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AN EPIDEMIOLOGIC STUDY ON CONGENITAL MALFORMATIONS IN NAGOYA

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ABSTRACT

The subjects analysed in the present study were 41,835 total births in Nagoya in 1965, consisting of 41,028 live births and 807 late stillbirths. Among the stillbirths 42 babies were the malformed and of 644 deaths in the subsequent four years 96 deaths with malformations were identified. Average linking rate of death and live birth certificates was 96.1 percent. The incidences of congenital malformations per 1,000 births were 3.30 in total births, 2.34 in live births and 52.04 in late stillbirths. Those in the cardiovascular system were 1.20 in total births, 1.17 in live births and 2.48 in late stillbirths. The corresponding figures were 0.93, 0.34 and 30.98 in the central system and 0.69, 0.56 and 7.43 in the alimentary system, respectively.

Significantly greater relative risks were observed with shorter gestational period, lower birth weight and higher birth order. They were also noted in older working mothers with heavy physical loads, twin births and illegitimate births.

Analyses by major anatomical system revealed significantly greater relative risks with shorter gestational period in the cardiovascular, central nervous and alimentary systems, with lower birth weight in the cardiovascular system and with higher birth order in the central nervous system. Paternal age and parental age difference exerted insignificant effects on malformations, though an increasing tendency of risk with advancing paternal age and with wider parental age difference was interestingly noted in the malformations of the central nervous system.

INTRODUCTION

The importance of congenital malformations not only in clinical medicine, but also in public health is clearly recognized from the following aspects.

1. Despite the remarkable decrease in deaths from infectious diseases, deaths from congenital malformations have not been reduced appreciably, but show a tenden-

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cy to increase over the decades.[1]
2. Congenital malformations are the first killer of infants under one year of age.[1]
3. Approximately forty percent of early fetal deaths are supposed to be due to malformations.[2]
4. Congenital malformations are the second most commn consumer of pediatric hospital beds.[3]
5. Economic and psychological burdens of parents with malformed babies are beyond all imagination.
6. There has been increasing interest in congenital malformations, with many reports on phocomelia due to thalidomide and on german measles syndrome.
7. Very little attention has been paid to the prevention, early detection and rehabilitation of the affected children by health authorities at large.

Though congenital malformations and monstrosities were recognized and depicted in artistic expressions of primitive people,[4] the door of their origin has been mysteriously locked and decorated by superstitions and fears, for centuries. Only in recent years was it opened more and more widely by the advances in medical science, especially in medical genetics, in experimental teratology and in the epidemiology of teratogenesis. Congenital malformations are now etiologically considered as the outcome of intricate interaction between host and environment. This indicates the importance and urgency of epidemiological investigations in this particular field.

In Japan, population based epidemiological investigations are very few. This rarity encouraged the authors to undertake a series of works on the epidemiology of congenital malformations in a metropolitan area, Nagoya.

The preliminary report of the present investigation has already been presented by one of the authors (T.T.).[5] In this paper the results of further statistical analyses are included, and the authors intend:

1. To demonstrate the frequency and distribution of congenital malformations by major anatomical system;
2. To compare the frequency distributions of some contributing factors to congenital malformations between malformed and non-malformed babies;
3. To evaluate the importance of each specific factor by one of the statistical procedures, relative risk.

MATERIALS AND METHODS

The present study was based on 41,835 total births registered in Nagoya in 1965, which consisted of 41,028 live births and 807 late stillbirths (after eighth month of pregnancy), excluding the babies born to the mothers of foreign nationality. Live born babies were followed once or twice a year by linking the live birth certificates with the death certificates by the end of 1968. Six hundred seventy deaths were observed during the follow-up period.

Among them the death certificates of 644 deaths were successfully linked with

their birth certificates, attaining the linking rate of 98.7% in 1965, 96.1% in 1966, 87.8% in 1967 and 76.3% in 1968. The average linking rate was 96.1 percent. Twenty six deaths which failed in linking were finally identified as babies born out of Nagoya in 1965 and died in Nagoya thereafter.

The information available on stillbirth, live birth and death certificates were all examined for each baby. These were residence, birth date, sex, illegitimacy, gestational period, birth weight, single or multiple birth, place of delivery, attendant at birth, birth order, parental age, parental occupation, wedlock duration, date of death, cause of death and stillbirth, autopsy or operation findings and so forth. Cause of death or stillbirth and autopsy or operation findings were deliberately and systematically looked over on each death or stillbirth certificate. The baby was assigned as "malformed" when any form of malformation was listed as either underlying or contributing cause of death and also when malformation was detected in case of autopsy or operation performed.

Forty two babies (males 19, females 22 and unknown 1) among 807 late stillbirths and 96 babies (males 49 and females 47) among 644 deaths after live births were finally identified as malformed babies in this study.

All statistical analyses and data processing were accomplished by the FACOM 230-60 computer at Nagoya University Computation Center and by the HITAC 201 computer at Department of Epidemiology, Aichi Cancer Center Research Institute.

