et al., 2013). Especially in Rome, women reported drinking regularly before and after pregnancy, yet 65% of Roman women denied drinking during pregnancy, and "the few who admitted consumption, declared just a drink per month [or] per week" (Morini et al., 2013, p. 405). These contradictions between self reported maternal drinking and biomarker evidence led to the conclusion that "…mothers from Mediterranean countries tend to lie or underreport their toxic habits…and questionnaires often result [in] unreliable and useless [information]" (Morini et al., 2013, p. 405).

1.3. Population-based prevalence studies of FASD in Italy

Research into the prevalence and characteristics of FASD among first grade students in the Lazio region of Italy, where Rome is located, revealed a prevalence of FAS of 4 to 12 per 1000, and FASD was estimated to be 2.3% to 6.3% (May et al., 2011a). This is higher than commonly-accepted estimates for mainstream western populations. Complete maternal interview data from the Lazio study are analyzed here to identify specific maternal characteristics that are associated with a child diagnosed with FASD. Given misrepresentation or underreporting by many women, such factors are not easily determined.

2. Methods

2.1. Institute of Medicine (IOM) diagnostic categories of FASD

The major outcome variable in this risk analysis is a child diagnosed with a FASD in the first grade. Children ages 6 and 7 are at an excellent age for accurate diagnosis of FASD, as their cognitive and behavioral development can be tested with discriminating tests and behavioral checklists. Revised diagnostic criteria for FASD of the U.S. Institute of Medicine (IOM; Stratton et al., 1996; Hoyme et al., 2005) were employed. Each child was examined for: (1) physical growth and facial and other dysmorphology, (2) cognitive/behavioral development, and (3) their mothers were interviewed about alcohol use, health, and social risk factors. Also, other known anomalies of genetic and other teratogenic origins were ruled out. Final diagnoses were made by medical geneticists via a formal, data-driven, multi-disciplinary, case conference which carefully considers empirical findings in each of the above three domains (May et al., 2006, 2011a). Because physical traits are most directly and definitively linked with prenatal alcohol exposure (May et al., 2010, 2013c), the diagnosis is primarily driven by dysmorphic physical features (especially 3 cardinal facial features, microcephaly, and specific other minor anomalies). The revised IOM diagnostic guidelines have been utilized and validated in multiple populations (May et al., 2010, 2013b; May et al., 2014b).

IOM diagnoses for FASD are: FAS, PFAS, alcohol-related neurodevelopmental disorder (ARND), alcohol-related birth defects (ARBD; Stratton et al., 1996). Specific criteria for each are described in detail elsewhere (Hoyme et al., 2005). Diagnosis of FAS or PFAS without a confirmed history of alcohol exposure is allowed by revised IOM criteria. In this study, prenatal alcohol use was directly confirmed by the mother's interview in 61% of the cases. Where diagnosis of FAS or PFAS was made without direct maternal confirmation of use, required criteria for FASD dysmorphia were met, poor neurodevelopment was documented from testing, and collateral reports frequently confirmed prenatal alcohol use. Women from middle and upper SES populations in Europe and the USA have demonstrated a reluctance to admit drinking during pregnancy even while reporting alcohol use both before and after the same pregnancy (Morini et al., 2013; Wurst et al., 2008). Diagnosis of the less dysmorphic forms of FASD, such as ARND, is not allowed without direct confirmation of prenatal alcohol use, because neurobehavioral traits alone are not definitive indicators of prenatal alcohol use (May et al., 2013c). Because of these discrepant links to prenatal drinking, we have used both the diagnosis of a FASD, and the isolated data on neurobehavioral outcomes to model the most significant risk factors.

2.2. Overall Lazio study design and sampling

Mothers of first grade students from two health districts of the Lazio region were interviewed. The overall study was a cross-sectional, active ascertainment, case-control design of the prevalence and characteristics of FASD. Forty-three schools were randomly selected from the 68 elementary schools in the districts. Total first grade enrollment in selected schools was 1989 children. Positive consent forms were returned by 49% of the parents. The total sample of children was 976. The 46 children diagnosed with a FASD were significantly different from randomly-selected, normal controls ($n = 116$) on all key indicators of FASD of physical growth and development as reported elsewhere (May et al., 2006a, 2008a, 2011a) and summarized here in Table 3. Eight children had FAS, 36 PFAS, one ARND, and one ARBD. All procedures were approved by the Ethics Committee of the Italian health districts and the University of New Mexico IRB (approval no. 03-089).

