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Prenatal Alcohol Exposure and Development at Preschool Age: Main Results of a French Study

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Very high levels of alcohol consumption during pregnancy are harmful for the central nervous system of the child and affect morphogenesis and growth. The aim of this study was to investigate the effects of moderate prenatal alcohol exposure on development at preschool age in a longitudinal study. Pregnant women were interviewed on their alcohol consumption during pregnancy at their first visit to the maternity hospital of Roubaix, France. The development of their 160 children was assessed at the age of 4½. Multiple regression analyses indicated that consumption of 1.5 oz of absolute alcohol (approximately 3 drinks) or more during pregnancy was significantly related to a decrease of 7 points on the general cognitive index of the McCarthy scales, after controlling for confounders. This level of consumption was also related to a higher score on minor neurological anomalies, a lower height of the child, and a higher score on facial features. This level of 1.5 oz of absolute alcohol/day should not be interpreted as a biological threshold, because the study does not allow conclusions to be drawn regarding the effects of lower levels of alcohol consumption. Alcohol consumption during pregnancy can affect the development of the child, at levels well below those associated with fetal alcohol syndrome.

Key Words: Alcohol Consumption in Pregnancy, Child at Preschool Age, Child Development.

THE EFFECTS of high doses of maternal alcohol consumption on the child were first described in 1968 by Lemoine et al.,[1] followed in 1973 by Jones and Smith,[2] who introduced the expression fetal alcohol syndrome (FAS). Characteristics[3] of FAS include (1) a pre- or postnatal growth retardation; (2) central nervous system dysfunction (neurological anomalies, delayed mental development, an alteration of cognitive functioning, behavioral problems, and/or structural anomalies, such as a microcephaly or brain malformations; and (3) facial features, including short palpebral fissures, flat midface, philtrum anomalies, and a thin upper lip. Other facial anomalies were described,[4] as well as an increased frequency of nonspecific congenital malformations, especially cardiovascular and musculoskeletal anomalies. For FAS children, the most damaging long-term consequence is their impaired mental development, which can range from subtle cognitive dysfunction to severe mental retardation.[5] As described, FAS has been observed in children of alcoholic mothers. The literature on alcohol and pregnancy has expanded from maternal alcoholism and FAS to include studies concerning effects of moderate alcohol use during pregnancy. The term "moderate" alcohol consumption does not rely on any agreed definition of level of risk and is used to characterize levels of drinking that would be socially acceptable. In 1976, an association was found between moderate alcohol consumption, in the range of 1.5 oz of absolute alcohol per day (1.5 oz AA/day) and lower birthweight.[6] Further studies brought consistent results on the effects of alcohol in pregnancy on prenatal growth.[7] Streissguth et al.[8] initiated a long-lasting follow-up study investigating the effect of moderate alcohol consumption on the development of the child. An association of alcohol consumption with motor and mental development, vigilance, and attention was found at various ages.[9]

Other cohort studies brought inconsistent results.[10–14] However, these studies were mainly conducted in populations with very low alcohol consumption and thus only small effects can be expected. Their sample size was too small to give sufficient power to detect such small differences. Some were also conducted in populations among whom alcohol drinkers also used illicit drugs. A Canadian cohort study investigated children until 6 years of age.[10,15,16] Results were not consistent over time. In Cleveland,[11,17] a cohort of 359 children was followed at 6 months, and 1, 2, 3, and 4 years with tests of psychomotor development and language. When the single FAS child of the sample was excluded, there was no significant relationship between alcohol consumption and development; however, the alcohol consumption of these women was very low. Landesman-Dwyer et al.[18] found behavioral problems related to prenatal alcohol exposure among 128 4-year-old children. Russell et al.[19] investigated 175 children at the age of 6, and no relation was found between the maternal level of alcohol consumption and performance on a psychomotor test. However, a group of women was identified as having drinking problems, and their children had significantly poorer results on a language test and on the verbal scale of the Wechsler Preschool and Primary Scale of Intelligence. A large European study investigated 1,240 18-month-old children, and no relationship was found between alcohol consumption and psychomotor tests. In this study,

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too, the level of alcohol consumption was very low.[12] In Detroit, Jacobson et al.[20] investigated 382 13-month-old children. Scores on the psychomotor and mental scales of the Bayley were related to alcohol consumption. The percentage of children with a mental scale lower than the 10th percentile was doubled in children of women consuming 0.5 oz AA/day and showed a dose–response relationship.