RESULTS

I. Fequency of congenital malformations by major anatomical system and type of malformation (Table 1)

One hundred and thirty eight malformed babies in total birth were distributed as follows: 36.2% in the cardiovascular system, 28.3% in the central nervous system, 21.0% in the alimentary system and 14.5% in miscellaneous organs. It was interestingly noted that in live births the cardiovascular system accounted for one half of the malformed, whereas in stillbirths the central nervous system accounted for about 60% of the malformed. And it was also worth noting that in the central nervous system 10 of 14 malformed in live births were hydrocephalus, whereas 15 of 25 malformed in stillbirths were anencephalus.

Sex difference in frequency of congenital malformations by major anatomical system was not revealed, but some interesting sex differences were observed in some specific malformations. Three cases of tetralogy of Fallot in live births were all females. Five cases of spina bifida in total birth were all males. Four of 5 cases of cleft lip and/or palate were males and 3 of 4 cases of Down's syndrome were females.

Multiple malformations were observed in 8 cases: 4 cases in live birth; hydrocephalus with spina bifida (2), congenital heart disease with atresia of bile duct (1) and congenital heart disease with perineal fissure (1), and 4 cases in stillbirths;

Table 1 Frequency of Congenital Malformations by Major Anatomical System and Type of Malformation

1965 Birth Cohort, Nagoya

Major System and Type of Malformation	Total Births No. (%)	Live Births No. (%)	Stillbirths No. (%)
CARDIOVASCULAR SYSTEM	50 (36.2)	48 (50.0)	2 (4.8)
Septal defect	7	7	0
Tetralogy of Fallot	3	3	0
Patent ductus arteriosus	1	1	0
Congenital heart disease	39	37	2
CENTRAL NERVOUS SYSTEM	39 (28.3)	14 (14.6)	25 (59.5)
Anencephalus	16	1	15
Hydrocephalus	16	10	6
Spina bifida	5	2	3
Microcephalus	1	1	0
Arhinencephalus	1	0	1
ALIMENTARY SYSTEM	29 (21.0)	23 (24.0)	6 (14.3)
Cleft lip, Cleft palate	5	5	0
Intestinal atresia	6	6	0
Anal atresia	2	2	0
Defect of Pancreas, Liver and Biliary tracts	5	5	0
Others	11	5	6
MISCELLANEOUS	20 (14.5)	11 (11.5)	9 (21.4)
Defect of lung	3	1	2
Omphalocele	2	2	0
Down's syndrome	4	4	0
Others	11	4	7
TOTAL MALFORMATIONS	138 (100.0)	96 (100.1)	42 (100.0)
NUMBER OF BIRTHS	41835	41028	807
RATE PER 1,000 BIRTHS			
CARDIOVASCULAR SYSTEM	1.20	1.17	2.48
CENTRAL NERVOUS SYSTEM	0.93	0.34	30.98
ALIMENTARY SYSTEM	0.69	0.56	7.43
MISCELLANEOUS	0.48	0.27	11.15
TOTAL MALFORMATIONS	3.30	2.34	52.04

anencephalus with spina bifida (1), hydrocephalus with phocomelia (1), craniopagus (1) and malformations of palate, pharynx and extremities (1). These multiple malformations were classified in Table 1 according to their main type of malformations.

When all types of malformations were considered together, the frequencies of malformation per 1,000 births were 3.30 in total births, 2.34 in live births and 52.04 in stillbirths, i.e., malformations in stillbirths were 22.2 times more frequent than those in live births.

II. Season and residence

Seasonal distribution of congenital malformations was analysed by month of delivery, grouping the year into four seasonal quarters. No clear seasonal pattern

of malformation was, however, noted in the three types of births and also when analysed by major anatomical system. Nagoya consisted of 14 jurisdictional districts in 1965. They were grouped into 6 areas according to their socio-cultural characteristics. The frequency of malformations was compared among these six areas.

In total and stillbirths no significant geographic difference was observed, while in live births malformations were more prevalent in the west area of Nagoya and most prevalent in Nakamura.

III. Gestational period

The frequency distribution of congenital malformations by gestational period was presented in Table 2 with the relative risks. In total births, relative risks increased remarkably when gestational period became shorter; 8.44 in the eighth month and 3.07 in the ninth month compared with full term births.

This relationship was also observed in live births, though the relative risk of 4.20 in the eighth month was below the significance level of five percent. The importance of gestational period in total births was evaluated by major anatomical system and presented in Table 3.

In the cardiovascular system no malformed baby was observed in the gestational period of eighth month, but there were four malformed in the ninth month with significant relative risk of 3.53.

In the central nervous system a clear and significant increase in relative risk was noted along with shortening period of gestation.

In the alimentary system and miscellaneous organs extremely large and highly significant relative risks were observed in the gestational period of eighth month.