2.3. Developmental (IQ, cognitive and behavioral) testing for FASD suspects and controls

In the overall study, children suspected of having, and eventually diagnosed with, a FASD and all randomly-selected control candidates were provided identical physical exams. Neurobehavioral testing was also provided: Rustioni Qualitative

Table 1
Italian maternal and paternal demographic characteristics by FASD child diagnosis, randomly-selected controls, and community mothers.

Maternal characteristic	Mothers of children with FASD ($n = 40$)	Mothers of R–S control children ($n = 108$)	Community mothers ($n = 758$)	Test score	p
Height (cm)	160.8 (7.1)	162.8 (6.2)	163.9 (6.1)	$F = 5.95$	.003[a]
Weight (kg)	64.7 (13.0)	61.9 (8.8)	62.9 (11.0)	$F = .98$	.376
BMI	25.1 (5.0)	23.3 (3.3)	23.4 (3.8)	$F = 3.45$	.032
Location (% Rural)	30.8	18.7	22.0	$\chi^2 = 2.43$	.297
Education (% by category)					
None/elementary/Junior high	61.5	43.8	42.4		
Senior High	28.2	43.8	44.8		
Post Senior High/Degree	10.3	12.4	12.8	$\chi^2 = 5.654$	.227
Employed (%)	48.7	63.9	61.6	$\chi^2 = 2.95$	.229
Age at index pregnancy	30.7 (5.2)	29.3 (5.4)	30.0 (4.9)	$F = 1.62$	.199
Gravidity	2.7 (1.7)	2.4 (1.1)	2.3 (1.0)	$F = 2.55$	.079
Parity	2.2 (1.3)	1.9 (.6)	1.9 (.7)	$F = 2.13$	.120
Index child's birth order	1.7 (1.4)	1.5 (.7)	1.6 (.7)	$F = 1.11$	.330
Marital status					
Married	92.5	85.8	89.0		
Divorced/widow/Separated	.0	6.6	6.2		
Cohabitation/re-married/Single	7.5	7.5	4.8	$\chi^2 = 5.578$	.233
Father has legal problems (% Yes)	12.8	2.9	3.9	$F = 8.03$	.018

[a] Dunnett's C Post Hoc comparison at $p = .05$ level (one-tailed) shows significant difference between FASD vs. Community groups

Test of language understanding (Rustioni, 1994), Raven's Colored Progressive Matrices for non-verbal learning (Raven et al., 1976), the Italian translation of the Wechsler Intelligence Scale for Children-Revised (WISC-R) (Rubini and Padovani, 1986), the Personal Behavior Checklist (PBCL; Streissguth et al., 1998), Pelham Disruptive Behaviors Disorder (DBD) Scale (filled out by both parents and teachers) for inattention and hyperactivity/impulsivity (Pelham et al., 1992), and Questionario Osservativo per l'Identificazione Precoce delle Difficoltà di Aprendimento (IPDA; "Questionnaire for Early Identification of Learning Difficulties", Terreni et al., 2002).

2.4. Maternal sample and questionnaire

Maternal risk data were gathered by in-person interviews from mothers of three different aggregates: (1) mothers who gave birth to a child with FASD ($n = 39$), (2) mothers of randomly-selected children confirmed to be normal ($n = 108$), and (3) all other mothers of consented first grade children in these schools ($n = 758$) whose children were neither screened positive into the full study nor randomly-selected. All were interviewed on maternal risk factors before, during, and after the index pregnancy including: childbearing, drinking, marital status, SES, demographics, and religiosity. The participation from each group was high: 85% of mothers of children with FASD, 93% of random selectees, and 92% of the remaining community mothers.