Other aspects of development, such as growth, have also been studied in relation to alcohol exposure. Height was investigated in most of these studies. In some studies, an association was found with alcohol exposure when the child was young, but disappeared with increasing age.[21,22] However, height was related to prenatal alcohol exposure in a study of 668 children at the age of 6 years.[23]

In young children with FAS, neurological signs, such as tremors, motor incoordination, weak grasp, difficulty with eye-hand coordination, seizures, hypotonia, or increased muscle, tone were observed.[5] Motor development is delayed and of poor quality in FAS children.[2] Motor functioning was examined in the Seattle study at 4 years and showed associations between alcohol exposure and motor function and balance.[24]

Few studies have investigated facial anomalies in relation to prenatal alcohol exposure. A higher frequency of facial anomalies was found by Day et al.[25] at the age of 3,[25] but not at the age of 6[23] or in two other studies at preschool age.[26,27]

Our objective in the present study was to determine to what extent moderate alcohol consumption in pregnancy affects child development in the same areas as those observed in FAS: central nervous dysfunction, including delayed psychomotor development and neurological anomalies, growth, and facial features. This paper presents the main results of a French study completed in Roubaix, in a population that included a high proportion of alcohol drinkers of varying amounts and who were not usually consumers of illicit drugs.

METHODS

Population and Measure of Alcohol Consumption

Between May 15, 1985 and January 15, 1986, 782 women of French origin who had their first contact with the obstetric department of the public hospital of Roubaix were contacted. Among those, 698 were successfully interviewed[28]; 684 were interviewed at their first prenatal visit in the hospital, and 14, without hospital antenatal care, were interviewed during their postnatal stay. This latter group, although interviewed retrospectively, was entered in the study, because it typically included a high proportion of heavy drinkers.

The interviews were conducted with a structured questionnaire, in which alcohol consumption was assessed by number of glasses on weekdays and at weekends. Separate questions inquired about beer, wine, and stronger alcohol. Average alcohol consumption was calculated as the number of glasses of alcoholic beverage consumed weekly. A glass was estimated to contain about 0.5 oz AA, whatever the drink. The alcohol consumed in this population in the North of France is mainly beer; this hospital is located in an area of low socioeconomic level and of high alcohol consumption.[29]

The present study was based on a 4½-year follow-up of a subsample of children. A subsample of 347 women was selected for further investigation, including biological assays[30] and morphological examination at birth.[28] This subsample deliberately overrepresented women with high levels of alcohol consumption. Among this subsample, 326 women gave birth to singleton babies. The results obtained at birth, on birthweight and on facial features,[28,31] and the publication of the first results on long-term consequences of moderate alcohol consumption,[32] led us to decide on a follow-up of these children at preschool age, although such a follow-up had not been originally planned. Children were excluded from the study if their mothers were known as alcohol abusers by the obstetric team, but declared very low or no alcohol consumption ($n = 8$) or if data on alcohol consumption during the first trimester was missing ($n = 3$). For practical reasons, the follow-up was limited to the 241 children still located in the area of Roubaix. Twenty-eight families declined the follow-up assessment and 53 never showed up at the clinics; 160 children participated in the follow-up. Consent was given by parents by participating in the child assessment, although the actual objective of the study (effects of alcohol consumption) was not given, because of risk of bias in participating and data collection. The study was approved by the Commission Nationale Informatique et Liberté.

Procedure

The investigations were conducted by the medical doctors and psychologists of the seven clinics of Maternal and Child Health (Protection Maternelle et Infantile) covering the area of Roubaix and its surroundings. It had been planned that the children would be examined at the age of 4 years ½ ± 2 months; but, for practical reasons, some children were assessed slightly later. The mean age at assessment was 55.7 ± 2.7 months.

The psychologist performed the test of psychomotor development of the child and interviewed the parents on the stimulations of the child at home. The medical doctor interviewed the parents on all medical and social questions and examined the child, including detection of minor neurological signs and facial features. All investigators were blind to the alcohol exposure data.

Developmental Assessment

Measures of child development were selected to assess psychomotor development, minor neurological signs, postnatal growth, and facial dysmorphology.