IV. Birth weight

The importance of birth weight in congenital malformations was evaluated only in live births, because the information of birth weight was available only on live birth certificates. This was summarized in Table 4. By reconstructing Table 4, the frequency of malformations by birth weight category per 1,000 births could be obtained as follows;

17.0 per 1,000 live births in less than 2,000 grams,
4.0 per 1,000 live births in 2,001 - 2,500 gram,
2.7 per 1,000 live births in 2,501 - 3,000 grams
1.9 per 1,000 live births in 3,001 - 3,500 grams and
0.6 per 1,000 live births in more than *3,501* grams.

The increase in the frequency of malformations was clearly observed with decreasing birth weight. The relative risks of 6.36 in birth weight of less than 2,000 grams and 0.23 in that of more than 3,501 grams were significant at 0.1% and 1% respectively. The relationship of birth weight to congenital malformations was also evaluated by major anatomical system (Table 5).

In the cardiovascular system increasing relative risk of malformations with

Table 2 Frequency Distribution of Congenital Malformations with Relative Risk by Gestational Period in Month

1965 Birth Cohort, Nagoya

Gestational Period in Month	Total Births					Live Births					Stillbirths				
	CM (-)		CM (+)		R.R.	CM (-)		CM (+)		R.R.	CM (-)		CM (+)		R.R.
	No.	(%)	No.	(%)		No.	(%)	No.	(%)		No.	(%)	No.	(%)	
8	401	(1.0)	10	(7.2)	8.44***	213	(0.5)	2	(2.1)	4.20	188	(24.6)	8	(19.0)	0.66
9	991	(2.4)	9	(6.5)	3.07***	877	(2.1)	5	(5.2)	2.54*	144	(14.9)	4	(9.5)	0.54
10	40264	(96.7)	119	(86.2)	1.00	39801	(97.3)	89	(92.7)	1.00	463	(60.5)	30	(71.4)	1.00
Total	41656	(100.1)	138	(99.9)		40891	(99.9)	96	(100.0)		765	(100.0)	42	(99.9)	

CM (-) : congenital malformations absent
CM (+) : congenital malformations present
R.R. : Relative Risk

*P < 0.05 **P < 0.01 ***P < 0.001

Table 3 Frequency Distribution with Relative Risk of Congenital Malformations in Total Births by Anatomical System and Gestational Period

1965 Birth Cohort, Nagoya

Gestational Period in Month	CM (-)		C.V.S.			C.N.S.			A.S.			MISC.		
	No.	(%)	No.	(%)	R.R.	No.	(%)	R.R.	No.	(%)	R.R.	No.	(%)	R.R.
8	401	(1.0)	0	(0.0)	–	3	(7.7)	9.41***	4	(13.8)	16.73***	3	(15.0)	17.72***
9	991	(2.4)	4	(8.0)	3.53**	4	(10.3)	5.08***	1	(3.4)	1.69	0	(0.0)	–
10	40264	(96.7)	46	(92.0)	1.00	32	(82.1)	1.00	24	(82.8)	1.00	17	(85.0)	1.00
Total	41656	(100.1)	50	(100.0)		39	(100.1)		29	(100.0)		20	(100.0)	

**P < 0.01, ***P < 0.001

C.V.S. : CARDIOVASCULAR SYSTEM, C.N.S. : CENTRAL NERVOUS SYSTEM,
A.S. : ALIMENTARY SYSTEM, MISC. : MISCELLANEOUS

Table 4 Frequency Distribution with Relative Risk of Congenital Malformations in Live Births by Birth Weight

1965 Birth Cohort, Nagoya

Birth Weight in Grams	Live Births				R.R.
	CM (-)		CM (+)		
	No.	(%)	No.	(%)	
- 2000	636	(1.6)	11	(11.5)	6.36***
2001 - 2500	2462	(6.1)	10	(10.4)	1.48
2501 - 3000	13979	(34.2)	38	(39.6)	1.00
3001 - 3500	17532	(42.8)	33	(34.4)	0.63
3501 +	6293	(15.4)	4	(4.2)	0.23**
Total	40932	(100.1)	96	(100.1)	

**P < 0.01, ***P < 0.001

decreasing birth weight and decreasing relative risk with increasing birth weight was noted with statistical significance. This association was also observed in the alimentary system without statistical significance. In miscellaneous organs the relative risk of 10.99 in birth weight of less than 2,000 grams was highly significant.

V. Birth order

Birth order was defined as the number of babies born after the sixth month of pregnancy, irrespective of live or still borns.

In total births the frequency of congenital malformations increased with advancing birth order; 2.6, 3.4, 5.2 and 10.8 per 1,000 total births for birth order 1, 2, 3 and 4 plus, respectively. The risk of malformations accordingly increased with advancing birth order in total and live births (Table 6). The relative risk of 1.96 and 4.13 for birth order 3 and 4 plus in total births and 4.10 for birth order 4 plus in live birth were significant at less than 5 or 0.1 percent level. The general pattern of increasing risk of malformations with advancing birth order was also observed when analysed by major anatomical system (Table 7). Significant relative risks were 3.10 and 5.60 for birth order 3 and 4 plus in the central nervous system.

