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THE PROBLEM OF COMPARATIVE ANALYSIS OF BIRTH PREVALENCE OF CONGENITAL CARDIOVASCULAR MALFORMATIONS

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A number of published papers have dealt with the comparison of birth prevalences of congenital cardiovascular malformation (CCVMs). The feasibility of meaningful intercountry comparison was explored during the visiting fellowships to Dr Andrew Czeizel of Charlotte Ferencz and Dr Francine Lys. Data from three Hungarian studies, one USA and one Belgian study are presented here for selected CCVMs. Differential perinatal and diagnostic circumstances which lead to possible causes of bias involve four main domains: study population, ascertainment of cases, categorization of CCVMs and diagnostic definitions. Unique features are highlighted as a descriptive framework which will promote the comparability of epidemiologic data from various regions.

INTRODUCTION

Congenital cardiovascular malformations (CCVMs) constitute a problem of major concern in all industrialized countries. Vital records in Hungary serve to illustrate their importance. As the infant mortality rate has dramatically decreased during the past decades, the proportion of deaths due to congenital anomalies (CAs) and within the latter category, due to CCVMs has been increasing (Table I). In 1985, CCVM caused 12 times as many infants deaths as all infectious diseases combined.

Earlier reported birth prevalences of CCVMs varied from 2.03 to 18.5 per 1000 births /1,2,3/ raising questions about the reasons of such differences. Since then reported comparative

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studies have failed to take into account specific circumstances which may have led to these deviations /4,5/. The feasibility of meaningful intercountry comparisons was explored during the visiting fellowships to Dr. A. Czeizel of Dr. C. Ferencz and Dr. F. Lys as each of us is concerned with the magnitude of the problem of CCVMs in our respective study areas in Hungary, USA and Belgium.

This paper presents comparative data and discusses population and methodological differences which may affect the reported birth prevalence of CCVMs.

MATERIALS AND METHODS

a.) In Hungary the results of three previous studies are summarized.

i.) The Hungarian Congenital Malformation Registry (HCMR) has operated since 1970 with multiple sources of ascertainment /6/. All deliveries take place in hospitals, malformed babies are treated in pediatric clinics and the autopsy of all dead infants is obligatory. The notification of CAs from birth till the age of one year is mandatory and it is exclusive task of physicians. Continuous checking of notified diagnoses and evaluation of lethal, major and mild CAs are major functions of the HCMR. Minor anomalies are excluded.

ii.) Budapest study: an ad hoc epidemiologic study was organized to determine the birth prevalence of CCVMs among 52,569 total and 51,956 livebirths of Budapest residents in 1963-1965. The multiple sources of ascertainment included records of all pathologic and pediatric cardiologic institutions as well as preschool examinations of these birth cohorts. All CCVMs were verified by pediatric cardiologists or by autopsy reports /7/.

iii.) Szolnok study: in this "optimal approach" study an active search for cases of CCVMs was performed utilizing the alphabetic list of all liveborn children (N=5,978) in Szolnok county, 1963-1965 /8/. A single cardiologist succeeded in ascertaining the cardiac diagnosis in 5,644 children (94.4 %). CCVMs found were verified by pediatric cardiologists or by autopsy.

b.) The Baltimore-Washington Infant Study (BWIS) is a case-control investigation in a defined area which is ongoing since 1981 and includes the State of Maryland, Washington, D.C. and adjacent counties of Virginia, USA. Medical, sociodemographic, genetic and environmental exposure data on families of infants with CCVMs are compared to equally collected information on controls. Among the 90,000 annual births, cases with confirmed diagnoses are identified through multiple sources, including files of all pediatric cardiology centers, pathology departments

TABLE I

Infant deaths in Hungary

Year	Livebirths	Infant deaths		Cause-specific infant deaths						
				Infectious diseases		Congenital anomalies		Cardiovascular malformations		
		N	‰	N	%	N	%	N	%	/%/+
1960	146,461	6,976	47.6	173	2.5	916	13.1	334	4.8	36.5
1965	133,009	5,166	38.8	67	1.3	915	17.7	381	7.4	41.6
1970	151,819	5,449	35.9	283++	5.2	930	17.1	353	6.5	38.0
1975	194,240	6,380	32.8	233++	3.7	1,113	17.4	502	7.8	45.1
1980	148,673	3,443	23.2	35++	1.0	719	20.9	284	7.4	39.5
1985	130,200	2,651	20.4	19++	0.7	575	21.7	224	8.4	39.0