2.5. Basic statistical analysis

Data were processed via EpiInfo (Dean et al., 1994) and SPSS Version 20 (IBM, 2011). Chi square tests were performed on categorical level data, and t-tests and one-way analysis of variance (ANOVA) on interval level data. Post-hoc analyses were performed using Dunnett's C tests. Analyses explore the full range of possible maternal risk factors from this sample, where, according to the six, blinded field interviewers, some mothers of alcohol-exposed children may have underreported prenatal drinking. Overt inconsistencies or suspected misrepresentation occurred with 10.3% of mothers of FASD children, 1.9% for mothers of randomly-selected controls, and 1.6% for community mothers ($\chi^2 = 14.19$, $p = .001$). Given the exploratory nature of the study, the alpha level for reporting statistical differences was set at .05 (two-tailed).

2.6. Sequential regression strategy

Sequential regression analyses were designed to test hypotheses of maternal risk by structuring the sequence of variables entered into prediction equations of FASD diagnosis. The sequence of entry and the blocks of variables were based on the logic, which emerged from descriptive analyses (see Tables 1–3). The first block of variables, three measures of maternal drinking during pregnancy (number of drinks per week during second and third trimester of pregnancy plus binge behavior during pregnancy) tested the extent to which FASD diagnosis and neuropsychological issues could be predicted by this self-reported behavior. Two additional blocks of drinking variables were then entered to provide insight regarding possibly deceptive reports of drinking during pregnancy. The second block evaluated prediction added by consideration of three reports of current (at time of interview) drinking behavior: current binge behavior, current number of drinks/week, and whether the mother reported that she drinks alone. The next block evaluated prediction added by consideration of three additional drinking variables: binge in three months preceding the index pregnancy, number of drinks/week before pregnancy, and whether there are alcohol problems in the family. The fourth block of variables evaluated added prediction of child characteristics by maternal physical characteristics: weight, height, and BMI. The fifth block considered added prediction by a set of eight childbearing indicators: age of mother at index pregnancy, whether vitamins were taken by the mother, whether the mother reported stress during the pregnancy, gravidity, parity, and whether the mother reported experiencing one or more health or life problems during the pregnancy. The sixth and final block of variables consisted of eight demographic indicators: mother's education level, location (rural, suburban or urban), whether the mother lives with her husband, number of rooms in the home, partner's income, mother's income, total family income, and partner's job status.

Two sequential regressions were evaluated. For the first logistic regression, the dependent variable was FASD diagnosis (FASD vs. normal controls). For the second multiple regression, the dependent variable was derived as the first principal component score of neuropsychological status in a PCA analysis that included three tests administered to the child: Raven, Pelham inattention, and Pelham hyperactivity. The component scores were positively skewed, so that a logarithmic transformation was applied. This resulted in a distribution with a mean of .25 and a standard deviation of .21. Attempts to apply structural equation modeling to diagnosis and neuropsychological status using EQS (Bentler and Wu, 2006) were not successful, even with robust estimation.

2.7. Data preprocessing and assumptions

Varying amounts of data were missing on the measures, from none for FASD diagnosis to almost 40% missing for mother's report of current drinking alone. The SPSS multiple imputation procedure was used to create five complete data sets, each with $n = 162$. Impossible negative values (e.g., negative income) were set to zero. Relative efficiency for all variables was greater than .9. Exploratory work with transformed predictors suggested no advantage to use of transformations.

3. Results

Analysis of demographic characteristics indicated that mother's height (cm) and BMI differed significantly among the three sample groups (Mothers of Children with FASD, Mothers of Control Children, and Community Mothers). Mothers of FASD children are shorter than Control mothers and Community mothers. FASD mothers were also shown to have significantly higher BMI scores, = 25.1 than Control (= 23.3) and Community mothers (= 23.4). Marital status did not differ significantly among groups, as the percentage married was high for all groups (85.8 to 92.5%). No other demographic characteristics reached statistical significance. One paternal variable, legal problems among husbands of FASD mothers, was reported significantly more (12.8%) than among husbands of other groups (see Table 1).

The three groups differed significantly in drinking characteristics (Table 2). More mothers of FASD children reported consuming alcohol "anytime in their life" than did the other mothers. More Control mothers reported consuming anytime in the last year (74.5%) than FASD (71.8%) or Community mothers (63.3%).

Table 2
Italian maternal drinking characteristics & behavior before and during pregnancy by FASD child diagnosis, randomly-selected controls, and community mothers.