VI. Paternal age

The evaluation of paternal age at birth on the risk of congenital malformations revealed greater risk for fathers over 45 years old compared with fathers aged 25 - 29. The relative risks for fathers over 45 years old were 2.63 and 4.06 in total and live births. They were, however, below significance level of five percent.

Table 5 Frequency Distribution with Relative Risk of Congenital Malformations in Live Births by Major Anatomical System and Birth Weight

1965 Birth Cohort, Nagoya

Birth Weight in Grams	CM (-)		C.V.S.			C.N.S.			A.S.			MISC.		
	No.	(%)	No.	(%)	R.R.	No.	(%)	R.R.	No.	(%)	R.R.	No.	(%)	R.R.
- 2000	636	(1.6)	6	(12.5)	5.99***	1	(7.1)	5.49	2	(8.7)	5.49	2	(18.2)	10.99***
2001 - 2500	2492	(6.1)	6	(12.5)	1.53	0	(0.0)	–	3	(13.0)	2.10	1	(9.1)	1.40
2501 - 3000	13979	(34.2)	22	(45.8)	1.00	4	(28.6)	1.00	8	(34.9)	1.00	4	(36.4)	1.00
3001 - 3500	17532	(42.8)	13	(27.1)	0.47*	7	(50.0)	1.40	9	(39.1)	0.90	4	(36.4)	0.80
3501 +	6293	(15.4)	1	(2.1)	0.10*	2	(14.3)	1.11	1	(4.3)	0.28	0	(0.0)	–
Total	40932	(100.1)	48	(100.0)		14	(100.0)		23	(100.0)		11	(100.1)	

* $P < 0.05$, *** $P < 0.001$

C.V.S. : CARDIOVASCULAR SYSTEM, C.N.S. : CENTRAL NERVOUS SYSTEM,
A.S. : ALIMENTARY SYSTEM, MISC. : MISCELLANEOUS

Table 6 Frequency Distribution with Relative Risk of Congenital Malformations by Birth Order

1965 Birth Cohort, Nagoya

Birth Order	Total Births					Live Births					Stillbirths				
	CM (-)		CM (+)		R.R.	CM (-)		CM (+)		R.R.	CM (-)		CM (+)		R.R.
	No.	(%)	No.	(%)		No.	(%)	No.	(%)		No.	(%)	No.	(%)	
1	21494	(51.6)	57	(41.3)	1.00	21080	(51.5)	40	(41.7)	1.00	414	(54.3)	17	(40.5)	1.00
2	15890	(38.1)	54	(39.1)	1.28	15664	(38.3)	39	(40.6)	1.31	226	(29.7)	15	(35.7)	1.62
3	3472	(8.3)	18	(13.0)	1.96*	3401	(8.3)	11	(11.5)	1.70	71	(9.3)	7	(16.7)	2.40
4+	822	(2.0)	9	(6.5)	4.13***	771	(1.9)	6	(6.3)	4.10***	51	(6.7)	3	(7.1)	1.43
Total	41678	(100.0)	138	(99.9)		40916	(100.0)	96	(100.1)		762	(100.0)	42	(100.0)	

* $P < 0.05$, *** $P < 0.001$

Table 7 Frequency Distribution with Relative Risk of Congenital Malformations in Total Births by Major Anatomical System and Birth Order

1965 Birth Cohort, Nagoya

Birth Order	CM (-)		C.V.S.			C.N.S.			A.S.			MISC.		
	No.	(%)	No.	(%)	R.R.	No.	(%)	R.R.	No.	(%)	R.R.	No.	(%)	R.R.
1	21494	(51.6)	23	(46.0)	1.00	14	(35.9)	1.00	12	(41.4)	1.00	8	(40.0)	1.00
2	15890	(38.1)	20	(40.0)	1.18	15	(38.5)	1.45	11	(37.9)	1.24	8	(40.0)	1.35
3	3472	(8.2)	4	(8.0)	1.08	7	(17.9)	3.10*	4	(13.8)	2.06	3	(15.0)	2.32
4+	822	(2.0)	3	(6.0)	3.41	3	(7.7)	5.60*	2	(6.9)	4.36	1	(5.0)	3.27
Total	41678	(100.0)	50	(100.0)		39	(100.0)		29	(100.0)		20	(100.0)	

* $P < 0.05$

C.V.S. : CARDIOVASCULAR SYSTEM, C.N.S. : CENTRAL NERVOUS SYSTEM,
A.S. : ALIMENTARY SYSTEM, MISC. : MISCELLANEOUS

Table 8 Frequency Distribution with Relative Risk of Congenital Malformations by Maternal Age

