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Twinning in Susceptible Mothers

An Exploratory Study of International Data by Payami's Models Suggests "Reproductive Maturity" as a Risk Factor

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Abstract. An attempt has been made to apply Payami's models to maternal age-specific twin birth prevalences in several countries. The models disclose the heterogeneity of a cohort and spell out the risks to susceptible members (who will actually get the disease) according to age (or time). Payami's method specifies that the typical cohort of susceptibles is ascribed to two exposures: a potent and generalised exposure and a very low or no risk secondary exposure. The models have been adjusted to international data from current as well as old populations, of Occidental and Japanese origin. Results show that cohorts of twin-prone mothers aged 25 to 45 are homogeneous. A single dominant etiology is suggested which applies to both MZ and DZ twins. Heterogeneity, from 10% to 25%, is present in all countries whenever the 20-24 age group is involved. A separate study of illegitimate twin births from Denmark reduces the heterogeneity and shows that MZ illegitimate twin births are due to a secondary exposure responsible for a distinct twinning etiology. The age-specific risks of a MZ illegitimate twin birth are much higher than those of any comparison group, and are constant until age 35 years. This suggests a single-hit exposure akin to a neuroendocrine stimulus which short-cuts the usual age-dependent etiologic pathway. MZ and DZ twins both experience the same maternal age specific risks, an observation which underscores the common etiology of both types of twins. Risks increase with age from age 20 to 45 years. The pattern according to age varies among countries and time periods. Occidental populations have a pattern varying from an exponential to a more linear increase in old and recent populations, respectively. Only present-day Japan displays a logarithmic-like growth curve. The concept of "reproductive maturity" is introduced, and related to the secular trend of the DZ twin birth risk and to its variation across countries. Two new conclusions are drawn: a) The

higher the rate of reproductive maturity, the less the DZ twin birth risk and, b) Reproductive maturity determines the maternal age-specific gonadotropin levels.

Key words: Twinning, Cohort, Etiologic heterogeneity, Illegitimacy, Reproductive maturity, Mathematical models

INTRODUCTION

Cohorts are amenable to the study of risk defined as the probability of an event occurring in disease-free individuals in the course of a time interval [20]. An alternative term for risk is cumulative incidence. More often than not cohorts are heterogeneous as to the risk, ie, all of the individuals of the cohort are not equally susceptible to the forthcoming event [20,25]. While the majority of members of a cohort may be at high risk, some others may be at very low risk because of environmental or constitutional resistance or effect modification by other risk factors. This being so, the distribution of waiting times to the forthcoming event, instead of following a simple geometric law expected under a constant risk in a homogeneous cohort [25], would rather conform either to a lognormal distribution [30] or, more generally, to a right-skewed distribution the parameters of which remaining to be determined [13]. This might occur in cases where the risk increases with time or under a two-hit model [4,21].

Payami proposed a new method to deal with a heterogeneous cohort [26]. The typical cohort comprises two groups, one at high risk and the other at very low risk. Payami applied his method to HIV seroconversion, Huntington's disease and juvenile-onset diabetes. He showed that homosexuals are heterogeneous as to the risk to seroconvert, about 47% of them having a constant 15% risk to seroconvert during any of the three six-month intervals of the study. This was a typical cohort data base. The results were shown to agree well with the clinical observations of the study base. In the case of Huntington's chorea, a retrospectively accrued group of patients, he could show that the age-specific risk of the disease increases in such a way that a multiplicative or an additive model equally fits the data, and that the cohort is characterized by a highrisk group including from 80% to 86% of individuals. This result was rather unexpected as the disease is held to be homogeneous, being due to a single dominant gene. On the other hand, a low risk group is not out of the question as rare cases of the disease might be due to new mutations or different alleles with low penetrance. As to diabetes, neither models could fit the data. This is interpreted as being due to the complex etiologic heterogeneity of the disease; accordingly, a two-group model was too simplistic to accommodate the data. This conclusion is not unexpected, and is suggested by the complex interrelationships of diabetes with HLA antigens.

This paper is concerned with the application of Payami's method to the study of twinning. Twinning is a complex problem as far as etiology is concerned [23]. It is also of importance to community health as it is related to an increased risk of morbidity in offspring and may bring about problems at the moment of confinement. From an epidemiological standpoint, the twin birth prevalence shows a secular trend [8,18,33].

In many countries, the birth prevalence of dizygotic (DZ) twins decreases while an increase in the prevalence of monozygotic (MZ) twins is apparent since some time [2,14]. These trends are not thoroughly accounted for by changes in maternal age or parity. Further, the between-country prevalence of twin births also shows considerable variation, with Blacks having the highest frequency, followed by Whites with intermediate values, and then by Orientals with the lowest frequency [3]. All of this variation is accounted for by a difference in the DZ twinning risk. We decided to fit Payami's models to data of international origin considering that it might help to look into the age-specific twinning process in susceptibles to uncover any potential heterogeneity of mothers, and to describe the pattern of risk according to age. The specific interest of this class of models is to disclose the cohort structure and to determine the pattern of risks to susceptibles only; the approach thus differs from the computation of the classical twinning risks one might estimate from data from a whole population of mothers including those who will never bear twins. Nevertheless, the computed risks will be classical cumulative incidence rates. This study is thus largely an attempt to generate hypotheses about the epidemiology of twinning from an unusual point of view. This is the first in-depth attempt – aside from Payami's original investigation – to assess the yield of this new approach to a community health problem.

METHODS

The objective of Payami's method is to disclose the heterogeneity of risk within a cohort and to uncover the age-specific risks of an event for either its best represented or high-risk group. However, the models may not reproduce the age-specific risks of the high-risk group (the typical case) if it is of small size; rather, the models can then yield the age- or time-specific risks of the low-risk group if its size is large in comparison with that of the high-risk group. Be this as it may, the computed risks are considered valid provided there is a substantial difference in risk between the two groups [26]. Payami's method uses the usual age-specific events from a cohort (or cross-section of a population) as they would present in a classical study of risk by the actuarial method [20]. Table 1 reports the parameters of the method introduced hereunder. The method first posits that a cohort of H individuals is composed of S susceptibles who will actually get the disease or the trait, where S may be either equal to H (homogeneous case) or smaller

Table 1 - Parameters of Payami's models

Interval	At risk	New event	Risk according to model		
			Constant	Multiplicative[a]	Additive[b]
1	S	D_1	R	R_1	R_1
2	$S\text{-}D_1$	D_2	R	$m.R_1$	$k+R_1$
3	$S\text{-}D_1\text{-}D_2$	D_3	R	$m^2.R_1$	$2k+R_1$

[a] m is the multiplicative constant.
[b] k is the additive constant.

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than H (heterogeneous case). In the course of time (only three age groups or time intervals of equal length are dealt with), there will occur D_1, D_2 and D_3 new events corresponding to the three time intervals.

