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Coffee Consumption during Pregnancy and Selected Congenital Malformations: A Nationwide Case-Control Study

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Abstract: Finland leads the world in per capita coffee consumption. To evaluate the hypothesis that coffee consumption during pregnancy is teratogenic, 755 pairs of mothers of malformed children and their controls were personally interviewed soon after delivery. After excluding tea drinkers and pairs with inadequate information, the study group included 706 pairs. Study subjects consisted of mothers of children with 112 defects of the central nervous system, 241 orofacial clefts, 210 structural defects of the skeleton, and 143 cardiovascular malformations. The coffee consumption during pregnancy was similar for the mothers of malformed or non-malformed children. The comparison of the mothers drinking at least four cups of coffee a day during pregnancy with those not consuming coffee at all showed a relative risk point estimate of 1.0 with the 95 per cent confidence limits of 0.7 and 1.3. (*Am J Public Health* 1983; 73:1397-1399.)

Introduction

Three epidemiological investigations have reported an association between coffee consumption and defective pregnancy outcome.¹⁻³ One of them found an increased frequency of malformations in children born to mothers who were heavy coffee drinkers.² In addition, case reports have implied that moderately high coffee intake is teratogenic.⁴ High doses of caffeine produce congenital defects in various experimental animals.⁴⁻⁶ These findings have been of concern to obstetricians,⁷ and the US Food and Drug Administration has removed caffeine from the "generally regarded as safe" (GRAS) list and warned about the ingestion of caffeine during pregnancy.⁸ On the other hand, two recent epidemiological studies did not show a teratogenic risk for children of mothers who drank coffee during pregnancy.⁹⁻¹⁰ Results from a pilot study in Finland indicated no relation between coffee consumption and the prevalence of congenital malformations detectable at birth.¹¹

Materials and Methods

Our study covers the whole of Finland, current population 4.7 million, annual number of births about 65,000. The occurrence of notified malformations detectable at birth has been 1.7 per cent of all births in recent years.

Finland has the highest per capita coffee consumption of any nation of the world: 13.0 kg a year during 1978-1980 in comparison with 2.4 kg in the United Kingdom and 5.1 kg in the United States.¹²

According to the local coffee producers, an average cup of Finnish coffee contains 100 mg of caffeine. Decaffeinated

coffee is rarely sold in Finland. Soft drink beverages also seem to be an insignificant source of caffeine in Finland.*

The primary data are derived from the Finnish matched-pair Register of Congenital Malformations. Notification of all congenital defects detected during the first year of life is compulsory. Each mother selected for special study (see below) is matched with a control mother whose delivery immediately preceded that of the study mother in the same Maternity Welfare District.** Nonmatched modifying and confounding factors are considered in the analysis of the data. The validity of the present approach has been previously discussed in detail.¹³

The primary notifications and the death certificates are reviewed by a pathologist trained in teratology who selects reliably diagnosed "marker" defects (approximately one-third of all notified malformations) to be studied in detail.¹³ These consist of defects of the central nervous system, orofacial clefts, selected structural malformations of the skeleton, and selected cardiovascular defects. All mothers with babies having these marker defects and their controls are interviewed by midwives soon after delivery at their local Maternity Welfare Center in the time of their first postpartum visit. The questionnaire consists of 80 items including information on the family, previous pregnancies, and details of the latest pregnancy. The retrieval rate of the questionnaires has been better than 99 per cent.

In addition to routine interviews by midwives, special interviews concerning coffee were incorporated into an ongoing study regarding environmental exposures during pregnancy and are included in this report.¹⁴ This additional information was collected by two experienced interviewers who traveled around the country. More than 95 per cent of the mothers accepted participation. The mean interval from delivery until special interview was 84 days for case mothers and 91 days for controls.

In the present investigation, 755 pairs of mothers were interviewed between January 1980 and April 1982. Thirty-five pairs that included habitual tea drinkers and 14 pairs with inadequacies in the forms were excluded, leaving 706 pairs in the analysis: 112 babies of the index mothers had defects of the central nervous system, 241 orofacial clefts, 210 structural defects of the skeleton, and 143 cardiovascular malformations.

The differences in the coffee consumption during pregnancy between the case mothers and their controls were tested by means of a paired t-test.¹⁵ The relative risk (odds ratio) point estimates and their 95 per cent confidence limits were calculated using the maximum likelihood procedure described by Pike and colleagues.¹⁶ Multiple logistic regression analysis¹⁷ was applied to study the effect of potential confounders.

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*In our study, only 4 per cent of the mothers reported drinking bottled beverages most days during pregnancy, 15 per cent drank at least one bottle a week, and 85 per cent of the mothers said they consumed these drinks less than one bottle a week.

**Finland is divided into 1,329 districts with a central unit in each district.

TABLE 1—Coffee Consumption during Pregnancy of the Pairs of Case and Control Mothers (all malformation groups)

	Cups of coffee a day	Control Mothers						TOTAL
		0	1-3	4-6	7-9	10-15	23-25	
Case Mothers	0	58	78	48	10	6	—	200
	1-3	93	135	64	14	12	1	319
	4-6	40	59	26	4	9	—	138
	7-9	10	11	3	4	—	—	28
	10-15	6	12	2	—	—	—	20
	23-25	1	—	—	—	—	—	1
	TOTAL	208	295	143	32	27	1	706

Results

Before pregnancy, 96 per cent of the 1,510 mothers were coffee drinkers (including 53 mothers who occasionally also drank tea), 2.5 per cent were tea drinkers; 1.5 per cent of the mothers consumed neither coffee nor tea. The number of mothers consuming coffee sharply declined after the onset of pregnancy, during which time 70.0 per cent of the mothers were coffee drinkers, 2.5 per cent were tea drinkers, and 27.5 per cent ingested neither coffee nor tea.