+ within infant deaths due to CAs

++includes viral hepatitis and tuberculosis, previously categorized elsewhere

TABLE II

Diagnosis -specific live birth

ICD Code	CCVM group	HCMR (Isolated + complex) 1970-1982 N	‰	1983-1986 N	‰	Ad hoc Budapest Isolated + complex N	‰
745.0	Common truncus	89	0.04	18	0.04	9	0.17
745.1	Transposition of great vessels	259	0.12	92	0.18	15	0.29
745.2	Tetralogy of Fallot	257	0.12	48	0.09	29	0.56
745.3 745.4	Ventricular septal defect	2,463	1.16	1,053	2.03	73	1.41
745.4	Atrial septal defect, type II.	618	0.29	203	0.40	39	0.75
745.6	Endocardial cushion defect	63	0.03	16	0.03	0	-
746.1-2 746.5-6	Tricuspid and mitral defects	42	0.02	14	0.03	2	0.04
746.3-4	Aortic stenosis etc.	282	0.13	103	0.20	28	0.54
746.7	Hypoplastic left heart	48	0.02	20	0.04	4	0.08
746.9	Complex CCM	1,008	0.47	365	0.71	11	0.21
747.0	Patent ductus arteriosus	477	0.22	172	0.34	39	0.75
747.1	Coarctation of aorta	132	0.06	37	0.07	11	0.21
746.0 747.3	Pulmonary stenosis	238	0.11	126	0.25	15	0.29
746.8 747.7-8	Other CCVMs	211	0.10	50	0.10	6	0.12
747.9	Unspecified CCVMs	2,730	1.29	267	0.52	7	0.13
	Total	8,917	4.19	2,566	5.02	288	5.55
	Live birth			511,021			

+ All case were affected by Down syndrome

++ Three further cases were transferred to other CCVM group

prevalence of CCVMs in Hungary

epidemiologic study 1963-65				Active search in Szolnok county 1963-65					
Multiple		Total		Isolated+complex		Multiple		Total	
N	‰	N	‰	N	‰	N	‰	N	‰
5	0.10	14	0.27	2	0.35	0	-	2	0.35
1	0.02	16	0.31	3	0.53	0	-	3	0.53
3	0.06	32	0.62	3	0.53	0	-	3	0.53
24	0.46	97	1.87	11	1.95	0	-	11	1.95
9	0.17	48	0.92	5	0.89	0	-	5	0.80
20	0.38	20+	0.38	1	0.18	2	0.35	3	0.53
1	0.02	3++	0.06	1	0.18	0	-	1	0.18
6	0.12	34	0.65	8	1.42	0	-	8	1.42
0	-	4	0.08	0	-	0	-	0	-
0	-	11	0.21	6	1.06	2	0.35	8	1.42
6	0.12	45	0.87	8	1.42	1	0.18	9	1.59
4	0.08	15	0.29	3	0.53	0	-	3	0.53
0	-	15	0.29	6	1.06	0	-	6	1.06
3	0.06	9	0.17	3	0.53	1	0.18	4	0.71
1	0.02	8	0.15	0	-	1	0.18	1	0.18
83	1.	371	7.14	60	10.6	7	1.24	67	11.87
		51,956						5,644	

as well as vital records; controls chosen by computer algorithm are representative of the birth cohort. Prevalence at livebirth data for the years 1981-1982 have been reported /4/.

c.) The Hainaut Registry of Congenital Anomalies (HRCA) has been operating since 1979 and participates in the EUROCAT Program of the European Economic Community for birth defects surveillance /9/. The study area includes the south of Hainaut province and the city of La-Louviere in Belgium. The total resident population in the study area is approximately 762,000. The total number of births is about 8,000 per year. The registration of CAs is based on multiple sources of ascertainment and includes notification from obstetricians and pediatricians and active reviews of relevant files in the participating hospitals, as well as files of the pediatric specialty units in the University Hospitals, Brussels. In the year 1986, a collaborative project was started in several EUROCAT centres including Hainaut /10/ which records cases affected by CCVM up to the age of one year. Data presented here were collected in 1986-1987.