Starting with this, three different possible models may be fitted to the age-specific data. First, the risk may be constant with age (or time), in which case R_1, R_2 and R_3 simply becomes R. The second type of model is multiplicative wherein the interval-1 risk is multiplied by the constant m to make up the interval-2 risk, and multiplied by m^2 to make up the interval-3 risk. At last, there is the additive model, wherein the constant k adds up to the interval-1 risk to make up the interval-2 risk, and the constant 2k adds up to the interval-1 risk to make up the interval-3 risk.

Payami also shows how the parameters of Table 1 may be estimated readily by the method of maximum likelihood with data obtained from only three age groups (or time intervals). Further, the constant risk model may be tested for goodness of fit by chi-square as one of the three available equations is left unused. The reader is referred to Payami's original paper for the details of equations solving.

As our data include all known twin-bearing mothers from their respective population, they all are susceptible; accordingly, the age-specific risks may be viewed as a cumulated risk function over age. It will vary between 0 and 1. Estimates of age-specific risks in susceptibles and percent cohort homogeneity were obtained applying Payami's equations to the twin prevalence from age-group triplets. For instance, the first three estimates of risk were found for the 20-24, 25-29 and 30-34 age groups. This age-group triplet was relied upon to estimate the constant, multiplicative, and additive models. Then, the younger age-group was put aside and the age-specific risks of the next triplet, ie, the 25-29, 30-34 and 35-39 age groups, were estimated. Again, all the three models were fitted. Last, risks were estimated on the data triplet involving the 30-34, 35-39 and 40-44 age groups and, again, the three models adjusted. Not all the models actually fitted the data. Unlikely solutions may be obtained for any one model. For example, the constant age-specific risk model was not very popular because the risk of a twin birth actually increases with age in susceptibles in most data sets. Such a maladjustment may be diagnosed through percent cohort homogeneity that may point out higher than 100% homogeneity, or simply set out negative results. On the other hand, the multiplicative risk model may not be credible if an age-specific risk is established at a value higher than one. And, at last, a specific model may not be estimable at all, thus yielding an impossible solution. These diagnoses are described as « no solution » within the tables displaying the age-specific risks. Since Payami's models are in a stage of investigation, we decided to present, all the same, those models wherein an age-specific risk was as high as 1.2, and those with percent homogeneity as high as 110%. These decisions were also taken to allow for errors in the original data bases. All other solutions at variance with these restrictions were plainly discarded (and not included in the tables of risk) as yielding highly unlikely solutions. However, all the solutions set out in the tables are not necessarily acceptable; for instance, if a risk of 1.2 may be acceptable to describe a 40-45 year-old twinning risk, thus allowing for random errors among others, it must be plainly discarded as implausible for an earlier age group. In the following, any mention to age-group triplets will simply be referred to as "triplets".

Age-specific risks were then plotted with the aid of a non parametric weighted least-square smoothing technique (lowess) [5]. Plotted risks were those of the additive models

only. They were exclusively used because, granted the above-detailed criteria, they yielded goodness-of-fit to data more often than multiplicative models. But in order to describe the age-specific risks adequately across the five age groups and, accordingly, to prevent any assessment bias related to a possible curvature of the age-specific pattern, only the central age-specific estimate of each triplet was used for plotting. For example, for the 25-29, 30-34 and 35-39 triplet, only the 30-34 age-group risk was retained for plotting. If the next triplet had any solution, the 35-39 age-group would be retained. This rule was applied consistently to all additive models estimated. The first and last age-group risks were those of the corresponding triplets as a starting and an ending data point had to be included in the plot. Any exception to the preceding rules was submitted to the principle of conservatism; at any rate, the age-specific risks used for plotting are underlined in the tables.

DATA

Data used in this study were retrieved from the published literature on twins. This investigation proceeded along three steps. First, we relied on large sample size studies wherein twin births were presented according to five specific maternal-age groups, that is 20-24, 25-29, 30-34, 35-39 and 40-44 years. Unfortunately, some studies had large sample sizes but unconventional maternal-age groupings, and had to be discarded. Others had too small sample sizes, and were also rejected to avoid lack of precision. Twin births occurring prior to age 20 years were put away altogether as the interval was open in most studies and of presumably unequal length across studies. Further, the number of twin births occurring in this age group was too small to yield any stable estimates of risk. At last, data bases were required to be broken down into the DZ and MZ twin categories obtained by applying Weinberg's differential method. In all, four studies from as many countries were retained. These were Denmark (1896-1910) [12], Finland (1961-1964) [12], Canada (1952-1967) [10] and Japan (1974) [15]. Table 2 presents the main features of twin births in the four countries. Payami's models were adjusted to these data to estimate cohort homogeneity and to describe maternal age-specific risks for susceptibles.

Table 2 - Features of twin births from studied populations

Country	Years	Crude twinning rate/1000			Studies
		Total	MZ	DZ	
Finland	1921-1940	14.9	—	—	Eriksson & Fellman (1967)
Finland	1961-1964	14.3	3.1	11.2	Eriksson & Fellman (1967)
Denmark	1896-1910	13.9	3.9	10.0	Eriksson & Fellman (1967)
Sweden	1954-1962	10.7	3.3	7.4	Eriksson & Fellman (1967)
Canada	1952-1967	10.4	4.0	6.4	Elwood (1978)
Quebec	1608-1730	- not available -			Charbonneau & Légaré (unpubl)
Japan	1974	5.8	3.9	1.9	Inouye & Imaizumi (1981)

The second and third steps of this investigation are concerned with hypotheses testing. The second step is an attempt to reiterate the patterns obtained in the first four countries. It was attempted on populations, either of smaller sample size (Quebec: 1608-1730) [6] but of interest because very old data were at stake, either of similar ethnic background (Finland: 1921-1940) [12], wherein a secular trend could be examined, or of similar geographical area and contemporaneity (Sweden:1954-1962) [12]. However, for this second step, MZ and DZ twin births were combined to assess risk by age for reasons of small sample size and because the maternal age-specific MZ and DZ twin births risks were not shown to differ in the first four countries. The third and last step of this study is also concerned with hypotheses testing. We wanted to know how the risk factor "illegitimacy of twin births" influenced the age-specific pattern of risk, size of risk, and cohort homogeneity. For this, we relied on data from Denmark (1896-1910). Though illegitimate twin births from Finland were also available, they were of much too small sample size to be of any use.