1965 Birth Cohort, Nagoya

Maternal age in Years	Total Births					Live Births					Stillbirths				
	CM (-)		CM (+)		R.R.	CM (-)		CM (+)		R.R.	CM (-)		CM (+)		R.R.
	No.	(%)	No.	(%)		No.	(%)	No.	(%)		No.	(%)	No.	(%)	
- 19	345	(0.8)	1	(0.7)	0.95	331	(0.8)	0	(0.0)	–	14	(1.8)	1	(2.4)	1.57
20 - 24	12720	(30.5)	39	(28.3)	1.00	12478	(30.5)	28	(29.2)	1.00	242	(31.7)	11	(26.2)	1.00
25 - 29	20113	(48.2)	70	(50.7)	1.14	19797	(48.4)	50	(52.1)	1.13	316	(41.4)	20	(47.6)	1.39
30 - 34	7080	(17.0)	19	(13.8)	0.88	6946	(17.0)	11	(11.5)	0.71	134	(17.5)	8	(19.0)	1.31
35 +	1435	(3.4)	9	(6.5)	2.05*	1377	(3.3)	7	(7.3)	2.27*	58	(7.6)	2	(4.8)	0.76
Total	41693	(99.9)	138	(100.1)		40929	(100.0)	96	(100.0)		764	(100.0)	42	(100.0)	

* $P < 0.05$

In the central nervous system an increasing riskof malformations with advancing paternal age appeared to be observed, but in other system no such tendency was observed.

VII. Maternal age

The relationship of maternal age at birth to the risk of malformations was summarized in Table 8.

Young mothers, less than 20 years old, had no significantly large relative risk. Older mothers, 35 years old or more, had significant relative risks of 2.05 in total births and 2.27 in live birth, compared with the mothers aged 20 - 24.

The analyses in total births by major anatomical system revealed rather large relative risks of 2.17 for younger mothers, less than 20 years old, in the cardiovascular system and 3.55 for older mothers, 35 years or more, in the central nervous system.

In miscellaneous organs the relative risks, compared to mothers aged 20 - 24, were 3.59 for mothers 30 - 34 years old and 5.71 for mothers 35 years old or more. They were, however, a little short of the significance level of five percent.

VIII. Parental age difference

Parental age difference was obtained by simple numeric substraction of mother's age from father's age at birth.

The relative risk of unity was assigned to the age difference of -2 to +2 years. The relative risks of more than unity were observed in wider age difference groups in total, live and still births. The relative risks of less than unity were noted in wider age difference in an opposite direction (fathers were younger than mothers) in total, live and stillbirths. All relative risks in this analysis were, however, not large enough to reach the significance level.

The analysis in total births by major anatomical system demonstrated the large relative risks with wider age difference in the cardiovascular system (1.49 for age difference of 3 to 7 years and 2.02 for that of 8 years or more) and in the central nervous system (1.45 for that of 3 to 7 years and 1.59 for that of 8 years or more). The relative risks of 1.52 was observed for younger father than mother group in miscellaneous organs. They were, however, all insignificant in a statistical sense.

IX. Single or twin birth (Table 9)

Among 41,835 total births 439 multiple births were observed, which were all twin births.

The frequencies of congenital malformations per 1,000 total births were 3.2 for single births and 11.4 for twin births. The difference was significant at less than five percent.

The relative risks of malformations for twin births were 3.57 in total births, 3.27 in live births and 1.08 in stillbirths. Only the relative risk of 3.57 in total births

Table 9 Frequency Distribution with Relative Risk of Congenital Malformations by Single or Multiple Birth

1965 Birth Cohort, Nagoya

	Total Births					Live Births					Stillbirths				
	CM (-)		CM (+)		R.R.	CM (-)		CM (+)		R.R.	CM (-)		CM (+)		R.R.
	No.	(%)	No.	(%)		No.	(%)	No.	(%)		No.	(%)	No.	(%)	
Single	41263	(99.0)	133	(96.4)	1.00	40532	(99.0)	93	(96.9)	1.00	731	(95.6)	40	(95.2)	1.00
Twin	434	(1.0)	5	(3.6)	3.57**	400	(1.0)	3	(3.1)	3.27	34	(4.4)	2	(4.8)	1.08
Total	41697	(100.0)	138	(100.0)		40932	(100.0)	96	(100.0)		765	(100.0)	42	(100.0)	

** $P < 0.01$

reached the significance level of one percent.

Three malformed babies in live births were cases of tetralogy of Fallot, duodenal atresia and microcephaly. Two malformed in stillbirths were cases of hydrocephaly and abdominal malformations.

X. Illegitimacy

There were five malformed babies among 554 babies born to the mother out of wedlock; two in live births and three in stillbirths. The frequency of malformations was 9.0 per 1,000 total births in illegitimate births, whereas it was 3.2 in ligetimate births. The difference was significant at less than five percent.

The relative risks of malformations for illegitimate births were 2.83 in total births, 1.75 in live birth and 0.94 in stillbirths. The latter two were insignificant.