Psychomotor development was assessed with the McCarthy scales of Children Abilities,[33] which include five subscales: verbal, perceptual performance, quantitative, memory, and motor. The General Cognitive Index (GCI) includes the items of three subscales (verbal, perceptual performance, and quantitative). It reflects children's global cognitive functioning and has a mean of 100 in the average population; the subscales have a mean of 50. The test has been translated in French and standardized in France.[34]

The examination of the child with minor neurological dysfunction developed by Touwen[35] was conducted after modifications. Modifications were made (1) to shorten the examination because the children had been given the McCarthy Test just prior and may have been tired and (2) to select items easy to appreciate by doctors not familiar with this examination. Selected items were: (1) items that are included in any neurological examination, such as reflexes, equilibrium with closed eyes, blow out cheek, finger nose pointing, and twist hands; (2) items that we thought relatively easy to assess, such as a test of balance, syncinesia, and hopping. The instruction was to code as an anomaly if there was any doubt. Thus, anomalies include minor anomalies or failures on a skill passed by the majority of children at a given age. The 26 items included in the score are shown in Table 1.

Clinical examination included measure of height and detection of facial features similar to those observed in FAS, with a detailed examination of the forehead, nose, eyes, and midface. All of these features were qualitatively appreciated by the examiner, except length of the palpebral fissures, hypertelorism, philtrum length, and posterior rotation of the ears that were measured. A score of facial anomalies was established (Table 2), similar to the one used at birth.[28]

Table 1. Minor Neurological Anomalies Included in the Score

Syncinesia other hand	Finger noise pointing
Syncinesia homolateral lower limbs	Right hand, opened eyes
Syncinesia controlateral lower limbs	Left hand, opened eyes
Equilibrium	Right hand, closed eyes
Equilibrium eyes closed	Left hand, closed eyes
Arms out straight	Hopping
No good extension	Walking on heels
Median deviation	Quality of execution
Horizontal deviation	Associated movements
Associated movements	Reflexes
Trembling	Knee
Blow out cheek	Achillis
Blow out	Biceps
Twist hands	Triceps
Passive resistance elbow	
Passive resistance wrist	

Table 2. Facial Features Included in the Score

Bulged forehead	Deep nasal bridge
Synophris	Upturned nose
Short palpebral fissure	Short nose
Antimongoloide slants	Long philtrum
Strabismus	Hypoplastic philtrum
Epicanthic folds	Indistinct cupid bow
Eyelid ptosis	Thin upper lip
Hypertelorism	Retrognathia
	Posterior rotation of ears

Covariates

A number of potentially confounding factors were assessed at various stages. Data on pregnancy and the child at birth were extracted from the maternity records. At follow-up assessment, at 4½ years, parents were interviewed on the child's health, sleep or feeding disorders, problems at school, life events and sociodemographic characteristics. The quality of stimulation of the child at home was assessed by the psychologist, using three subscales of the Home Observation for the Measurement of the Environment[36]: language stimulation, academic stimulation, and variety in experiences.

Analysis

During the assessment, some children refused to participate in part of the examination, so the sample size differs slightly from one aspect of development to another. Light drinking was defined as 0 to 1.49 oz AA/day, and heavy drinking was defined as ≧1.5 oz AA/day. This cut-off point for alcohol consumption was chosen from results of prior research in this study[31] and in previous studies in France.[6] Alcohol consumption also was considered in six classes (0, 0.01–0.49, 0.5–0.99, 1.0–1.49, 1.5–2.49, and ≧2.5 oz AA/day) to search for a dose–response relationship.

Multiple regression analysis was used to control for confounders.[37] Factors were included in the model if they were considered to be established correlates of the studied outcome variable, or if they were associated with both the outcome variable and alcohol consumption in our study. The respective proportion of the two types of covariates varies according to outcome. For psychomotor development and height, main determinants are known; for neurological and facial features, covariates were mostly identified from our data.

The tables show mean differences of outcome variables between the heavy and light drinkers and their standard errors. For psychomotor development, the following covariates were included in the main model: birth order (1, 2, 3, ≧4), maternal level of education (primary, secondary, higher), present maternal employment (Y/N), family status (mother living alone, living with a companion employed or living with a companion unemployed), score of family stimulation (≦14, 15–18, ≧19), gender (M, F), age of the child at examination, and examiner (for further details, see Ref. 38). Other models were also considered, including tobacco consumption during pregnancy and birthweight. Tobacco consumption in pregnancy has been suspected to have a deleterious effect on cognitive development,[39] and a low birthweight can also be a risk factor for impaired cognitive development.[40] The same models were used for the GCI and for the five subscales. For neurological anomalies, confounders taken into account were birth order, maternal level of education, present maternal employment, and child age at examination, examiner. For height, birth order, maternal level of education, present maternal employment, family status, height of the mother, gender, and child age at examination were taken into account; for facial characteristics, birth order and examiner were considered. No correction was made for multiple comparisons. All analyses were conducted with SAS software (procedure general linear models (GLM)) [41] at the INSERM National Computer Center.