Maternal drinking variable	Mothers of children with FASD (n = 39)	Mothers of R–S control children (n = 108)	Community mothers (n = 749)	Test score	p
Characteristics					
Age first tried alcohol	16.4 (6.8)	14.9 (5.9)	15.6 (5.3)	F = .81	.444
Age first began drinking regularly	20.1 (5.1)	22.2 (6.8)	20.6 (5.4)	F = 2.81	.061
No. yrs consuming alcohol	13.7 (9.6)	10.3 (8.7)	10.5 (9.7)	F = 2.11	.122
Percent consuming alcohol anytime in life	76.9	76.4	64.7	χ^2 = 7.85	.020
Percent consuming alcohol anytime in last year	71.8	74.5	63.3	χ^2 = 6.13	.047
No. drinks consumed per month (current)	14.5 (40.2)	6.6 (12.0)	4.9 (9.7)	F = 10.72	.000[a]
No. drinks consumed per week (current)	3.5 (9.5)	1.5 (2.8)	1.3 (2.6)	F = 8.27	.000[a]
Current drinking companions (%)					
Alone	.0	2.8	1.0		
Partner	.0	20.8	12.9		
Friends/relatives	19.2	20.8	22.0		
Alone & w/partner	7.7	2.8	.5		
Alone, w/partner & friends/relatives	11.5	1.4	2.7		
Partner & friends/relatives	61.5	51.4	61.0	χ^2 = 29.3	.001
Alcohol problems in family (% Yes)	26.3	5.6	11.8	χ^2 = 11.74	.003
Quantity/Frequency					
Total no. of standard drinks per day 3 months before pregnancy, Mean (SD)	.94 (1.65)	.63 (.76)	.54 (.72)	F = 5.03	.007
Average no. of standard drinks per week during pregnancy, Mean (SD)	1.12 (3.20)	.49 (1.76)	.66 (2.20)	F = 1.15	.317
Drinks consumed per drinking day during pregnancy, Mean (SD)	.44 (.60)	.31 (.52)	.27 (.51)	F = 1.98	.139
Binge, 3 drinks per occasion during pregnancy (% Yes)	5.1	.0	1.3	χ^2 = 5.70	.058
Binge, 3 drinks per occasion, current (% Yes)	10.3	6.5	4.3	χ^2 = 3.67	.160
Timing					
Drinks consumed per drinking day, 1st trimester, Mean (SD)	.32 (.51)	.23 (.45)	.22 (.56)	F = .59	.553
Drinks consumed per drinking day, 2nd trimester, Mean (SD)	.37 (.53)	.22 (.44)	.21 (.42)	F = 2.80	.061
Drinks consumed per drinking day, 3rd trimester, Mean (SD)	.36 (.54)	.22 (.44)	.20 (.42)	F = 2.59	.076

[a] Dunnett's C Post Hoc comparison at p = .05 level (one-tailed) shows significant difference between FASD vs. Community groups.

In addition, the groups differed on the number of drinks consumed per month at the time of interview (FASD, = 14.5; Control, = 6.6; Community, = 4.9), and on the number of drinks consumed per week at interview (FASD, = 3.5; Control, = 1.5; Community, = 1.3). In both cases, post-hoc analyses indicate significant differences between the FASD and both other groups. Mothers of Control children and Community mothers reported more occasions of drinking with only a partner (20.8% and 12.9%, respectively vs 0% for FASD group), and the mothers of FASD children endorsed more categories of drinking companionship that included the option of "alone" (19.2% of mothers of FASD children vs. 4.2% of Controls and 3.2% for Community mothers). The total number of standard drinks consumed per week three months before pregnancy was reported to be low among all groups, yet significantly higher (= .94) for the FASD group. Four variables approached significance. Mothers of children with FASD reported lower age of regular drinking onset and one or more binges of 3 or more drinks per occasion before pregnancy (5.1% vs. .0 and 1.3%). Drinking reported in the second and third trimester of the index pregnancy was higher for the mothers of FASD children.

The three groups differed in the percentage of respondents endorsing an "alcohol problem" in the child's family, 26.3% for the FASD group, 5.6% for Controls, and 11.8% for the Community (Table 2).

Table 3 presents the characteristics of children in the two clinical categories: children with FASD and controls. These subjects, the variables, and data listed in Table 3 are utilized exclusively in the advanced analysis that follows. Physical variables are significantly

Table 3
Child characteristics for Lazio region sample by FASD diagnosis and randomly-selected controls.