RESULTS

The birth prevalences of CCVMs in the Hungarian studies are summarized in Table II. The total CCVM birth prevalences per 1000 livebirths were 4.69 and 6.07 in the HCMR in 1970-1982 and 1983-1986, respectively. In the earlier Budapest cohort this rate was 6.99, while the active search study resulted in a 11.87 rate in Szolnok county during the same period. The diagnosis-specific rates are displayed for two time periods of the HCMR and for the two regional studies which separated isolated, complex (more than one CCVM) and multiple (CCVM associated with non-cardiac CAs) categories.

Comparison of diagnosis-specific rates of the Hungarian, USA and Belgium studies is shown in Table III. (The dataset of the HCMR with considerable underascertainment in this group of CAs is excluded from further analysis). The livebirth prevalences vary widely with considerable differences in the major diagnostic groups of CCVMs. Some of the variability may obviously be expected from the relatively small number of cases in each study, however, each study population was derived from a fairly large livebirth cohort. Despite the wide range of study years, population size and methods involved in each study, narrow ranges of rates are seen in CCVM groups which are

TABLE III

Comparative diagnosis-specific live birth prevalence of CCVM/1000 in the Hungarian, Baltimore-Washington (BWIS) USA and Hainaut Belgium studies.

CCVM	Budapest Hungary 1963-1965 N = 371	Szolnok Hungary 1963-1965 N = 67	BWIS USA 1981-1982 N = 664	HAINAUT EUROCAT 1986-1987 N = 132	Range	Ratio Max/Min
Common truncus	0.27	0.35	0.56	0.12	0.12-0.56	4.7
Transposition of great vessels	0.31	0.53	0.21	0.30	0.21-0.53	2.5
Tetralogy of Fallot	0.62	0.53	0.26	0.53	0.26-0.62	2.4
Ventricular septal defect	1.87	1.95	0.86	3.14	0.86-3.14	3.7
Atrial septal defect type II.	0.92	0.89	0.32	1.07	0.32-1.07	3.3
Endocardial cushion defect	0.38	0.53	0.36	0.29	0.29-0.53	1.8
Congenital aortic stenosis	0.65	1.42	0.11	0.11	0.11-1.42	12.9
Hypoplastic left heart	0.08	/0.00/	0.27	0.24	0.08-0.27	3.4
Patent ductus arteriosus	0.87	1.59	0.09	0.06	0.06-1.59	26.5
Coarctation of aorta	0.29	0.53	0.24	0.42	0.24-0.53	2.2
Congenital pulmonary stenosis	0.29	0.71	0.19	0.53	0.19-0.71	3.7
Other CCVMs	0.54	2.84	0.23	-	-	
Total	7.14	11.87	3.70	7.48	3.70-11.87	3.2
Livebirths	51,956	5,644	179,697		-	-

easily recognizable at or soon after birth: tetralogy of Fallot, transposition of the great arteries and endocardial cushion defects, as well as in coarctation of aorta, an exception, which may confirm the rule. The widest ranges of prevalence rates are seen for patent ductus arteriosus and congenital aortic stenosis, both of which were in excess in Hungary. In both Hungarian studies the diagnosis of ductus patency required its presence after 21 days of life in newborns over 2500 g or after three months of life in newborns under 2500 g or in autopsied infants a ductus diameter greater than that of the pulmonary artery. The other two studies excluded PDA in premature infants. While these definitions are not exactly the same, the diagnostic restrictions alone cannot explain the differences observed. With respect to aortic stenosis one might consider overascertainment due to the inclusion of clinical diagnosis in Hungary. Other diagnosis specific variations do not show such a proportionate difference of maximal and minimal values.

DISCUSSION

Recognizing the wide variations in the birth prevalence of various types of CCVM one must ask whether the differences are <u>real</u>, that is they indicate true differences in etiologic factors, whether they represent random variations of relatively rare conditions or whether they are due to population and methodologic differences? Detailed attention was therefore given to the definition of possible sources of bias in the study of CAs in today's health care environment. It was found that the valid assessment of reproductive outcome events is influenced by a unique set of factors which relate to perinatal practices, neonatal management and, in the case of CCVM, to specific applications of modern diagnostic technologies. Major factors relevant to CCVM prevalence estimates fall into 4 domains (Table IV).