Table 3. Alcohol Consumption during the First Trimester

Oz AA/day	No.	% of women
0.0	50	31
0.1–0.49	26	16
0.5–0.99	20	13
1.0–1.49	31	19
1.5–2.49	21	13
≧2.5	12	8
Total	160	

RESULTS

Loss to Follow-up

The 160 children who came to the assessment were compared with the 81 children who did not participate; there was no significant difference in maternal alcohol consumption before pregnancy or during the first trimester, tobacco consumption, and sociodemographic variables (such as maternal educational level, age, birth order, and growth characteristics at birth). The only exception was that small-for-date children were slightly less frequently assessed.

Alcohol Consumption

Levels of drinking during the first trimester of pregnancy in the studied sample are shown in Table 3. One should remember that the heavier drinkers were overrepresented in the sample. Heavy drinking (≧1.5 oz AA/day) was related to an older maternal age, a high parity, a low level of education, unemployment of the father, or present companion (Table 4). Although not significant, there was a trend for heavy drinking to be associated with heavy cigarette smoking, maternal unemployment, a lower score of family stimulation, and a lower birthweight. Health status of the child reported by the parents was not related to alcohol consumption; there was no relation of alcohol consumption with separation of parents or moving to another house. However, heavy drinkers were more numerous among mothers of children assessed late.

Psychomotor Development

In our sample, the GCI of the McCarthy scales had a mean of 100.4 and a standard deviation of 19.0. The crude data (Table 5) showed a significant relation between alco-

Table 4. Heavy Drinking during the First Trimester According to Maternal and Child Characteristics

		Heavy drinkers*	
	n	%	*p* value
Birth Data			
Mother's age			
≤19	13	8	0.001
20–24	48	15	
25–29	48	10	
≥30	51	39	
Birth order			
1	50	6	<0.001
2	39	28	
3	32	9	
≥4	39	41	
Cigarettes/day during pregnancy			
0	112	18	0.14
1–9	26	19	
≥10	22	36	
Gender			
Male	79	18	0.37
Female	81	23	
Birthweight			
<2500	12	33	0.26
≥2500	148	20	
4½ Year Data			
Maternal level of education			
Primary	84	27	0.02
Secondary	56	16	
Higher	19	0	
Mother present employment			
No	98	24	0.13
Yes	62	14	
Family status			
Mother living alone	23	22	
Mother living with father or companion			0.02
Unemployed	20	45	
Employed	114	17	
Score of family stimulation†			
≤14	37	27	0.21
15–18	69	23	
≥19	54	13	
Child age at examination in months			
≤53	42	12	0.03
54–56	67	19	
>56	51	31	

* Consumption of at least 1.5 oz AA/day during pregnancy.

† Part of the HOME (Home observation for measurement of the environment).[36]

hol consumption during pregnancy and GCI, verbal, performance, and quantitative scales. When alcohol consumption was considered in six classes (Table 6), the trend was significant or nearly significant for the same scales.

All of the social and cultural characteristics of the mother or father or present companion (educational level, occupational activity, family status) were strongly related to the GCI in the expected direction: higher GCI in children of mothers with higher education and employment, living in families in which the father was employed, as was the score of family stimulation.[38] GCI was related to birth order. Cigarette smoking during pregnancy was associated with a lower score for the GCI. Children assessed at older ages had a lower GCI than those assessed younger. Birthweight, gender, health problems, or life events were not significantly related to the GCI.

After controlling for confounders (Table 5), the GCI was 7 points lower for children whose mothers consumed 1.5 oz AA/day or more during pregnancy in comparison with the children of the women who drank less. The quantitative scale was also significantly related to alcohol consumption in pregnancy. For the performance and verbal subscales, the trend was the same.

Other models of multiple linear regression were performed, including tobacco use and birthweight, respectively, and excluding the six children whose mothers were interviewed after birth: the relation between GCI and alcohol consumption was only slightly modified ($p = 0.026$ with tobacco use and $p = 0.033$ with birth weight). When alcohol consumption during the first trimester was considered in six classes, there was no dose–response relationship between alcohol consumption and the GCI (Table 6).