Measure	FASD mean (SD) (n = 46)	Randomly selected controls mean (SD) (n = 116)	Test score	p
Child physical characteristics				
Age (months)	79.8	79.5	t = −.442	.659
Sex (% male)	50.0	52.6	χ^2 = .09	.766
Height	38.2 (29.5)	60.7 (26.1)	t = 4.76	<.001
Weight	41.4 (30.5)	67.2 (25.6)	t = 5.05	<.001
Head circumference (OFC) centile	24.8 (28.1)	55.2 (26.8)	t = 6.42	<.001
Palprebral fissure length (PFL) centile	20.1 (18.8)	31.1 (16.6)	t = 3.67	<.001
Narrow vermilion border of the upper lip (% Yes; a score of 4 and 5)	93.5	21.6	χ^2 = 69.96	<.001
Smooth Philtrum (% Yes; a score of 4 and 5)	89.1	13.8	χ^2 = 81.98	<.001
Total dysmorphology score	11.9 (4.1)	3.6 (2.9)	t = 210.19	<.001
Child neurocognitive performance				
Raven centile	53.9 (23.2)	71.0 (21.2)	t = 4.48	<.001
Rustioni (number of errors made)	8.0 (2.3)	5.3 (2.5)	t = −4.41	<.001
PBCL-36	9.1 (6.1)	3.9 (3.7)	t = −3.31	.004
Inattention (Pelham)	6.7 (7.9)	2.2 (3.7)	t = −3.65	.001
Hyperactivity (Pelham)	4.2 (6.2)	2.2 (4.3)	t = −2.03	.047
WISC verbal	91.8 (15.3)	103.1 (16.0)	t = 2.85	.006
WISC nonverbal	94.6 (16.9)	113.7 (17.5)	t = 4.41	<.001
WISC overall	92.3 (15.9)	109.3 (17.7)	t = 3.97	<.001

different between groups on all variables that differentiate FASD diagnoses: height, weight, head circumference, palpebral fissure length (eye opening), narrow vermilion border of the upper lip, smooth philtrum, and total dysmorphology score. All comparisons of cognitive/behavioral data are statistically significant between groups. Children with FASD perform more poorly, on average, than normal controls on verbal and non-verbal IQ tests (Raven, Rustioni, and WISC). Behavioral checklists indicate more problem behaviors, inattention, and hyperactivity than among controls.

3.1. Sequential logistic regression of maternal risk variables predicting FASD diagnosis

Table 4 summarizes the sequential progression of the logistic regression. The range of results over the five imputations shows that only maternal risk blocks 1 (drinking during pregnancy) and 3 (drinking variables other than current behavior or drinking during pregnancy) consistently provide statistically significant contributions to prediction of FASD diagnosis. Although addition of childbearing and demographic variables appears to increase variance that is accounted for and classification success, only the results at Block 3 can be interpreted unambiguously. Thus, self-report of drinking behavior accounts for about 25% of the variance in FASD diagnosis and correctly classifies about 80% of the cases. Because of the discrepancy in sample sizes between FASD ($n = 46$) and control ($n = 116$), this is not much better than would be achieved by classifying all cases as non-FASD (about 72%).

Individual variables do not fare well in predicting FASD diagnosis, once each of them is adjusted for all others (Table 4); although, again, there is no question that blocks containing drinking during pregnancy and other drinking variables are predictive of diagnosis and therefore, maternal risk. The only variable for which the pooled coefficient is statistically significant, after adjusting for all other variables, is "alcohol problems in the child's family." With an odds ratio of 9.14 and a 95% confidence interval from 1.6 to 50.7, the odds of a child having FASD are about 9 times greater if there are alcohol problems reported by the interviewee.

3.2. Sequential multiple regression predicting neuropsychological status

Table 5 summarizes the sequential progression of the multiple regressions by imputation. Predictors in each maternal risk variable block in the multiple regression analysis are the same as for the logistic regression analysis. For each of the imputations, it is only the third block, drinking variables other than mother's current drinking and prior to index pregnancy, that significantly adds to prediction of child neuropsychological function. Note that unlike the logistic regression predicting FASD diagnosis, the three measures of drinking during pregnancy, taken together, did not result in significant prediction of status.