In the cardiovascular system the relative risk for illegitimate births was 1.53 and in the alimentary system it was 2.68, though they were insignificant.

In the central nervous system the realtive risk could not be calculated because of no malformed cases in illegitimate births.

In miscellaneous organs there were 17 malformed in legitimate births and 3 in illegitimate births, rendering the highly significant relative risk of 13.23 for illegitimate births.

XI. Occupation

Parental occupation at birth was classified by the classification of occupation used for the population census in 1965 in Japan. The distribution of malformations by paternal occupation was so disperse that no certain tendency of clustering was detected.

Among mothers only 7.6% were engaged in some kind of occupation at birth and the rest were housewives. Working mothers were grouped into two categories by physical load; sales, agriculture or service workers and employees in other occupations. The distribution of malformations was analysed by these two categories, including housewives in the latter category (Table 10).

In total births the frequency of malformations was 9.8 per 1,000 births in sales agriculture and service workers, whereas it was 3.1 in the employees in other occupations and housewives. This difference was significant at less than 0.1 percent. A significant difference was similarly observed in live births, but not in stillbirths.

The relative risks of malformations for sales, agriculture and service workers were 3.15 in total births and 3.20 in live births.

The relationship of maternal occupation to congenital malformations in total births was analysed by major anatomical system and summarized in Table 11.

Significantly large relative risks of malformations in sales, agriculture and service workers were observed in the cardiovascular and central nervous systems.

Table 10 Frequency Distribution with Relative Risk of Congenital Malformation by Mother's Occupation

1965 Birth Cohort, Nagoya

Mother's Occupation	Total Births					Live Births					Stillbirths				
	CM (-)		CM (+)		R.R.	CM (-)		CM (+)		R.R.	CM (-)		CM (+)		R.R.
	No.	(%)	No.	(%)		No.	(%)	No.	(%)		No.	(%)	No.	(%)	
Sales, Agriculture and Service Workers	1009	(2.4)	10	(7.2)	3.15***	981	(2.4)	7	(7.3)	3.20**	28	(3.7)	3	(7.1)	2.01
Employees in Other Occupations and Housewives	40659	(97.6)	128	(92.8)	1.00	39926	(97.6)	89	(92.7)	1.00	733	(96.3)	39	(92.9)	1.00
Total	41668	(100.0)	138	(100.0)		40907	(100.0)	96	(100.0)		761	(100.0)	42	(100.0)	

** $P < 0.01$, *** $P < 0.001$

Table 11 Frequency Distribution with Relative Risk of Congenital Malformations in Total Births by Major Anatomical System and Mother's Occupation

1965 Birth Cohort, Nagoya

Mother's Occupation	CM (-)		C.V.S.			C.N.S.			A.S.			MISC.		
	No.	(%)	No.	(%)	R.R.	No.	(%)	R.R.	No.	(%)	R.R.	No.	(%)	R.R.
Sales Agriculture and Service Workers	1009	(2.4)	4	(8.0)	3.50*	4	(10.3)	4.61**	0	(0.0)	–	2	(10.0)	4.48
Employees in Other Occupations and Housewives	40659	(97.6)	46	(92.0)	1.00	35	(89.7)	1.00	29	(100.0)	1.00	18	(90.0)	1.00
Total	41668	(100.0)	50	(100.0)		39	(100.0)		29	(100.0)		20	(100.0)	

* $P < 0.05$, ** $P < 0.01$

C.V.S. : CARDIOVASCULAR SYSTEM, C.N.S. : CENTRAL NERVOUS SYSTEM,
A.S. : ALIMENTARY SYSTEM, MISC. : MISCELLANEOUS

DISCUSSION

One of the important objectives of epidemiologic study on any disease of unknown etiology is to detect the population based incidence figure and distribution of the disease. There are several large scaled surveys of congenital malformations in Japan[6][7][8][9], but they were almost based on hospital records in one or some major hospital. The authors were, therefore, encouraged to undertake a population based epidemiologic investigation of congenital malformations in a defined area, Nagoya.

The main shortcomings in the present study are non-inclusion of malformed children living during the study period and of the possible deaths with undetected malformations, in addition to the difficulty of ascertaining each malformed case, one by one, by the investigators themselves.

In our understanding, therefore, the malformations dealt in this study were rather serious major malformations. This is supported by the fact that malformation itself was the underlying cause of death in 128 of 138 malformed children.

In the present study the stillbirths were limited to the still borns after the eighth month of pregnancy. The main reasons were that about 60% of stillbirths before the eighth month of pregnancy were artificially induced and that the majority of stillbirths in this period were attributed to maternal diseases or disorders.[10] And the frequency of malformations among spontaneous stillbirths with known causes before the eighth month of pregnancy was far less than that among spontaneous stillbirths after the eighth month of pregnancy.[10]

The linking rate of birth and death certificates should be evaluated with the consideration of population migration during the study period.