Neuromotor Examination

Score Calculation. There were many refusals or missing data for several items: the neurological examination took place at the end of the assessment, after the test with the McCarthy scales, and some children were tired and refused to participate in one or more items (Larroque, in preparation). Few observations were totally complete, so we had to take missing data into account. We chose to (1) exclude children for whom >30% of items were missing ($n = 23$) and (2) assume that, for each child with <30% of missing items, for these missing items, the percentage of anomalies was the same as for the completed items. For each child, the score was thus calculated as:

$$\text{Score} = \frac{\text{number of anomalies} * \text{total number of items}}{\text{number of completed items}}.$$

Association with Alcohol Consumption. The mean score was 4.6 ± 3.0. Children of heavy drinkers had a higher number of minor neurological anomalies than the other children, a mean of 6.2 instead of 4.2 (Table 5). High birth order, low maternal level of education, present maternal unemployment, and low score for family stimulation were related to a higher neurological score. Tobacco consumption, family status, gender, birthweight, and age at examination were not related to this score. After controlling for birth order, maternal educational level, family status, present maternal employment, age at examination, and examiner, the difference in the number of neurological anomalies between children of heavy and light drinkers was 1.5 (Table 5), and this difference was significant. When alcohol consumption during the first trimester was considered in six classes, as found with the psychomotor test, there was no dose–response relationship (Table 6).

Table 5. Child Assessment by Maternal Alcohol Consumption during Pregnancy

Alcohol consumption during pregnancy (oz/day)	*n*	Mean value	Crude *d** (SD)	Adjusted *d*†	Adjusted *R*‡
McCarthy Scales§					
GCI					0.50
<1.5	123	103.2	—	—	
≥1.5	32	89.5	−13.7 (3.6)	−7.0 (3.2)	
p			<0.001	0.03	
Verbal					0.43
<1.5	123	49.8	—	—	
≥1.5	32	41.9	−7.9 (2.1)	−3.4 (2.0)	
p			<0.001	0.09	
Perceptual performance					0.44
<1.5	123	55.0	—	—	
≥1.5	32	48.4	−6.6 (2.7)	−3.6 (2.5)	
p			0.02	0.16	
Quantitative					0.29
<1.5	123	51.0	—	—	
≥1.5	32	44.8	−6.2 (2.0)	−5.5 (2.1)	
p			<0.001	0.01	
Memory					0.39
<1.5	123	49.3	—	—	
≥1.5	31	45.0	−4.3 (2.2)	+0.1 (2.1)	
p			0.05	0.95	
Motor					0.29
<1.5	123	58.2	—	—	
≥1.5	31	55.2	−3.1 (2.5)	−1.2 (2.6)	
p			0.22	0.65	
Minor Neurological Anomalies#					0.25
<1.5	111	4.2	—	—	
≥1.5	26	6.2	+2.0 (0.6)	+1.5 (0.7)	
p			0.002	0.03	
Children's Height‖					0.37
<1.5	124	106.0	—	—	
≥1.5	33	103.3	−2.7 (0.9)	−2.3 (0.8)	
p			0.002	0.006	
Score of Facial Features**					0.15
<1.5	125	2.5	—	—	
≥1.5	32	3.3	+0.8 (0.3)	+0.7 (0.3)	
p			0.02	0.04	

* Crude difference in mean value between children of heavy and light drinkers.

† Adjusted difference.

‡ Percentage of variance explained by the model, including all listed covariates.

§ Adjusted for birth order, maternal level of education, present maternal employment, family status, score of family stimulation, gender, age of the child at examination, and examiner.

Adjusted for birth order, maternal level of education, present maternal employment, age of the child at examination, and examiner.

‖ Adjusted for birth order, maternal level of education, family status, present maternal employment, gender, age of the child at examination, and mother's height.

** Adjusted for birth order and examiner.

Height of the Child

The mean height was 105.5 ± 4.6 cm. Children of heavy drinkers had a lower height than children of light drinkers (Table 5). Height of the child was highly related to height of the mother, a lower birth order, a higher level of education of the mother, present maternal employment, and growth measurements at birth. The health status of the child assessed by the parents was not related to the height of the child. The following confounders were included in the model: birth order, maternal level of education, family status, present maternal employment, gender, age of the child at examination, and mother's height. After taking into account these confounders, there was a significant difference of 2.3 cm between children of heavy and light drinkers (Table 5). To examine which part of this difference was explained by length at birth, this variable was added in the model. The difference was decreased (1.9 ± 0.8 cm, $p = 0.02$), but still significant. Table 6 shows a trend for decreasing height with increasing alcohol consumption.