The pooled regression coefficients of Table 5 indicate that in the logistic regression analysis, only one variable is significantly predictive: alcohol problems in the family, $t(161) = 3.40$, $p = .001$, $B = .19$ with 95% confidence limits from .071 to .3. Thus, children from families with alcohol problems have neuropsychological scores almost a full standard deviation below that of children from families without reported alcohol problems.

4. Discussion

The data have yielded significant maternal risk variables in both case control and multiple correlation analyses. First, case control comparisons yielded few obvious differences in the mothers' physical characteristics (short stature and higher BMI) or childbearing history. Socially, mothers of children with FASD were more likely to be married to men with legal problems and report more drinking in the nuclear family. Drinking style also differed; mothers of children with a FASD reported more drinking three months prior to pregnancy, more current drinking, and endorsed questionnaire items indicating that solitary drinking was more common.

The fact that there were no major differences in childbearing history between mothers of children with FASD and normal controls is similar to a recent study in the USA (May et al., 2014b) but differentiates this study from studies in lower SES populations. In low SES groups, which have higher fertility than this community, averages of gravidity, parity, stillbirths, miscarriages, and maternal age are frequently higher among the mothers of children with FASD (May et al., 2005, 2008a,b). High gravidity increases risk for FASD when the mother drinks. Also, the fact that mothers of children with a FASD had higher average body mass indexes is also contrary to findings in other, less well-nourished populations (May et al., 2004, 2005, 2008a, 2014a). The fact that mothers of children with FASD were shorter is in keeping with most studies of maternal risk where mothers of children with a FASD are smaller on average (May and Gossage, 2011).

The specific alcohol risk variables identified in this sample have been cited in mainstream populations before. Particularly, drinking three months prior to pregnancy is a common measure that provides an objective and generally reliable link to drinking patterns that continue into the weeks prior to pregnancy recognition, if not further into gestation (Floyd et al., 1999; May et al., 2014b; Morini et al., 2013). Drinking alone is also a common variable of risk in the general literature (Bacon, 1973; Bourgault and Demers, 1997; Glynn et al., 1983). Current drinking measures, especially 3 drinks or more per occasion and a higher average number of drinks per drinking day, differentiate risk in other populations (May et al., 2008a, 2013a, 2013b).

Multiple correlation analyses indicate that reporting of alcohol problems in the child's family proves to be the most robust measure of risk for FASD. When other variables of maternal risk are statistically controlled, alcohol problems in the child's family is the only individual variable that significantly predicts FASD. Endorsement of this measure by a mother elevates the likelihood of a diagnosis within the FASD continuum by 9 times and predicts poor neuropsychological functioning. This variable may be useful for identification of maternal risk in clinical and prevention settings (Floyd et al., 2007; May et al., 2008b, 2013a).

4.1. Strengths and limitations of the study

While there are a number of strengths to this study, there are also limitations. The major strengths include: using clinically diagnosed FASD children and information reported by their biological mothers to determine maternal risk for FASD, using a large population-based sample, and the use of multiple correlation techniques to control for other co-factors and determine risk for both the overall diagnosis of a FASD and a separate analysis of neurobehavioral outcome. One major limitation is that reporting of prenatal drinking is imperfect in this and other populations with relatively high education and SES (Alvik et al., 2005, 2006a, 2006b; Manich et al., 2012; Pichini et al., 2012). Both the retrospective reporting of quantitative drinking measures and under reporting may have weakened the predictive ability of these standard, single drinking measures. Nevertheless, current drinking measures and retrospective, pre-pregnancy drinking measures provide additional useful information and validity checks. Indeed, alcohol problems reported within the family of the respondents proved to be the best single predictor of both a diagnosis of FASD and poor neuropsychological outcomes. Second, the participation rate in this overall population-based study of FASD was not as high as desired. Limitations of study resources only allowed for single distribution of permission slips

Table 4
Logistic regression analysis of diagnosis (FASD vs. Control) as a function of maternal characteristics: results pooled over five imputations.