<u>I. Study population</u>

Population size may inversely affect case finding and

TABLE IV

Factors which affect birth prevalence studies of congenital cardiovascular malformations

Study population	Ascertainment	Categorization	Diagnostic definition
Population size	Health care system	Structure: anatomic and morphogenetic	Inclusion criteria
Birth status	Home deliveries	Function: physiologic	Secular changes in diagnostic definition
Live born, still born	Primary infant care	Mechanism: cellular, biochemical and biophysical	Core definition for epidemiologic case groups
Fetal diagnosis	Infant mortality		
Pregnancy termination	Reporting of CA		
Age window diagnosis	Obligatory, voluntary		
	Record sources		

diagnostic precision and for CCVM this means the uniform availability of specialty services in pediatric cardiology centers to all population subsets and the comparability of their methodologies. Greatest accuracy, achieved in relatively small regional populations, may yield too few cases of certain diagnosis for independent studies. Thus for each specific study purpose there may be an optimal population size.

Birth status

Vital statistics usually include information on live-and stillbirths. The latter are of great importance in etiologic and genetic studies but satisfactory diagnostic information is rarely available. Although stillbirths constitute only a small proportion (< 1 %) of the total birth cohort, this proportion is much greater among malformed infants and is selectively increased in certain diagnostic categories (e.g. Ebstein's disease).

Among livebirths the final information on CAs must be obtained from clinical sources as well as necropsy data to assure full ascertainment of all cases. In Hungary necropsy is compulsory for liveborn infants who died in the first year. This unique country practice is favourable for case finding but there is considerable variation in the interest and expertise of prosectors /11/.

Prenatal evaluation and consequent termination of affected pregnancies has been shown to have an increasing effect on the birth prevalence of neural tube defects /12/ and will, in time, also affect CCVM rates /13/. The maternal age limit for recommended prenatal studies varies by country (Hungary: over 38 yrs, Belgium: over 37 yrs, USA over 35 yrs) so that a differential effect may result as the maternal risk rises with each additional year. In each country urban-rural, sociodemographic and religious differences will also differentially affect the use of prenatal services and the consequent decisions.

Age window of diagnosis

Population studies have appropriately defined the birth cohort in time and place, however, great variation exists in

the postnatal period during which the child is "at risk" of recognition of the index malformation.

In the two Hungarian studies /7,8/ the period of diagnosis of CCVMs extended into the childhood years, similar to that reported from the Collaborative Perinatal Program /2/. However, in the New England Regional Infant Cardiac Program /1/, the BWIS /4/, and in the EUROCAT Hainaut Registry /9/ case recognition concludes on the infant's first birthday. This "diagnostic time window" will exclude certain CCVMs which are consistent with normal neonatal development and few clinical signs (e.g. atrial septal defect, mild coarctation of the aorta). In contrast, comparability is likely to be greater for malformations, such as transposition of the great arteries, in which neonatal symptomatology is prominent.

II. Ascertainment

Health Care System

Characteristics of the health care system will have a profound effect on case recognition. Countries where home births constitute more than a minimal proportion of total deliveries will suffer an unrecognizable loss of infants with severe CA and especially CCVM.

Even in industrialized countries an elevated infant mortality rate in specific population segments may be associated with unrecognized CCVM among infant deaths misclassified to infectious causes /14/.

Ascertainment bias will depend on the skill, experience and referral practices of primary obstetric and pediatric caretakers. Trained midwives and general practitioners may be less aware of the possibility of CCVM than pediatricians, while the experienced pediatricians will themselves diagnose, observe and follow infants with mild CCVM without early specialty referral.

Reporting of congenital anomalies

Regional and national birth defects registries favour the enrollment of visible CAs such as neural tube defects and facial clefts, while CCVM as the primary diagnosis is rarely included /15/. The HCMR which requires obligatory notifications of all types of CAs from all practice settings is favourable for

the enrollment of CCVM. However, the variability of reporting encountered in voluntary notification systems still exists and depends upon physician, patient and societal interest in the specific disorder.

In the HCMR the consciencious search of multiple information sources establishes the "best available" diagnosis utilizing discharge summaries, necropsy reports and, when necessary, patient recall for medical evaluation. This latter procedure is important for genetic counselling, but is not feasible for epidemiologic studies in which equivalent information must be obtained in cases and in controls.

The association of CCVM with non cardiac CA will lead to a differentially recognized CCVM population: on the one hand there may be little clinical or pathologic interest in the detailed evaluation of lethal disorders, such as anencephaly, or trisomy 13 or 18, but in other disorders such as Noonan and Down syndromes there may be enhanced awareness of possible CCVMs.