Facial Features

The mean number of facial features was 2.6 ± 1.7. The children of heavy drinkers had an higher number of facial features (Table 5). There are no known confounding factors for these facial features. However, we found that the score of facial features was related to birth order, increasing with the rank. It was neither related to age at examination, nor to neonatal characteristics. The association be-

Table 6. Child Assessment and Detailed Alcohol Consumption during Pregnancy

Oz AA/day	*n*	Mean value	Crude		Adjusted		
			*d**	(SD)	*d*†	(SD)	*R*‡
GCI of the McCarthy Scale§							0.53
0.0	48	99.7	—		—		
0.1 –0.49	25	105.6	+5.9	(4.5)	−2.9	(4.0)	
0.5 –0.99	20	108.8	+9.1	(4.8)	+6.6	(4.2)	
1.0 –1.49	30	103.2	+3.5	(4.2)	+2.2	(3.6)	
1.5 –2.49	21	87.8	−11.9	(4.8)	−9.0	(4.0)	
≧2.5	11	92.7	−7.0	(6.1)	+2.1	(5.4)	
p			0.003		0.03		
Score of Minor Neurological Anomalies#							0.28
0	44	4.1	—		—		
0 –0.49	24	4.9	+0.8	(0.7)	+1.5	(0.8)	
0.5 –0.99	18	4.1	0.0	(0.8)	−0.2	(0.8)	
1.0 –1.49	25	3.9	−0.1	(0.9)	+0.1	(0.7)	
1.5 –2.49	18	6.7	+2.6	(0.8)	+2.0	(0.8)	
≧2.5	8	5.0	+0.9	(1.1)	+0.6	(1.2)	
p			0.02		0.07		
Children's Height‖							0.38
0	49	106.2	—		—		
0 –0.49	26	105.9	−0.3	(1.1)	−0.3	(1.0)	
0.5 –0.99	20	106.7	+0.5	(1.2)	+0.2	(1.1)	
1.0 –1.49	29	105.4	−0.7	(1.0)	−1.1	(0.9)	
1.5 –2.49	21	104.0	−2.2	(1.2)	−2.4	(1.1)	
≧2.5	12	102.1	−4.1	(1.4)	−3.2	(1.4)	
p			0.04		0.09		
Score of Facial Features**							0.16
0	50	2.4	—		—		
0 –0.49	26	2.6	+0.1	(0.4)	+0.2	(0.4)	
0.5 –0.99	19	2.4	+0.2	(0.5)	+0.0	(0.5)	
1.0 –1.49	30	2.4	0.0	(0.4)	+0.1	(0.4)	
1.5 –2.49	21	3.4	+0.9	(0.4)	+0.8	(0.5)	
≧2.5	11	3.1	+0.7	(0.6)	+0.8	(0.6)	
p			0.31		0.47		

* Crude difference in mean value between children of alcohol consumers and abstainers by level of consumption.

† Adjusted difference between children of alcohol consumers and abstainers.

‡ Percentage of variance explained by the model, including all listed covariates.

§ Adjusted for birth order, maternal level of education, present maternal employment, family status, score of family stimulation, gender, age of the child at examination, and examiner.

Adjusted for birth order, maternal level of education, present maternal employment, age of the child at examination, and examiner.

‖ Adjusted for birth order, maternal level of education, family status, present maternal employment, gender, age of the child at examination, and mother's height.

** Adjusted for birth order and examiner.

tween the score and alcohol consumption was not modified when controlling for birth order and examiner (Table 5). The distribution of the mean score of facial features according to detailed maternal alcohol consumption indicated a lack of a dose response relationship (Table 6).

DISCUSSION

In this study, prenatal alcohol exposure was related to the development of the child at preschool age in different areas: psychomotor development, neurological state, growth, and facial features. Significant results were observed with a level of consumption of 1.5 oz AA or more/day. There was no dose–response relationship.

The rate of follow-up was 67% of the children who were still living in the Roubaix area at the age of 4½, 51% of the whole cohort. The high rate of loss to follow-up can be explained by the fact that families were not contacted between birth and the age of 4½, the follow-up having been decided late after the first stage of the study. Moreover, the study involved a population whom it was difficult to motivate for an active participation in such a study, which implied spending half a day with the child at the clinic. The rate of follow-up has to be compared with other studies: 70% at 18 months in Scotland[42] and 72% at 4 years in a U.S. population with a good social background.[11] The Seattle study is the only one with a higher rate of follow-up at 4 years.[32]

In our study, the children lost to follow-up probably did not cause serious bias; at birth, they did not differ from the other children, except for a higher rate of small for dates, independent from the level of alcohol consumption of the mother. However, it is not possible to exclude the possibility that the loss to follow-up could have been more frequent for children of heavy drinkers with a nonoptimal development than in the other groups, which would have led to an underestimation of the association between maternal alcohol consumption and child development.