Entry block	Variable name	B	S.E.	Sig.	Exp(B)	95% C.I. for	
						Lower	Upper
1 Drinking during pregnancy	Number of drinks/week during second trimester	16.07	16.72	.35	9.56E+06	.00	9.58E+21
	Number of drinks/week during third trimester	−16.34	16.71	.34	.00	.00	7.80E+07
	Binge 3 or more occasions during pregnancy (yes, no)	−12.89	14.10	.38	.00	.00	8.48E+07
2 Current drinking	Current total number of drinks/week	.10	.10	.29	1.11	.91	1.35
	Binge currently (yes, no)	.23	2.18	.92	1.26	.02	92.66
	Currently drink alone (yes, no)	.98	1.15	.41	2.66	.24	29.94
3 Other drinking variables	Binge 3 mo before index pregnancy (yes, no)	.10	2.04	.96	1.10	.02	60.87
	Alcohol problem in childs family (no,yes)	2.21	.86	.01	9.14	1.64	50.73
	Number of drinks/week in 3 mos before pregnancy	−.02	.08	.84	.98	.84	1.16
4 Mother's physical characteristics	Mother's height	.02	.38	.95	1.02	.47	2.25
	Mother's weight	−.08	.50	.88	.93	.33	2.63
	Mother's BMI	.26	1.29	.84	1.30	.09	19.32
5 Childbearing variables	Age at index pregnancy	.04	.05	.41	1.04	.94	1.16
	Vitamins taken during pregnancy (yes, no)	−.22	.76	.77	.80	.18	3.62
	Stress during pregnancy (yes, no)	−1.14	.63	.07	.32	.09	1.12
	Gravidity	−.18	.34	.60	.84	.43	1.63
	Parity	.06	.55	.91	1.06	.36	3.14
	Life problems during pregnancy (yes, no)	.20	.60	.74	1.22	.38	3.95
	Health problems during pregnancy (yes, no)	−.11	.57	.85	.90	.29	2.77
6 Demography	Education level	.04	.25	.86	1.04	.64	1.71
	Location (rural, suburban, urban)	.32	.41	.44	1.37	.62	3.06
	Live with husband (yes,no)	−.83	.94	.38	.44	.07	2.77
	Number of rooms in house	.29	.23	.19	1.34	.86	2.09
	Partner income	−1.09	.64	.11	.34	.09	1.29
	Mother's income	−.94	.60	.12	.39	.12	1.29
	Total family income	.00	.00	.18	1.00	1.00	1.00
	Partners job status	−.13	.22	.56	.88	.57	1.35
	Constant	24.94	67.68	.72			

Table 5
Multiple regression analysis of child's neuropsychological status as a function of maternal characteristics: results pooled over 5 imputations.

Entry block	Variable name	Unstandardized Coefficients		*t*	*p*	95.0% Confidence Interval for B	
		B	Std. error			Lower bound	Upper bound
1 Drinking during pregnancy	(Constant)	−.225	3.168	−.071	.943	−6.434	5.965
	Number of drinks/week in 2nd trimester	.257	.381	.674	.501	−.495	1.009
	Number of drinks/week in 3rd trimester	−.289	.381	−.758	.449	−1.041	.463
	Binge 3 or more occasion during pregnancys	−.257	.189	−1.359	.175	−.629	.115
2 Current drinking	Current total number of drinks/week	.005	.007	.717	.474	−.009	.019
	Binge currently (yes,no)	−.050	.145	−.344	.731	−.336	.235
	Currently drink alone (yes,no)	−.096	.070	−1.377	.175	−.236	.044
3 Other drinking variables	Binge 3 mo before index pregnancy (yes, no)	−.065	.140	−.462	.644	−.340	.211
	Alcohol problem in childs family (no, yes)	.190	.056	3.403	.001	.071	.300
	Number of drinks/week in 3 mos before pregnancy	.004	.004	.852	.395	−.005	.013
4 Mother's physical characteristics	Mother's height	.009	.019	.456	.648	−.029	.047
	Mother's weight	−.012	.026	−.452	.652	−.062	.039
	Mother's BMI	.032	.068	.472	.637	−.101	.165
5 Childbearing variables	Age at index pregnancy	−.002	.004	−.535	.594	−.010	.006
	Vitamins taken during pregnancy (yes, no)	−.064	.047	−1.354	.178	−.157	.029
	Stress during pregnancy (yes, no)	.016	.044	.355	.723	−.071	.103
	Gravidity	−.007	.024	−.307	.759	−.054	.039
	Parity	−.029	.035	−.822	.411	−.098	.040
	Life problems during pregnancy (yes, no)	−.021	.042	−.497	.619	−.104	.062
	Health problems during pregnancy (yes, no)	−.039	.042	−.920	.359	−.123	.045
6 Demography	Education level	−.026	.021	−1.221	.225	−.067	.016
	Location (rural, suburban, urban)	.022	.029	.755	.452	−.036	.081
	Live with husband (yes, no)	−.003	.054	−.050	.960	−.108	.102
	Number of rooms in house	.010	.015	.643	.520	−.020	.040
	Partner income	.008	.037	.208	.836	−.066	.081
	Mother's income	−.038	.042	−.898	.380	−.126	.050
	Total family income	2.713E−05	.000	.474	.638	−8.812E−05	.000
	Partners job status	−.005	.014	−.329	.742	−.032	.023