RESULTS

Tables 3, 4, 5 and 6 display the age-specific twin birth risks along with percent cohort homogeneity obtained from the various fitted models, for Denmark (1896-1910), Finland (1961-1964), Canada (1952-1967), and Japan (1974) respectively. The following

Table 3 - Maternal age-specific twin birth risks for susceptibles: Denmark 896-1910

MZ Prevalence by age group			827	1125	1057	821	301
Model[a]	Constant	% Homogeneity	Risk by age group[b]				
			20-24	25-29	30-34	35-39	40-44
×	1.9	74.9	0.27	0.49	0.91		
+	0.14	101.2	0.20	0.33	0.47		
×	1.4	107.0		0.32	0.44	0.60	
×	1.5	97.1			0.50	0.76	1.2
+	0.24	99.5			0.48	0.73	0.97
DZ Prevalence by age group			1350	2748	3038	2758	944
Model[a]	Constant	% Homogeneity	Risk by age group[b]				
			20-24	25-29	30-34	35-39	40-44
+	0.17	97.8	0.13	0.30	0.47		
×	1.5	110.0		0.26	0.40	0.59	
+	0.30	99.0			0.45	0.76	1.1

[a] × = multiplicative risk model; + = additive risk model.
[b] Underlined risks are those used for age-specific risk curves.

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Table 4 - Maternal age-specific twin birth risks for susceptibles: Finland 1961-1964

MZ Prevalence by age group			259	269	222	123	68
Model[a]	Constant	% Homogeneity	Risk by age group[c]				
			20-24	25-29	30-34	35-39	40-44
×	1.5	95.9	0.29	0.41	0.60		
×	1.5	91.0		0.43	0.64	0.95	
+	0.18	95.5		0.41	0.59	0.77	
						No sol.[b]	
DZ Prevalence by age group			758	1054	892	652	180
Model[a]	Constant	% Homogeneity	Risk by age group[c]				
			20-24	25-29	30-34	35-39	40-44
×	2.0	73.7	0.29	0.57	1.1		
+	0.19	93.0	0.23	0.42	0.60		
				No. sol.[b]			
+	0.27	98.8			0.52	0.80	1.1

[a] × = multiplicative risk model; + = additive risk model.
[b] No solution for this age-group-starting triplet. See the methods section.
[c] Underlined risks are those used for age-specific risk curves.

points are worth noting. First, both the additive and multiplicative models often show simultaneous goodness of fit of the same data triplets. This is expected as the risk has limited increase over only few age groups. However, the additive model fits the data more consistently, but the multiplicative model seems more appropriate to describe the increasing risks between ages 25 and 35 years. Further, both the additive and multiplicative models show valid adjustment of the first data triplet in many countries with the latter presenting with appreciable heterogeneity, while the former suggests near complete homogeneity. We will come back to this later on. The growth rate of the risk over age is not constant across several countries; this calls for different twinning patterns of risk across age in susceptibles from several countries. As to the constant risk model, it is not very helpful, except after age 30 years in Japan. This, however, may prove heuristic as the model accommodates both the MZ and DZ twinning risks after age 30 years of Japanese susceptible mothers only.

Second, within any specific age-group, well-fit models show consistent risks. For example, the 30-34 age-group risk of a MZ twin birth in Canada varies little (between 55% and 58%), except for the multiplicative model first data triplet when the cohort shows heterogeneity. Estimates of risk thus show reliability as the age-specific risks may be reproduced across models featured by near complete cohort homogeneity. Third, within-country MZ and DZ twin-birth risks are similar across age groups of susceptible

Table 5 - Maternal age-specific twin birth risks for susceptibles: Canada 1952-1967

MZ Prevalence by age group			227	228	166	91	28
Model[a]	Constant	% Homogeneity	Risk by age group[c]				
			20-24	25-29	30-34	35-39	40-44
×	1.5	89.5	0.34	0.52	0.80		
+	0.14	100.1	0.31	0.44	0.58		
×	1.3	100.1		0.44	0.58	0.76	
+	0.12	103.3		0.43	0.55	0.67	
×	1.3	99.9			0.58	0.77	1.0
+	0.17	100.8			0.58	0.75	0.92
DZ Prevalence by age group			432	444	417	257	41
Model[a]	Constant	% Homogeneity	Risk by age group[c]				
			20-24	25-29	30-34	35-39	40-44
			No sol.[b]				
×	1.5	97.5		0.39	0.60	0.92	
+	0.17	104.9		0.36	0.53	0.71	
+	0.29	99.2			0.59	0.88	1.2

[a] C = constant risk model; × = multiplicative risk model; + = additive risk model.
[b] No solution for this age-group-starting triplet. See the methods section.
[c] Underlined risks are those used for age-specific risk curves.

mothers. They all increase with age and are of the same order of magnitude, varying from about 0.25 at age 20 years to attain 1.0, as expected, by age 45 years. Fourth, all country mothers of both MZ and DZ twins, aged 25 years and above, present with near complete homogeneity of risk suggesting that the cohort mothers bound to give birth to MZ and DZ twins have similar age-dependent but, nevertheless, country-specific risks. In other words, no subgroup with a lower risk and, accordingly, a different etiology is pointed out by the model. High cohort heterogeneity nevertheless exists for data triplets involving the 20-24 age group (it is even more impressive for the triplet involving the 15-19 age group from Canada where it constitutes the only valid model – results not shown here); this observation could simply be dismissed on the basis of absence of consistency with the well-fit models pertaining to more advanced age-group triplets. Alternatively, among-country results involving the youngest age group also show consistency with heterogeneity varying from 10% to 25%. Were this genuine, a coexisting subgroup of young women would be called for, who may otherwise be considered at low risk given the dominant etiology, ie, women who had twins due to a distinct risk factor the relationship of which with twinning is actually negligible. The risk factor would mainly per-

Table 6 - Maternal age-specific twin birth risks for susceptibles: Japan 1974

MZ Prevalence by age group			2144	3945	1568	295	49
Model[a]	Constant	% Homogeneity	Risk by age group[d]				
			20-24	25-29	30-34	35-39	40-44
+	0.47	92.2	0.29	0.75	1.2		
×	1.2	98.9		0.68	0.85	1.1	
+	0.16	99.1		0.68	0.84	1.0	
C[b]	—	100.8			0.82	0.82	0.82
×	1.0	100.4			0.82	0.84	0.86
+	0.02	100.4			0.82	0.84	0.86
DZ Prevalence by age group			920	1836	794	194	28
Model[a]	Constant	% Homogeneity	Risk by age group[d]				
			20-24	25-29	30-34	35-39	40-44
+	0.47	90.6	0.27	0.74	1.2		
×	1.2	99.1		0.65	0.80	0.99	
+	0.15	99.5		0.65	0.79	0.94	
C[c]	—	102.0			0.78	0.78	0.78
×	1.1	100.1			0.78	0.87	0.97
+	0.09	100.1			0.78	0.87	0.96

[a] C = constant risk model; × = multiplicative risk model; + = additive risk model.
[b] Goodness-of-fit chi-square is 0.5 with 2 df ($P > 0.75$).
[c] Goodness-of-fit chi-square is 4.9 with 2 df ($P > 0.05$).
[d] Underlined risks are those used for age-specific risk curves.

tain to twins born to mothers aged 20 to 24 years or younger as the heterogeneity vanishes as triplets excluding the 20-24 age group are considered. Be this as it may, the across-country heterogeneity of the first triplet cannot simply be ruled out as inconsistent and, as such, must be amenable to interpretation.