When compared with the literature, our sample included a relatively high number of heavy drinkers because: (1) the study was conducted in an area of high alcohol consumption, and (2) heavier drinkers were oversampled. As in other stud-

ies in this field, alcohol consumption was assessed by interview using a detailed questionnaire. There are no effective means to control for the reporting of alcohol consumption, and it is likely that some very heavy drinkers reported low alcohol consumptions. The study was prospective, thus underreporting of alcohol consumption should be independent of the children's state, unknown at time of interview. However, six women, who did not receive prenatal care in the hospital, were interviewed after delivery. The exclusion of these six women did not change the results.

The misclassification of very heavy drinkers among heavy drinkers can overestimate the effects of heavy alcohol consumption, but their misclassification among nondrinkers or light drinkers also underestimates these effects. Besides, misclassification can make a real a threshold model appear as a dose–response relationship.[43] Whatever the statistical methods used in the analysis, misclassification on exposure makes it impossible to distinguish between dose–response and threshold models, and therefore to identify a threshold.

Children exposed to 1.5 oz AA/day during pregnancy had a GCI (IQ equivalent) 7 points lower than those exposed to <1.5 oz AA/day. The verbal, quantitative, and performance perceptive scales were also related to alcohol consumption during pregnancy. These results for preschool age are consistent with those of the Seattle study, which was conducted in a more privileged population of White married women, with a higher level of education.

The main difficulties when studying development in relation to pre- or perinatal events is to properly take confounders into account.[44] By definition, confounders are factors that are related to both exposure and health state (here psychomotor development). The effect of confounding when studying effects of prenatal exposures on development can be important, particularly in underpriviledged populations. The associations between a low social and cultural level of the parents, a suboptimal environment of the child and a lower IQ of the child are indisputable. So the absence of these social and environmental characteristics in the model would lead to a bias: the observed relationships with alcohol exposure could be due to other factors. A difficulty is the need to control for a large number of confounders, in relatively small samples, which reduces the precision in the estimation of parameters for the relation between exposure and outcome.[45]

Low associations between exposure to a toxin and development could be better shown in populations otherwise at low risk for impaired development. One problem is that it is difficult to find a low-risk population in whom the studied exposure would have a wide dispersion, because the exposure is often related to the socioeconomic level and more common in high-risk populations. Limiting studies to populations at low risk for the studied outcome would also make it difficult to test interactions between exposure and other risk factors. The consequence of prenatal exposures could be more severe in low socioeconomic populations, where, for example, nutritional deficits and low use of health care could exacerbate the effects on the CNS. Regarding alcohol, an interaction on IQ at 7 years was found between alcohol and a low level of education of the father, and a large number of children in the family in the Seattle study.[46] In the Detroit study,[20] there was an interaction with the age of the mother with the worst results occurring in exposed children of mothers older than 30 years. In the Canadian study,[15,16] an interaction was found between alcohol and tobacco at 12 and 24 months, but not at 36 months, with a lower score to developmental scales in children exposed to both alcohol and tobacco. In our study, we found no interaction with tobacco or the age of the mother.

Our results are similar to those of the Seattle study at preschool age.[32] Two other cohorts in which children were assessed at preschool age[11,16] did not find such a relation between prenatal alcohol exposure and psychomotor development at 4 years. Sample characteristics probably contribute to these differences in findings: number of heavy drinkers, level of consumption, and rate of follow-up. Thus, presently, results show an effect of prenatal alcohol consumption on child development in the level of 1 to 1.5 oz AA/day, but for lower levels of consumption results seem inconsistent.

In the Seattle study,[9] main results were obtained with alcohol consumption reported for the period before pregnancy, which has been interpreted as consumption around conception. In our study, relations with alcohol consumption of the first trimester were stronger than with consumption before pregnancy.[38] Some studies have shown the impact of a change in alcohol consumption in late pregnancy.[26,47] Characteristics of children of women who stopped drinking in the third trimester were intermediate between those of children of nondrinkers and those of children whose mothers continued drinking.