Table 1 shows that the pairs of case and control mothers are similarly distributed when classified according to their daily consumption of coffee during pregnancy. A paired *t*-test on the differences of the coffee ingestion within the pairs does not show statistical differences (Table 2). The breaking up of the pairs illustrates that also within the separate malformation groups the case and control mothers are evenly distributed throughout the different categories of coffee consumption (Table 3).

Relative risks (unadjusted) of giving birth to a malformed child are given in Table 4, with confidence limits.

Unadjusted relative risk estimate for coffee consumption (any quantity) during pregnancy was 1.1 with 95 per cent confidence interval 0.8-1.3 for all malformations. Multiple logistic regression analysis yielded an identical relative risk estimate of 1.1 (95 per cent confidence interval 0.8-1.3) when adjusted simultaneously for potential confounding by mother's age, smoking habits, and alcohol consumption during pregnancy. Adjusting for potential confounders did not materially affect the risk estimates for separate malformation groups.

Discussion

It is known that coffee drinking declines during pregnancy.¹⁸ About 25 per cent of our mothers stopped drinking

coffee during early pregnancy. Of those mothers who continued, 41 per cent did not change the quantity consumed, 4 per cent increased, and 55 per cent diminished the number of cups ingested. In two-thirds of the mothers, the change in coffee consumption took place during early pregnancy; 88 per cent of the mothers who completely stopped drinking coffee and 62 per cent of those who diminished their consumption said they did so because they found coffee distasteful. In all aspects, changes in coffee drinking were similar for the case and control mothers.

Linn, *et al.*,⁹ reported that only 5 per cent of the mothers in the US consumed four cups or more of coffee a day during pregnancy, and less than 1 per cent of the mothers had seven or more cups. Somewhat higher percentages of coffee consumption among American mothers of malformed children have been reported.¹⁰ Among our Finnish mothers, the habit of substantial coffee drinking was more prevalent: 26.5 per cent of the mothers consumed at least four cups of coffee a day during pregnancy, 7.2 per cent at least seven cups, and 3.5 per cent ten cups or more.

Our negative results are consistent with those of two recent investigations. Linn, *et al.*,⁹ analyzed 12,205 pregnancies without detecting an increased malformation rate for children of mothers who consumed coffee during pregnancy. We have calculated that their material probably contained almost 300 major malformations including clubfoot (the exact number was not given). Rosenberg, *et al.*,¹⁰ reported materially similar relative risks for various groups of congenital defects as compared with other malformed children which served as controls. The authors comment that the possibility of caffeine being a general teratogen, which would result in failure to detect an effect, is remote.

Potential distortion of the outcome in retrospective studies may be introduced by maternal recall bias arising from different recollection of past events by case and control mothers. We have no indication that recall bias was the reason for our not finding an association between coffee consumption and malformations. Mothers of malformed children would have to underreport systematically their coffee consumption during pregnancy for such a bias to conceal an actual risk increase. At the time of our study, there was no public concern or discussion on the possibility of coffee being teratogenic. During the interviews, no particular emphasis was made on coffee drinking; information on this habit formed only a minor part of data collection. Recall bias usually is a more realistic worry in epidemiological studies that end up with evidence for an increased risk.

The risk of a false negative result seems reasonably low, if the present malformations are considered as one group.

TABLE 2—Results of a Paired *t*-test Based on the Differences in Coffee Consumption within the Pairs (case minus control)

Malformation	<i>t</i> -value*	Degrees of Freedom
Central nervous system defects	-0.82	111
Orofacial clefts	-0.41	240
Skeletal defects	-0.19	209
Cardiovascular defects	-1.10	142
TOTAL	-1.10	705

*All differences are statistically non-significant.

TABLE 3—Case and Control Mothers According to Coffee Consumption during Pregnancy

Congenital Malformation		Cups of Coffee a Day						TOTAL
		0	1-3	4-6	7-9	10-15	23-25	
Central nervous system defects	case mothers	34	54	20	3	1	—	112
	control mothers	40	43	24	2	3	—	112
Orofacial clefts	case mothers	64	114	44	13	6	—	241
	control mothers	62	116	45	9	9	—	241
Skeletal defects	case mothers	59	92	41	9	8	1	210
	control mothers	64	85	38	17	5	1	210
Cardiovascular defects	case mothers	43	59	33	3	5	—	143
	control mothers	42	51	36	4	10	—	143
TOTAL	case mothers	200	319	138	28	20	1	706
	control mothers	208	295	143	32	27	1	706

TABLE 4—Relative Risk for Congenital Malformations According to Coffee Consumption during Pregnancy.*

Congenital Malformation	Relative Risk (95% confidence limits)		
	Number of Cups a Day		
	None	1-3	≥4
Central nervous system defects	1.0	1.4 (0.8-2.8)	1.0 (0.5-2.1)
Orofacial clefts	1.0	1.0 (0.6-1.5)	1.0 (0.6-1.6)
Skeletal defects	1.0	1.2 (0.7-1.9)	1.0 (0.6-1.7)
Cardiovascular defects	1.0	1.2 (0.7-2.2)	0.8 (0.4-1.4)
TOTAL	1.0	1.2 (0.9-1.5)	1.0 (0.7-1.3)

*The relative risk was calculated from 465 pairs discordant to coffee drinking.

The likelihood of error increases when selected malformation groups are analyzed separately. Nevertheless, the lower 95 per cent confidence limits remained below unity in the present study. Our overall negative result is further substantiated by no trend toward a higher risk for the heavier coffee drinkers. If the malformation groups were further divided into smaller collections, the uncertainty concerning the conclusions would grow because of decreasing study size. For rare malformations, it would be difficult, if not impossible, to show that coffee is without substantial risk.

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