Figures 1, 2, 3 and 4 display scatter plots of MZ and DZ age-specific risks for the above populations. It is clear that MZ and DZ age-specific twin birth risks are identical within any population and are dependent upon age. However, the increase according to maternal age is very different across populations: Denmark presents with an exponential growth of risk, Finland and Canada have an apparent linear increase in risk, and Japan sets forth a logarithmic increase. These results also parallel a secular trend in the increase of the growth curve: the oldest population (Denmark 1896-1910) with its exponential growth curve, opposes Japan (1974), characterized by an inverse growth trend, while Canada (1952-1967) and Finland (1961-1964) have intermediate (ie, linear) risk increase.

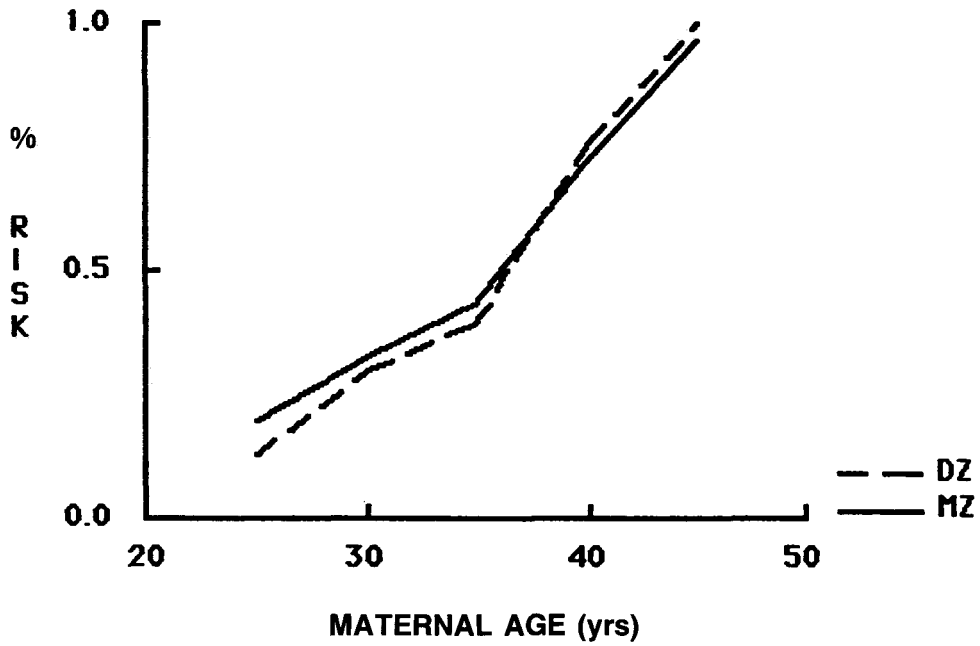

Fig. 1. Maternal age-specific MZ and DZ twinning risks: Denmark 1896-1910.

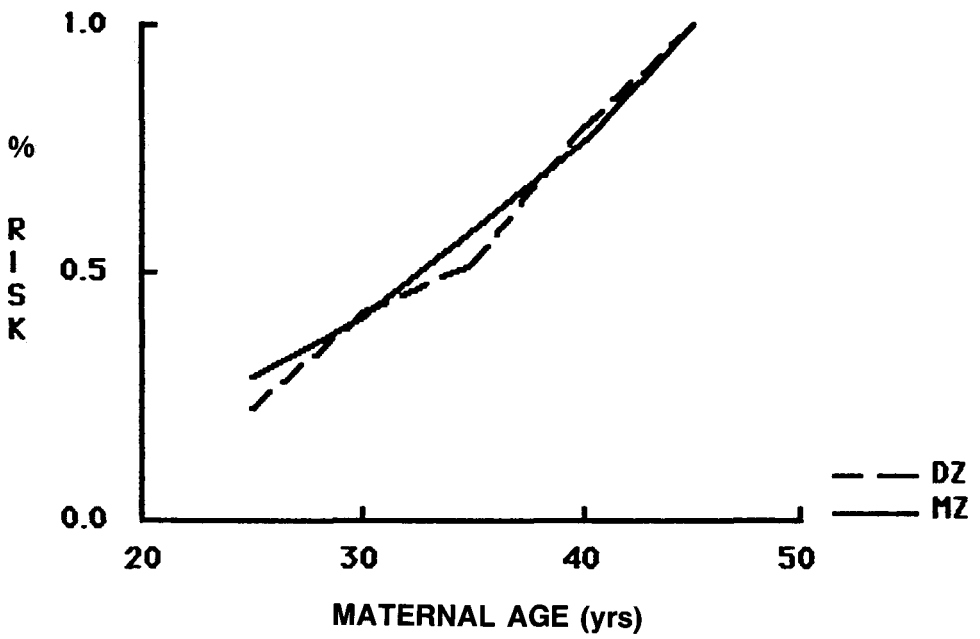

Fig. 2. Maternal age-specific MZ and DZ twinning risks: Finland 1961-1964.

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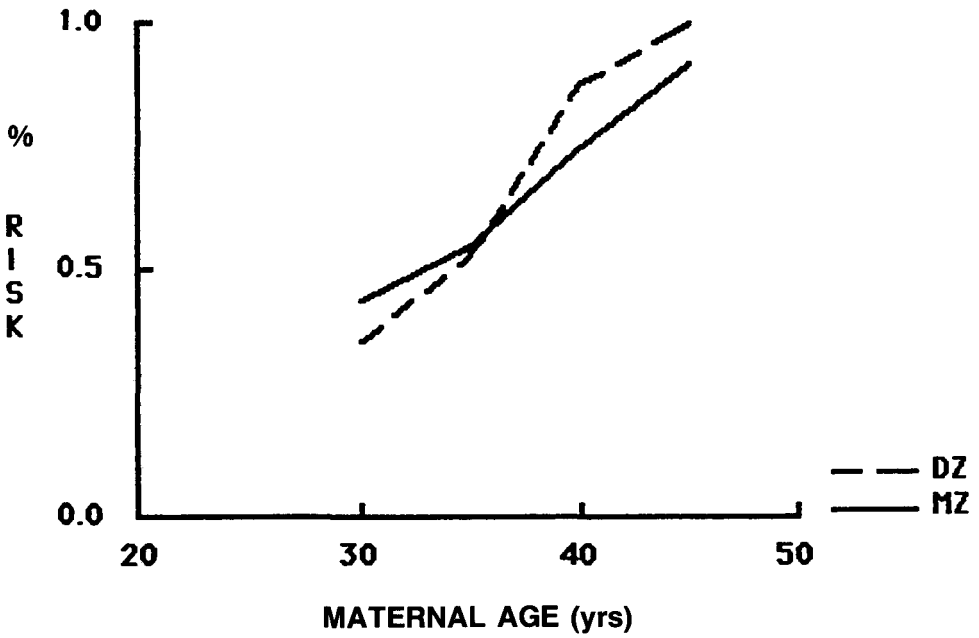

Fig. 3. Maternal age-specific MZ and DZ twinning risks: Canada 1952-1967.