In our study, the three subscales composing IQ: verbal, perceptual performance, and quantitative varied according to alcohol consumption. In the Seattle study, the effects of alcohol consumption were seen on the performance scale at 4 years, and on the verbal and performance scales at 7 years. Memory scale was not related to prenatal alcohol exposure in our study, whereas at 7 years short-term memory was related to alcohol exposure in the Seattle study.[46] The sensitivity of a test to detect differences depends on its reproducibility. For the McCarthy scales, the five subscales are standardized to have the same distribution, but they do not have the same reproducibility: the reproducibility of the verbal scale is better than that of the memory and motor scales.[34]

Delayed motor development and neurological anomalies are part of the FAS. Animal studies have shown deficits in reflexes and in tasks requiring balance and motor coordination in relation to prenatal alcohol exposure.[48,49] In our study, we found a higher number of minor neurological anomalies in children of women consuming 1.5 oz or more/day than children exposed to <1.5 oz AA/day. The question can be raised of the usefulness of considering these soft neurological signs, which are not a source of disability and that may disappear with age. However, these signs are a marker of the integrity of CNS, in the same way as psychomotor development. Motor

investigation is both part of neurological examination and psychomotor development assessment, especially in very young children. Moreover, the assessment of motor skills partly relies on verbal expression in the explanations given to the child and requires verbal comprehension. However, another interest of assessing these soft neurological signs is that they may be less affected by the social environment than mental development.

To the best of our knowledge, no other study included a neurological examination similar to ours. The Seattle study used the motor scales of psychomotor tests and a specific test of fine and gross motor skill was used at 4 years.[24] Motor skill and balance were related to alcohol consumption. In other studies using psychomotor tests (such as the Bayley scales, the McCarthy or the Griffith assessment), there was no relationship between alcohol consumption and the motor assessment, except in the Detroit study[20] in which the motor scale showed lower performances with alcohol consumption at a level of ≥2 oz AA/day. Our study showed a higher number of minor neurological anomalies in children of heavier drinkers, but these results need confirmation.

We also found that children exposed to 1.5 oz AA or more/day measured 2 cm less than children exposed to <1.5 oz AA/day. Similar results were found in some studies,[19,50,51] but not in others.[12,15,22,26,52,53] The lowest level of alcohol consumption found to relate significantly to height is 0.5 oz AA/day.[23,25] In this latter study, main confounders were taken into account, including nutrition. However, in this population, which was also of low socioeconomic level, there was no relationship between alcohol consumption and nutrition indicators, and inclusion of nutrition in the model did not change the results. Thus, nutrition could not be a major confounder in our study.

We found higher scores of facial features in children exposed to 1.5 oz AA or more/day during pregnancy, compared with children exposed to <1.5 oz AA/day. These results are consistent with those observed in other studies.[19,25,26,27,52] In the study by Day et al.,[23] at 6 years, there was no more relation between prenatal alcohol consumption and morphological anomalies, although there had been one at 8 months and 3 years.[25,50] In our study, children were examined at 4 years, and there was a decrease in the number of the facial features when compared with birth, but there was still a significant relation with prenatal alcohol exposure. In a study in which 44 FAS children were seen at an interval of 10 years,[5] facial anomalies were less numerous when the children were older. The same phenomenon was seen in another FAS study.[54] The indistinct philtrum, thin upper lip, and the short palpebral fissures remained the most common signs.

In the analysis on detailed alcohol consumption, there was not a dose–response relationship between alcohol consumption and outcome. Our highest consumption group (≧2.5 oz AA/day) had better results than the class 1.5 to 2.49 oz AA/day for psychomotor development and minor neurological anomalies. However, this class (>2.5 oz AA/day) contains only a few subjects, and the results could be due to random fluctuations. Self-selection bias could be another explanation; as previously described, participation in the study could be related to the development of the child; and, among very heavy drinkers, the most affected children may not have come to the assessment.

Women were asked about high occasional consumptions, but only four women answered positively. This indicator (occasional heavy drinking) was related to mental development in the Seattle study, and animal experiments have shown that exposure leading to a high peak of alcohol blood concentration was more toxic than the same dose ingested regularly.[55] However, in human studies, it is difficult to separate the effects of occasional heavy consumption from those of regular consumptions, because these two behaviors are highly related.

This study has shown a relation between prenatal alcohol exposure and the development of the child at preschool age in different areas: psychomotor development, neurological state, growth, and facial features. These results were observed with a level of consumption of 1.5 oz AA or more/day. These levels should not be interpreted as a biological threshold; the study, with its limited sample size, especially for the light drinkers, does not allow conclusions about lower consumptions. This study confirms the results of the Seattle study in which development at 4 and 7 years was affected with consumptions of 1 to 1.5 oz AA/day and indicates that prenatal alcohol consumption must be taken into account in prenatal care, even for lower levels than those related to FAS.

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