III. Categorization

Although CCVMs are structural abnormalities of the heart and intrathoracic vessels, it is difficult to classify, group and code these malformations.

Various systems of classification of CCVM have been recommended /16,20/ and the stated importance of each of those systems gives evidence of a lack of consensus and therefore, unsatisfactory comparisons between the different coding sets.

Categorization of CCVM according to etiology or pathogenesis may be the desirable objective but as few etiologic factors or pathogenetic mechanisms are known such groupings are not yet possible.

At this time CCVM may be categorized into anatomic, physiologic (clinical) or embryologic developmental groupings and each method serves a specific purpose.

An anatomic description of the abnormal heart provides the diagnosis for the clinicians and pathologists. Phenotypic variability is very great and grouping of similar lesions is necessary. A precise morphogenetic evaluation may be of clinical significance as detailed anatomic studies continue to

uncover information which guides the surgeons in on-site decision making during intracardiac repair /21,22/. Morphogenetic studies define the heterogeneity of simple lesions, such as atrial and ventricular septal defects by variations in their location and histopathology /23/.

When a CCVM consists of several abnormal components the term "complex CCVM" was used in the Hungarian studies /7,8/ and an attempt was made to separate groupings which form an entity, (e.g. tetralogy of Fallot) from those which may represent associated or coincidental lesions /24/. As the question of causation remains prominent, one wishes to distinguish a "leading" abnormality and subsequently arising components. In this sense some complex malformations have been interpreted in different ways: in the hierarchical classification of Fyler /1/, used also in the EUROCAT Hainaut Registry /9/, the hypoplastic left heart syndrome is placed ahead of transposition of the great arteries, while the BWIS places all looping and conotruncal abnormalities ahead of obstructive lesions /25/.

The clinical care of patients with CCVM requires a physiologic classification of the circulatory consequences of anatomic alterations. Abbott /26/ provided the fundamental framework of 3 major groupings:

- the "acyanotic group": abnormalities in which the cardiac septa are intact,
- the "cyanose tardive" group: septation defects leading to pulmonary overcirculation, but possible late shunt reversal,
- "cyanotic group": major structural alterations of the heart itself which result in systemic hypoxia by pulmonic outflow obstruction or by transposed great vessels.

A classification by embryonic mechanism has been proposed by Clark /27/ which distinguishes hemodynamic (flow), as well as tissue and cellular abnormalities (mesenchymal migration, matrix and cell death). However present knowledge is inadequate to appropriately define the cascade of genetic, biochemical and biophysical forces which mould cardiac development.

IV. Diagnostic definitions

The uncertainties of classification affect the definitions

of CCVM groups for epidemiologic studies.

Inclusion criteria must define CCVM by diagnostic certainty according to the confirmatory examinations used (cardiac catheterization, surgery, autopsy and in recent years, echocardiography)/28,29/.

Comparable "diagnostic windows" are difficult to establish. The reported increase in VSD prevalence /30/ was in several pediatric cardiology studies subsequently shown to be due to the development and increasing use of new diagnostic technologies /28,31,32/.

Such secular changes in diagnostic definitions reflect the continuing advances in Pediatric Cardiology. Improvements in invasive and non-invasive techniques increase the sophistication of therapeutic interventions and the understanding of morphologic changes and thus some "old" cardiac diagnoses (e.g. Lutembacher's disease) have become obsolete, while newly defined entities (e.g. atrioventricular discordance) have been added. However, institutions and pathologists will not uniformly identify these complicated anomalies.

For the purpose of epidemiologic use it is necessary to maintain a simple nomenclature and to define CCVM subgroups without major morphologic variations which might distort the findings and hence the interstudy comparisons.

Generally accepted core diagnoses and possible variations in inclusion criteria are listed in Table V. The definitions are based on the work of Becker and Anderson /23/ who advocate the recognition of three features: morphology of the chambers, their connections and their relationships. In the majority of cases these features will be concordant (diagnoses 1-11), while TGA (diagnosis 12) and variants, noted under "allocation problems" represent discordant relationships.

It is noted that unequivocal diagnostic boundaries cannot easily be established. Thus there remains a major research methodologic problem for comparative purposes. A "common language" must identify a few and well defined diagnoses with a single code for each and every baby.