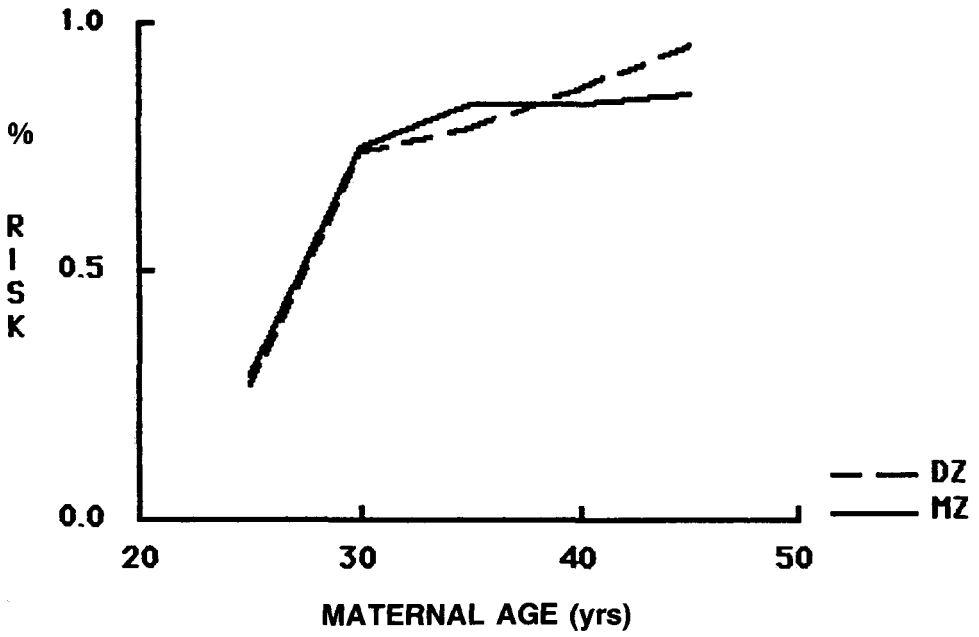

Fig. 4. Maternal age-specific MZ and DZ twinning risks: Japan 1974.

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In order to further look into this trend, we turned to very old data (Quebec: 1608-1730) with smaller sample size. We also tested a similar population at an earlier point in time (Finland: 1921-1940) and another but contemporaneous population of similar geographical area (Sweden:1954-1962). Table 7 sets out the age-specific risks of combined MZ and DZ twin births for the three populations. Worthy of note here is the very

Table 7 - Maternal age-specific combined DZ and MZ twin birth risks for susceptibles: Quebec 1608-1730, Finland 1921-1940, Sweden 1954-1962

QUEBEC 1608-1730							
Prevalence by age group			44	75	86	88	37
Model[a]	Constant	% Homogeneity	Risk by age group[c]				
			20-24	25-29	30-34	35-39	40-44
×	2.2	61.3	0.22	0.47	1.0		
				No sol.[b]			
+	0.30	99.5			0.41	0.70	1.0
FINLAND 1921-1940							
Prevalence by age group			3411	5755	5900	5005	1929
Model[a]	Constant	% Homogeneity	Risk by age group[c]				
			20-24	25-29	30-34	35-39	40-44
×	2.2	63.6	0.24	0.54	1.2		
+	0.16	97.5	0.16	0.32	0.48		
×	1.4	108.0		0.29	0.41	0.59	
×	1.6	96.4			0.47	0.76	1.2
+	0.26	99.5			0.46	0.72	0.98
SWEDEN 1954-1962							
Prevalence by age group			2138	2995	2651	1663	360
Model[a]	Constant	% Homogeneity	Risk by age group[c]				
			20-24	25-29	30-34	35-39	40-44
×	1.9	77.7	0.28	0.55	1.1		
+	0.17	100.9	0.22	0.39	0.55		
×	1.5	99.9		0.39	0.57	0.83	
+	0.15	106.0		0.37	0.51	0.66	
+	0.26	99.1			0.57	0.84	1.1

[a] × = multiplicative risk model; + = additive risk model.
[b] No solution for this age-group-starting triplet. See the methods section.
[c] Underlined risks are those used for age-specific risk curves.

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Table 8 - Maternal age-specific illegitimate twin birth risks for susceptibles: Denmark 1896-1910

MZ Prevalence by age group			196	86	22	40	6
Model[a]	Constant	% Homogeneity	Risk by age group				
			20-24	25-29	30-34	35-39	40-44
C[b]	—	93.4	0.63	0.63	0.63		
×	1.2	87.0	0.64	0.79	0.98		
+	0.14	87.4	0.64	0.78	0.93		
				No sol.[c]			
					No sol.[c]		
DZ Prevalence by age group			324	288	188	134	46
Model[a]	Constant	% Homogeneity	Risk by age group				
			20-24	25-29	30-34	35-39	40-44
×	1.4	87.0	0.38	0.55	0.78		
+	0.13	93.4	0.35	0.49	0.62		
				No sol.[c]			
×	1.5	98.5			0.52	0.77	1.1
+	0.23	100.4			0.51	0.75	0.97

[a] C = constant risk model; × = multiplicative risk model; + = additive risk model.
[b] Goodness-of-fit chi-square is 3.1 with 2 df ($P > 0.10$).
[c] No solution for this age-group-starting triplet. See the methods section.

low homogeneity (from 61% to 63%) of the Quebec and Finland populations for mothers aged 20-24 years. Otherwise, the age-specific risks offers no substantial difference with those computed previously. Figure 5 displays the age-specific risk curve for the Quebec population. It is even more exponential-like in the old data base from Quebec. The early population of Finland (1921-1940) was also plotted (Fig. 7); its pattern of growth reminds that of old populations like Quebec (1608-1730) and Denmark (1896-1910). At last, Sweden (1954-1962), a population contemporaneous with Finland (1961-1964), was plotted in Fig. 6 and shows a similar type of increase with age.