per child. But participation in the maternal interviews of those who consented was outstanding. Therefore, the risk factors described should be representative of risk among the large number of women in this community who did participate.

4.2. Implications

These findings add to growing evidence on maternal risk for FASD in Italy. They may resonate with other populations as well. We examined multiple measures of maternal risk in a relatively large middle-SES population similar to others in the Mediterranean in an attempt to identify variables linked to actual diagnoses and cognitive/behavioral outcomes of children with FASD. Informed with maternal risk data such as these, selective and indicated prevention programs might identify more women at risk and employ prevention/intervention activities with them and their families.

Author disclosures

Role of funding source This research was funded in part by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), as a pilot project as part of the International Consortium for the Study of FASD [(CIFASD)— AA014811 and AA014828] and also by UO1 AA11685. Italian operations were supported by a grant from the Health Department of the Lazio Regional government, Assessorato alla Sanità della Regione Lazio, and a grant by SITAC Onlus.

Contributors Philip May was the principle investigator (PI) and Maurco Ceccanti the Co-PI of the NIH grant that funded this research and Drs. Ceccanti, May, and Tabachnick, along with assistance from Julie Hasken, were the major writers and final editors of all drafts. Jason Blankenship, Barbara Tabachnick, Wendy Kalberg, and David Buckley all played major roles in data analysis and preparation of text for the methods and results sections. Jan Gossage collected and managed data in the field and in program offices in both Italy and the USA. Luther Robinson, Melanie Manning, and Gene Hoyme generated all dysmorphology data and made final diagnoses of the children in the field. Daniela Fiorentino and Giovanna Coriale oversaw all study and data collection activities in Italy along with Drs. Ceccanti and Romeo. Each author read, edited, contributed to, and approved various drafts of the manuscript.

Conflict of interest statement None of the authors have any conflicts of interest to declare.

Acknowledgements

Faye Calhoun, Kenneth Warren, and Ting Kai Li of NIAAA and Edward Riley of SDSU facilitated the establishment of the international collaboration in many ways. In Italy many people assisted in initiating the project. Luca Deiana, Luciana Chessa, Michele Stegagno, and Agatino Battaglia, were all instrumental in facilitating the early collaboration in Rome and Lazio. Maternal interviewers were: Lucia Cupelli, Irene Di Stefano, Marcella Scamporrino, Anna Maria Galli, Federica Cereatti and Francesca De Rosa. Stefano Giacomelli coordinated maternal interviews and was supportive in many different ways. We also thank managers, school physicians and psychologists from ASL RMG* and RMH from whom we received assistance: P. Trecca,* C. Carapellese,* Di Giovanni, G. Versace, V. De Carolis, N. Roma, C. D'Anna, L. Asci, G. Gironda, S. Gagliardi, and A. Pontecorvi. Those who assisted from the School Office of Lazio Region* and Rome Province were: L. Signori,* R. Massacesi,* and M.T. Silani. We thank F. Valeriani from SIFIP. Finally, in addition to two of the authors of this paper (Daniela Fiorentino, and Giovanna Coriale), the psychological testing of the children was carried out with assistance from Francesca De Rosa, Corinna Ceoldo and Primavera Alessandra Spagnolo.

Co-author Jason Blankenship, who performed much of the initial data analysis and some text writing, passed away on October 29, 2013 when the manuscript was in the final stages of completion.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2014.10.017.

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