Ninety of 96 malformed in live births (93.8%) could be successfully linked within two years after births. In the 3rd and 4th year the rates were less than 90%. The average linking rate of 96.1% in the present study is believed to be sufficient enough to investigate the incidence figure and distributions of malformations, as compared with the linking rate of 97.4% reported by Chase.[11]

In the present investigation the incidences of congenital malformations, all types considered together, were 0.33% in total births, 0.23% in live births and 5.2% in late stillbirths.

Kennedy[12] extensively reviewed the world literature, more than two hundred in number, on the incidence of congenital malformations. He showed the average incidence of 0.83% from the data of 19 papers based on official records, birth certificates and retrospective questionnaires. The minimum incidence among these 19 papers was 0.15%.[13] Our incidence rate of 0.23% in live births might be lower than the true figure in a strict sense, because malformed children alive for the study period and possible deaths with undetectable malformations were not included in the authors' series, as mentioned above.

The incidence based on hospital records in Japan ranges from 0.45% to 1.94%.[8] These figures are not comparable with ours because not only of the difference

in the source of information, but also of the difference in diagnostic criteria and time of ascertainment.

As to the incidence of congenital malformations in late stillbirths, Mitani[7] reported 10.8% among 675 autopsied late still borns. Landsman and others[14] showed the incidence of 22.91% in stillbirths on the basis of hospital records. Kolah and his associates[15] found the figure of 9.44% from hospital records. Saxen and Härö[16] reported the incidence of 13.34% by official questionnaire to maternity hospitals. These figures are not consistently uniform and may not be comparable with each other for similar reasons mentioned above.

Rather comparable malformation is a lethal one such as anencephaly. In the present study there were 16 anencephalic babies in 41,835 total births (0.38‰).

The incidence of anencephaly in total births was reported to be 0.63‰ by Neal[6], 0.62‰ by Mitani[7] and 0.68‰ by Moriyama[9] from hospital records in Japan. Our lower rate than these reports may be in part due to underreporting, that is inherent to death and stillbirth certificates.

The listing of various incidence figures of congenital malformations as a whole or by major anatomical system may be valuable in highlighting the magnitude of the problem in public health as well as in clinical medicine. It may, however, be rather confusing at the moment of wide diversity in criteria of diagnosis and in methods of reporting. The most urgent task of the epidemiologist in this field is believed to establish the valid basis of statistical comparability. This should be accomplished through international agreement for standardization of diagnostic criteria, time of ascertainment and other essentials.

Conway and Wagner[17] observed the abnormally high incidence of congenital malformation in males than in females (58 to 42) among 21,804 birth certificates in New York in 1952 to 1962. In our series no clear sex difference was detected. Among 138 malformed, males were 68 and females 69, rendering the sex ratio of almost unity.

Tokuhata and his associates[18] reported the higher incidence of malformations in females in both cardiovascular and central nervous systems and markedly higher incidence in males in other organ system. No significant sex preponderance in any major anatomical systems was demonstrated in our data: in the cardiovascular system (males 24 and females 26), in the central nervous system (males 21 and females 18) and in other orgen systems including alimentary system (males 23 and females 25).

The sex difference of cleft lip and/or cleft palate seems to be established with a certain consistency.[19] Cleft lip alone or cleft lip with cleft palate is more prevalent in males than in females. Cleft palate alone is more prevalent in females than in males. In our data also more males than females were observed for cleft lip and cleft palate, though the number of cases was not large enough to confirm the relationship with statistical significance.

Mckeown and Record[20] illustrated the relationship of some specific malfor-

mations to sex. According to their figure anencephaly is more frequent in females than in males and no clear sex preponderance in Down's syndrome. More females than males in Down's syndrome was reported by Conway and Wagner.[17] In our series there were 7 males and 9 females of anencephaly and one male and three females of Down's syndrome.

No significant seasonal patterns in malformations as a whole or by major anatomical systems were revealed in the present study. Tokuhata and his associates[18] reported that congenital anomalies, all forms considered together, were most prevalent among babies born during December - February period. This pattern remained in all anomalies in the cardiovascular system. For anomalies in the digestive system more prevalent period was June to August. Allen[21], however, noted no particular seasonal pattern for congenital cardiac malformations. Clear seasonal variations were presented by Klingberg[22] in polydactyly, syndactyly and cleft palate.

Congenital dislocation of the hip is also one of the congenital malformations reported to show seasonal pattern; more in winter than in summer.[23][24] Anencephaly is a controversial malformation as to seasonal pattern.[25][26] There were 16 cases of anencephaly in our series; one was born in December to February, five in March to May, seven in June to August and three in September to November. This distribution was not significantly different from the theoretical distribution of 16 cases based on the null hypothesis of equal distribution in four quarters in a year.

In live births there is found a significantly high incidence of malformations in Nakamura, Nagoya. This geographic difference may not simply be due to population density or other characteristics of the area at large. More intensive investigations are undoubtedly required to clarify the origin of this geographic difference and whether this difference is meaningful. Very detailed survey had been completed on various socio-cultural and physical factors of the pregnants in Nakamura. The analyses of this data will furnish some clues for this interesting phenomenon.