Finally, we tested the effect of illegitimate and strictly legitimate twin births broken down into the MZ and DZ components, on percent homogeneity and pattern of risk by age. Tables 8 and 9 display the results for Denmark (1896-1910). Many points are worth underscoring here. In the following, the term 'combined' will refer to the combination of illegitimate and legitimate twin births as set forth in Table 3. First, as to the risks. Aside from overall higher illegitimate MZ risks for otherwise early age groupings when compared with the combined counterpart from the same population and time period, the illegitimate MZ age-specific risks are given by a constant risk model, independent of age, while the illegitimate DZ age-specific risks, also higher than those computed on

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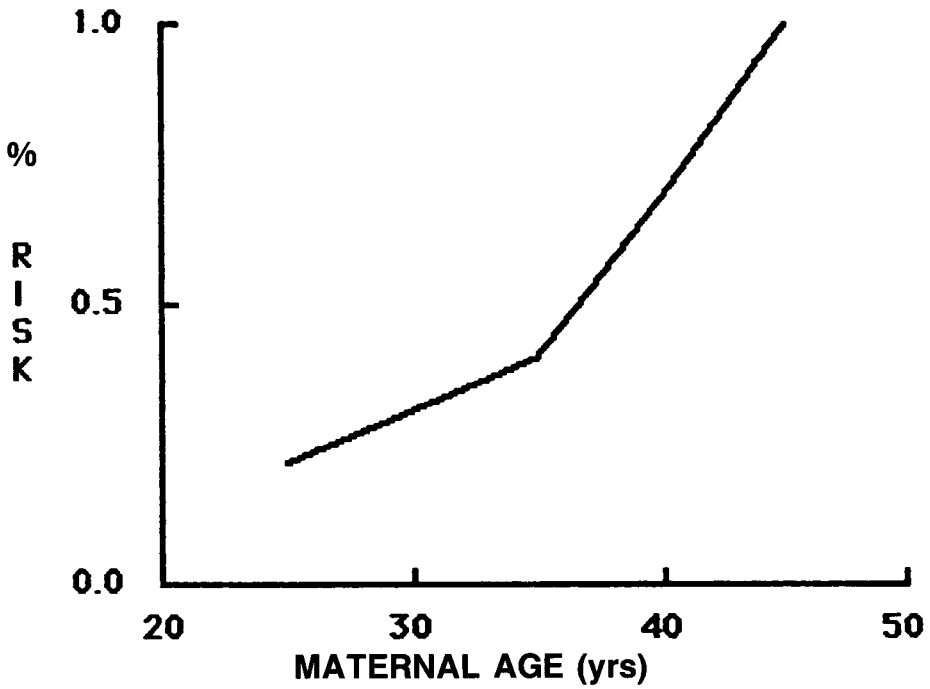

Fig. 5. Maternal age-specific combined twinning risk: Quebec 1608-1730.

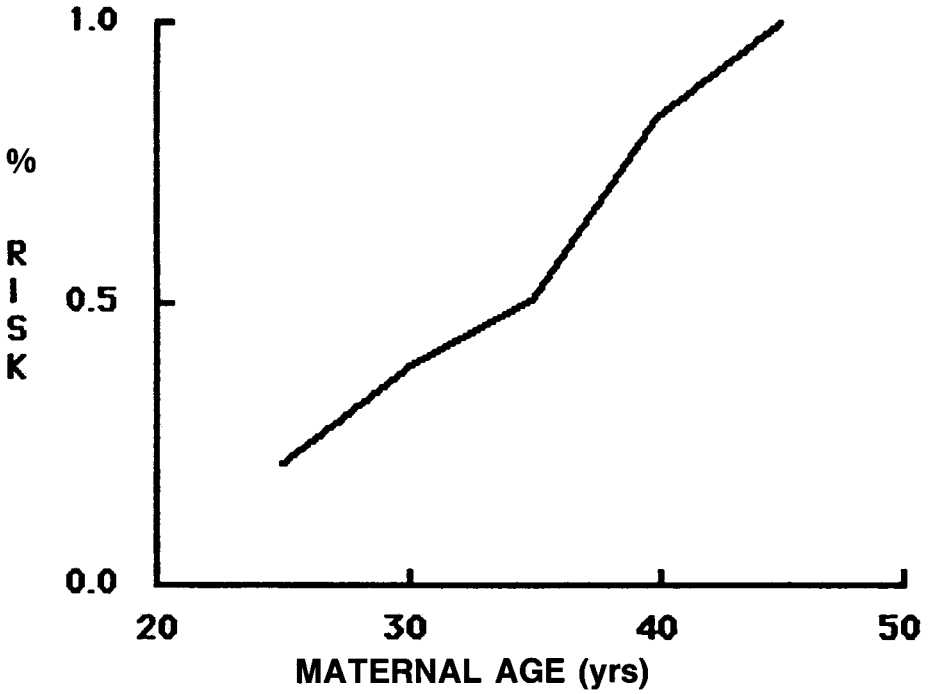

Fig. 6. Maternal age-specific combined twinning risks: Sweden 1954-1962.

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the combined DZ twin births, still depend upon age. Combined MZ and DZ illegitimate twins from Sweden (1954-1962) also highlight the goodness of fit of the constant risk model for the first two data triplets (results not shown here). Analyses of legitimate MZ and DZ (Table 9) corroborate the results obtained on illegitimate twins as the youngest age group risks prove to be lower than those of the combined MZ and DZ. Moreover, the legitimate MZ rules out the constant risk model as was the case with the combined MZ.

Second, the illegitimate MZ-twin maternal cohort is now much more homogeneous than its combined counterpart as if the heterogeneity of risk had somewhat been broken

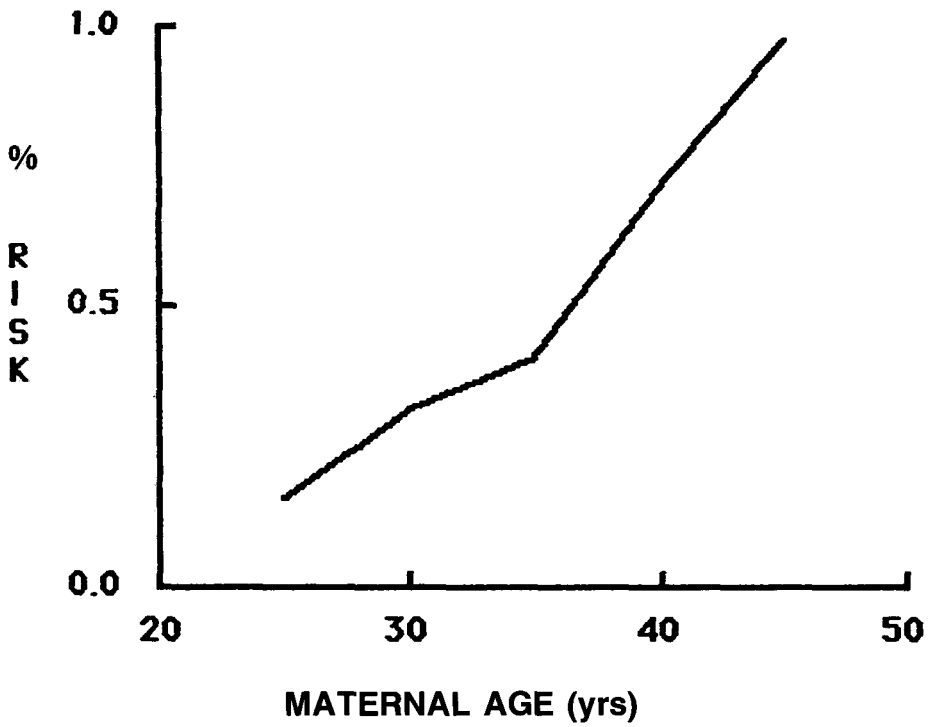

Fig. 7. Maternal age-specific combined twinning risks: Finland 1921-1940.

down by the restriction. Table 9 results pertaining to legitimate MZ twins put forward the same phenomenon; this is particularly obvious if one considers that the multiplicative model has become more unlikely with a 30-34 age group risk as high as 1.2, a figure hardly credible in the circumstances. One thus has to rely on the additive model with its consistent risks and nearly complete homogeneity. These results thus suggest that the cohort of women with MZ-illegitimate twin births is different from MZ married susceptible mothers, and that these differences may be perceived through the pattern of age-specific risks.