TABLE V

Major Cardiovascular Malformations (After Becker and Anderson /23/)

Diagnosis (Abbreviation)	Core definition	Allocation problems	
1. Atrial septal defect (ASD)	Defect in atrial inlet (sinus venosus), flap of fossa ovalis or atrial outlet (septum primum)	Outlet (primum) defects may be grouped here or with endocardial cushion (atrio-ventricular) defects	Fossa ovalis defects are due to perforation, deficiency or absence of the flap valve which is derived from the septum primum, Becker and Anderson disapprove of the term "secundum" defects
2. Ventricular septal defect (VSD)	Defect of membranous, muscular, outflow (subpulmonic) or atrio-ventricular part of ventricular septum	Atrio-ventricular defects may be grouped with endocardial cushion defects; subpulmonic defects with conotruncal abnormalities	Usually a single epidemiologic group, VSD is obviously heterogenous
3. Endocardial cushion defects (ECD)	Deficiency of atrio-ventricular septum with abnormal atrioventricular valves (common valve, "cleft" mitral valve)	Complete atrio ventricular canal may be categorized separately from atrial and ventricular defects (see above)	Entire spectrum of defects occurs in human trisomy 21.
4. Patent ductus arteriosus (PDA)	Postnatal persistence of ductal patency	Distiction of possible delayed ductal closure may vary in different studies	Persistent patency in premature infant and in full term newborn may be considered a "normal" finding

5. Coarctation of aorta (Coarc.)	Discrete obstruction or tubular hypoplasia of aortic arch	Atresia (interruption) of aortic arch may be included in or excluded from this group	
6. Aortic stenosis (AS)	Obstruction of left ventricular outflow at the aortic valve	Subaortic or supra aortic valve. Obstructions may be included in or excluded from this group.	Etiologically each type is likely to be distinct
7. Hypoplastic left ventricle (HLV)	Small chamber with mitral and/or aortic atresia	Combinations of severe left sided obstructive lesions may be described together as "hypoplastic left heart syndrome" (HLHS)	Variations occur in severity of obstruction and presence of VSD
8. Hypoplastic right ventricle (HRV)	Small chamber with pulmonary atresia	May be considered a severe form of pulmonic stenosis with intact ventricular septum	
9. Anomalous pulmonary venous drainage (APVB)	Intrapulmonary veins maintain connection with splanchnic plexus and drain into supra- or infra cardiac systemic veins	Definition varies of "total" anomalous drainage of pulmonary veins bilaterally or unilaterally (one whole lung) and "partial" (part of one lung) drainage	Usually a single epidemiology group, though probably heterogeneous
10. Truncus arteriosus (TA)	Single arterial trunk supplies systemic, pulmonary and coronary circulations	Pulmonary arterial atresia (Type IV truncus) with absent intrapericardial pulmonary trunk usually grouped with tetralogy of Fallot	

Table V. cont.

11. Tetralogy of Fallot (TF)	Anterior deviation of infundibular septum with stenosis, ventricular septal defect and overriding aorta	Ventriculo-arterial discordance with aorta from right ventricle is grouped as "double outlet right ventricle" with PS. Pulmonary atresia with VSD may be included
12. Transposition of great arteries (TGA)	Aorta arising from right (venous) ventricle, pulmonary artery from left (pulmonary venous) ventricle; also defined as ventriculo-arterial discordance with atrio ventricular concordance	Inclusion of "corrected" l-TGA (atrio ventricular discordance), or of double outlet right ventricle and "portial" transposition

CONCLUSION

Birth prevalence data of CA have been extensively monitored but comparative evaluations of CCVM have only recently demanded increased attention. The true significance of reported variations in CCVM livebirth prevalence was questioned on the basis of possible methodologic bias. This review discusses in detail the unique set of pre-, peri- and postnatal factors which may lead to dissimilarities in regional data sets and hence render invalid some comparative conclusions.

There is an obvious need to work toward increasingly uniform evaluation and reporting. It is suggested that every report should provide details on population, ascertainment, categorization and diagnostic methodologies so that data comparability can be assessed.

In addition, there is a need to define through expert efforts and acceptable simple nomenclature of major types of CCVMs with periodic updates according to new information. Since extensive international collaboration already exists with regard to morphogenetic studies of cardiovascular development as well as with regard to clinical management, a corollary effort could enhance epidemiologic methodologies and work toward a better understanding of etiologic risk factors in different populations.

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