Babies with shorter gestational period and lower birth weight had larger relative risks in the present study. This finding includes the important fundamental problem of whether congenital malformation per se affects gestational period and/or birth weight. And which is more associated with congenital malformations, gestational period or birth weight?

Yerushalmy and coworkers[27] reported that severe anomalies were more related to low birth weight than the length of gestation. This was also confirmed in our data by Takeuchi.[5]

Increasing frequency of malformations with advancing birth order was revealed in live and total births. Bock and Zimmerman[28], McDonald[29] and Naggan[26] found no such phenomenon, while Halevi[30] observed increasing frequency of Down's syndrome and malformations of the extremities with advancing birth order.

The effect of birth order on congenital malformations should be evaluated with consideration to, at least, maternal age, because these two factors are closely

related with each other. Takeuchi[5] reported that birth order had a significant effect on the frequency of malformations when analysed with maternal age group kept constant.

It was concluded by Edwards[25] that three main malformations in the central nervous system; anencephalus, spina bifida and hydrocephalus were more common in first births than in second births. Our data, in contrast, revealed with high statistical significance that babies of the birth order 3 and 4 or more were at greater risk of malformations in the central nervous system.

Most statistics on the frequency of congenital malformations have shown increasing incidence with advancing maternal age.[31] In our analysis also older mothers, 35 years old or more, were at greater risk of malformations in live and total births. Mothers aged less than twenty were also incriminated for malformations in the central nervous system.[32] This was not demonstrated in the authors' series.

The effect of paternal age on congenital malformations is still uncertain. Milham and Gittelsohn[33] failed to demonstrate the effect of paternal age on malformations. Newcombe and Tavendale[34], on the other hand, reported the significant effect of paternal age and parental age difference on production of malformations. In the present analyses no significant relationship of paternal age and parental age difference was revealed to the frequency of malformations as a whole. The interesting tendency, however, of increasing risk of malformations with increasing paternal age and with wider parental age difference was observed in one major anatomical system.

Twins were at greater risk of malformations than singletons. Hay and Wehrung [35] investigated the incidence of specific malformations among singletons, like-sexed twins and unlike-sexed twins. A substantially high incidence of anencephaly, hydrocephaly and congenital heart disease was observed in twins from like-sex pairs compared with twins from unlike-sex pairs and single births. Our twins weighed all less than 2,500 grams at birth. Crowded intrauterine condition in twin pregnancy may in part account for the greater risk of malformations.

Illegitimate births were also at greater risk of malformations than legitimate births. Tokuhata and his associates[18], in contrast, reported that congenital anomalies, all forms considered together, were slightly less often reported for illegitimate births than for legitimate births. And Edwards[25] concluded that anencephalus was relatively uncommon in illegitimate pregnancies and spina bifida and hydrocephalus showed no consistent relationship to legitimacy.

Illegitimacy is, however, an incriminated factor for premature births[18], low birth weight[36] and fetal deaths[36], which are well related to high incidence of congenital malformations. In our data there were significantly more younger and older mothers and more working mothers in illegitimate births than in legitimate births.

The interpretation, however, of the relative hazards of illegitimacy for congenital malformation is difficult. Our finding is believed to indicate that illegitimacy,

a sociological phenomenon, is significantly affecting the production of congenital malformation, a biological variable. How this occurs, therefore, appears to contain very important basic questions which require further investigations.

No consistent relationship of paternal occupation was revealed to congenital malformations either as a whole or by major anatomical system. Fujino[37] observed relatively more cases of cleft lip and ceft palate among fathers working in mining industries. Down's syndrome is also reported to be significantly prevalent in the paternal occupations of tailors, clock-makers and repairers of precision instrument, and tanners and furriers.[38] Association between congenital malformations and specific paternal occupations is believed to be indirect. It may be a reflection of such other factors closely related to specific paternal occupations as low income, poor dietary habits, poor education, poor medical care in general, poor personal hygienic practices, limited or delayed access to prenatal care and so forth.

The present study revealed a greater risk of congenital malformations for working mothers in sales, agriculture and service, whose working loads are supposed to be heavier than those in housewives and workers in other occupations. This may indicate, as reported by McDonald[29], the importance of heavy physical loads during pregnancy in the production of congenital malformations. It is, however, important to assess whether sociological backgrounds of working mothers themselves and environmental factors involved in their working conditions may have some etiological significance.

Finally the various biological and sociological factors considered in the present study are undoubtedly intercorrelated to a various degree.

In order to evaluate the relative importance of these confounding factors simultaneously and to demonstrate a clearer picture, so-called multivariate analysis is supposed to be rather promising.

An attempt to put in order the contributing factors, in importance, to congenital malformations is also required to make the preventive practices more effective.

This particular analysis is on-going and will be published elsewhere.

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