Table 9 - Maternal age-specific legitimate twin birth risks for susceptibles: Denmark 1896-1910

MZ Prevalence by age group			631	1039	1035	781	295
Model[a]	Constant	% Homogeneity	Risk by age group				
			20-24	25-29	30-34	35-39	40-44
×	2.2	66.7	0.25	0.55	1.2		
+	0.17	98.5	0.17	0.33	0.50		
×	1.5	98.9		0.33	0.49	0.74	
×	1.5	97.5			0.50	0.75	1.1
+	0.23	99.9			0.49	0.71	0.94
DZ Prevalence by age group			1026	2460	2850	2624	898
Model[a]	Constant	% Homogeneity	Risk by age group				
			20-24	25-29	30-34	35-39	40-44
+	0.18	96.8	0.11	0.29	0.47		
×	1.6	105.4		0.26	0.42	0.65	
+	0.31	98.9			0.45	0.76	1.1

[a] × = multiplicative risk model; + = additive risk model.

DISCUSSION

This study has been largely exploratory. It attempted to analyse and interpret the results of a new class of models, the application of which to community health problems is by and large a matter of empiric induction. By the very nature of its exploratory character, our study involves some limitations. Payami advocates that the models may be used for typical cohort as well as cross-sectional data; a bias could therefore be introduced if a secular trend in overall twinning risks has altered the age-specific configuration of risks. This might have occurred had an intervening risk factor changed over time, thus affecting the various cohorts differentially. I do not believe that the secular trend of twinning risks has been of such importance to cast serious doubt on our estimates of age-specific risks. Even the widespread use of gonadotropin-stimulating drugs may not have had such a large postulated effect. Furthermore, life-table methods are used in case of events that do not recur, that is, once an individual has the disease or the trait he or she is no more at risk which, obviously, is not the case for twins that can repeat themselves. However, the twinning recurrence rate is low enough to be confident that the error is minor given the large sample sizes used. Despite the limitations raised, the results obtained proved to be rather consistent and have helped in drawing tentative new conclusions. The latter may now be submitted to specific testing.

It has been shown that the cohort of women having either MZ or DZ twins between age 25 and 45 years is homogeneous. The homogeneity is nevertheless country- and

period-specific. This is to say that twin-prone women who had a first twin birth delivery after age 24 years have country- and period-specific age-dependent risks. Given a specific time period and country, the age-dependent risks are identical in all susceptible women. Thus, no subgroup of susceptibles with a different twinning etiology exists. This further suggests that MZ and DZ twinning processes both have a common pathway, a conclusion reached by several investigators [7,24]. Both types of risk are age-dependent and do not differ if not for higher but consistent age-specific risks of MZ than DZ twins. What happens before age 25 years supports a widely different conclusion. This age group (and presumably the earlier one) involves a substantial heterogeneous fraction, variable from country to country, with Japan (1974) having the lowest and Denmark (1896-1910) the highest.

Attempt to disclose heterogeneity was resolved through a separate study of legitimate and illegitimate MZ and DZ twin births from Denmark. It was shown that MZ twin-prone mothers only had constant risks until age 35 years. In other words, the risk of a MZ illegitimate twin birth was independent of age. A specific study of MZ legitimate twin births showed that they still presented with age-dependent risks. Our contention is then that illegitimate MZ twin birth mothers constitute a subgroup of all MZ twin-bearing mothers which, by nature, is at very low risk (or no risk at all given the dominant risk factor) of having twins but nevertheless get twins due to an unusual and distinct risk factor. The mechanism by which such MZ twins are produced is not akin with the standard mechanism which itself is age-dependent and presumably up to gonodotrophins, well known to rise with age [3]. The goodness of fit to a negative exponential suggests that illegitimate MZ twinning is due to a constant risk single-hit exposure. This might reflect the action of a potent psychoendocrine stimulus suspected to be involved in cases of out-of-wedlock twinning [1]. Such an exposure might release large amounts of FSH, short-cut the standard pathway whereby FSH normally piles up with age, and achieve a high probability of egg division. This mechanism is exactly the one that was relied upon to explain the unexpected high frequency of MZ embryos induced by the artificial hormonal induction of ovulation [7]. The mechanism pertaining to MZ legitimate twin births would still be age-dependent, and would induce twins presumably through the standard age-dependent hormonal pathway shared with DZ twinning. It is not impossible that both pathways actually stack up at early age groups (say 15 to 24 years) as the combined legitimate and illegitimate MZ risk is higher than the corresponding legitimate twinning risk. This might occur in cases of twins born to newly wed women yielding higher than standard twinning risks [11].

It has also been shown that the twinning risk increases with age in susceptibles. This is true in all countries. But the pattern of increase with age is variable. For example, in many countries, the increase seems linear during the first third of reproductive life, curvilinear during the second third, and linear anew thereafter until age 45 years of mothers. This is true for MZ as well as DZ twins. Plotting and joining the age-specific risks, the pattern points to a family of more or less similar curves according to age. Further, comparisons with data of different time periods suggested that an overall curvilinear pattern of risk by age may have lasted many centuries in most countries, altering only recently. The turning point might have coincided with the start of the 20th century. At this point the pattern of risk may have become less concave and more linear. Only Japan presented with an irreducible opposite pattern, best described by a logarithmic-

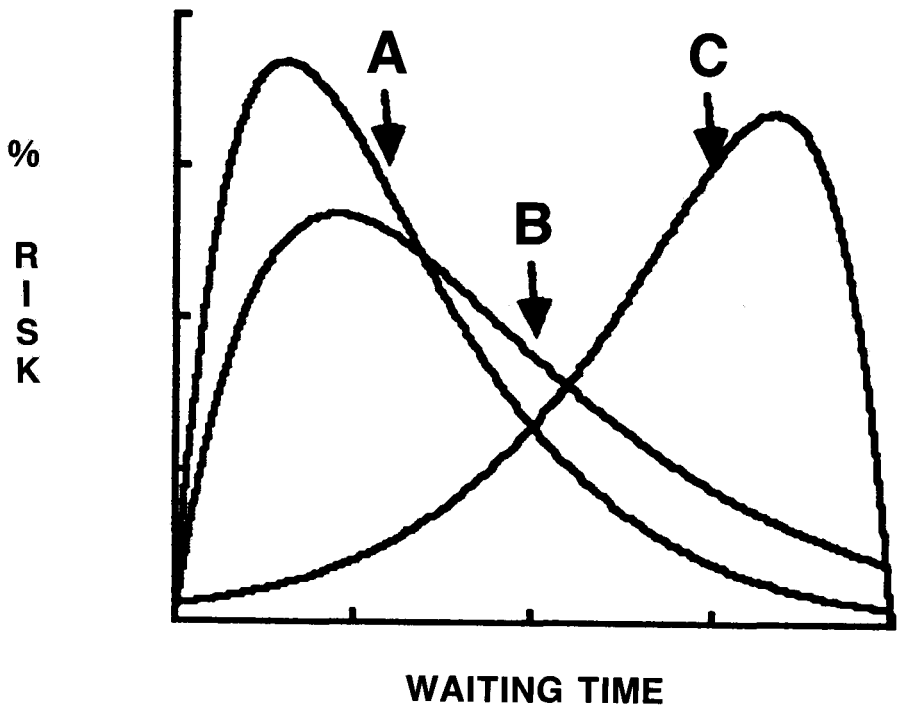

Fig. 8. Theoretical distributions of risk according to various types of relationships.

like curve, which might somewhat be interpreted as the upper limit of the gradual transformation of the family of curves, passing from convex to linear, and then to concave. This family of risk patterns according to maternal age is akin to the secular trend of DZ twins since the start of the 20th century and to variations of the twinning risks among countries. The relationship between both types of observations may be summarised as follows.

Should the (uncumulated) twin birth prevalence be plotted against maternal age, a distribution would be obtained. If the Japanese concave relationship is translated into a distribution of risk, a plot like the one in Fig. 8A would show. The plot has been drawn according to Grigg's primordial response function [13]. If, on the other hand, a convex curve is translated into a distribution of uncumulated risks, a reverse pattern is produced, also shown in Fig. 8C. Intermediate relationships (Fig. 8B) between the two elicit right or left skewed distributions of twin birth risks. It is tempting to make use of the features of these distributions to generate hypotheses pertaining to the secular trend of DZ twins birth prevalence and to its variations among countries. For instance, the Japanese distribution with its high peak and exponential-decay right tail suggests that twins are due to a potent risk factor (height of climax) with a short "pulse" (geometric right tail), involving no host interaction (short right tail). These features are suggested by an analysis of Grigg's primordial response model [13]. On the other hand, a lower peak associated with a longer right tail rather suggests either a less potent risk factor

with host resistance and modification, possibly similar to Sartwell's lognormal distribution [30], or Burch's two-hit model [4]. It might therefore be surmised that Japanese twin-prone susceptible mothers acquire reproductive maturity (RM) in a rather short time lag, the latter being measured by the waiting time from exposure to the peak height. On the contrary, patterns from populations like Canada and Sweden characterized by less right-skewed distributions of twin risks may be interpreted as delayed RM. And old populations like that of Quebec or those assessed about the turn of the 20th century with a left-skewed distribution of risks rather suggest that maturity is acquired late in the course of reproductive life of susceptible women. What I am suggesting is that the pattern of change in risk with maternal age reflects the rate of acquisition of RM defined as a state of hormonal regularity sufficiently robust to withstand the dissipative environmental or behavioral insults such as stress, smoking, etc. Full RM may be acquired early in reproductive life (Japanese women) and this might depend on a deterministic exposure, or it may be acquired later (Occidental women) and this might involve effect modification by either environmental or behavioral exposures.

Now, RM evolving through time may not be a feature of the sole twin-prone mothers. On the contrary, a secular trend in RM may have concerned all women of reproductive age. This is all the more likely that several investigators have noticed that the secular decline in the twinning rates was matched by a similar decline in birth rates [14,17]. A common cause may therefore be postulated. If it can be posited that the inferences concerning RM also apply to the whole of women of reproductive age including twin-prone mothers, far-reaching conclusions about the epidemiology of twins can be drawn. Granted that this generalisation holds, we can formulate the following relationship: *the higher the RM rate, the less the DZ prevalence risk*. In other words, the waiting time until the full acquisition of RM would be an error-prone process that may elicit hormonal dysfunctions capable of inducing DZ twins. Accordingly, an inordinately long time lag until attainment of full RM would enable the accumulation of hormonal dysfunctions culminating in an increased probability of multiple ovulation. Conversely, a short time lag until attainment of full RM would prevent or reduce hormonal dysfunctions, thus dampening the DZ twinning risk. This would explain why Japanese women featured by a high RM rate have a low DZ twinning risk, as well as the decreasing secular trend of DZ since the start of the 20th century. The secular trend might be related to a nutritional stimulus accelerating the RM rate since the start of the century in several countries and paralleling the earlier age at menarche [34]. For instance, the recent fall of DZ twins born to Nigerian mothers has been ascribed to a change in the traditional diet on behalf of a more European-like nutrition [22]. Because of the *quantum* difference of Japan with Occidental populations, we would rather favor genes at the origin of the mother's RM high rate and low DZ risk. This interpretation is in line with the demonstration of the maternal prenatal origin of DZ twins [29], the genetic determination of DZ twinning [28], and is suggested by studies of interracial crosses on the role of maternal genes in DZ twin prevalence [19].

It is difficult to assess the relationship of gonadotropins with RM. We would nevertheless speculate according to the following model: *RM determines FSH*. More specifically, the earlier in life the acquisition of full RM, the lower the level of FSH attained. This suggests that FSH is a response to inadequate or incomplete RM, and that FSH piles up, birth after birth, with its increasing risk of hormonal dysfunctions and

multiple ovulations, this as long as RM is not fully attained. Featured by particularly low rate of RM, historical populations will thus have high DZ twin birth risks even after age 40 years of mothers [27,32]. We therefore predict that the inordinately early RM of Japanese women would coincide with low gonadotropin levels, an observation which has actually been made [31].

This exploratory study was undertaken with a new class of models. The approach worked out by Payami [26] proved to be heuristic. Several new conclusions were set forth. Among them are the new concept of reproductive maturity and the one-hit mechanism at the origin of illegitimate MZ births. Needless to add that these conclusions will be of value only if they are tested by specific designs, and confirmed. Further, it would be no wonder if the concept of RM rate had consequences beyond that of twinning *per se*. For instance, it might apply to the field of breast, ovarian, and endometrial cancer for which Japan has particularly low incidence rates. This is all the more plausible that the twinning process has been thought to be related to breast cancer through an hormonal diathesis [16,35]. The recent suggestion that height, twinning, and breast cancer might be related [9] may be akin to the rate of attainment of reproductive maturity of various populations.

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