International variation in reported livebirth prevalence rates of Down syndrome, adjusted for maternal age

Andrew D Carothers, Christina A Hecht, Ernest B Hook

Abstract

Reported livebirth prevalence of Down syndrome (DS) may be affected by the maternal age distribution of the population, completeness of ascertainment, accuracy of diagnosis, extent of selective prenatal termination of affected pregnancies, and as yet unidentified genetic and environmental factors. To search for evidence of the latter, we reviewed all published reports in which it was possible to adjust both for effects of maternal age and for selective termination (where relevant).

We constructed indices that allowed direct comparisons of prevalence rates after standardising for maternal age. Reference rates were derived from studies previously identified as having near complete ascertainment. An index value significantly different from 1 may result from random fluctuations, as well as from variations in the factors listed above. We found 49 population groups for which an index could be calculated. Methodological descriptions suggested that low values could often be attributed to under-ascertainment. A possible exception concerned African-American groups, though even among these most acceptable studies were compatible with an index value of 1. As we have reported elsewhere, there was also a suggestive increase in rates among US residents of Mexican or Central American origin. Nevertheless, our results suggest that "real" variation between population groups reported to date probably amounts to no more than ±25%. However, reliable data in many human populations are lacking including, surprisingly, some jurisdictions with relatively advanced health care systems. We suggest that future reports of DS livebirth prevalence should routinely present data that allow calculation of an index standardised for maternal age and adjusted for elective prenatal terminations.

(*J Med Genet* 1999;**36**:386–393)

Keywords: Down syndrome; prenatal diagnosis; maternal age standardisation; epidemiology

MRC Human Genetics Unit, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK
A D Carothers

School of Public Health, University of California, Berkeley, CA, USA
C A Hecht
E B Hook

Department of Pediatrics, University of California School of Medicine, San Francisco, CA, USA
E B Hook

Correspondence to:
Dr Carothers.

Received 2 July 1998
Revised version accepted for publication 14 September 1998

Much information has been gathered world wide on the association of Down syndrome (DS) livebirth prevalence with maternal age.[1] This has assumed increasing importance with the advent of prenatal screening, relying as it does on accurate maternal age specific rates to determine a mother's risk of a DS livebirth.[2 3] In spite of continuing searches for temporal, racial, geographical, and environmental differences in rates, the only such preconceptional predisposing factors to have been identified unambiguously, apart from maternal age itself, are the presence of a chromosome 21 translocation or of gonadal mosaicism for trisomy 21, and the existence of previously affected offspring. Increased rates have been reported in Jews of non-European origin in Israel,[4] and in two different studies of Hispanics in California.[5–7] Study of DS rates is complicated by the need to adjust for various potential sources of bias (see below).

In particular, the strength of the maternal age effect, involving a near 100-fold increase in risk between maternal ages of 15 and 45 years, makes it essential at least to adjust for differences in the maternal age distribution before making comparisons between populations.

One method for doing this is to construct maternal age adjusted indices, analogous to standardised rates used for comparing mortality and morbidity.[8] These allow comparisons of prevalence between areas with widely differing maternal age related fertility patterns. We review here all published studies on DS rates world wide in which sufficient data are presented to allow a maternal age adjusted index to be derived. Our aim has been to derive an upper limit on the "real" variation between studied populations in age adjusted rates, rather than to obtain precise estimates for devising prenatal screening schedules applicable to specific populations. The latter aim, though necessary and worthwhile, cannot be done with currently available published data except for certain North American and European populations.[1 9] Besides maternal age effects and "real" underlying variations, other factors that must be borne in mind when comparing rates include the following.

Completeness of ascertainment. Ideally, rates should be determined from cytogenetic examination of all or a representative sample of livebirths in a particular setting. Also, statistical precision requires a sample of well over 100 000 livebirths, much greater than currently available from all newborn cytogenetic studies combined, let alone those on which maternal age data are available. Systematic clinical examination with cytogenetic investigation of suspected cases may be almost as effective in achieving complete ascertainment, but,

here too insufficient numbers are available from any single study. The great majority of studies, especially those involving over 100 000 livebirths, have abstracted diagnoses from two or more sources of already existing information, such as hospital and vital records, civil registers, reports from laboratories and so forth. These constitute overlapping incomplete lists, which can sometimes be used to estimate incompleteness of ascertainment.[10] To date, only studies using birth certificates have attempted this.[11 12] However, the completeness of reporting in these birth certificate studies has been so low (35 to 40%) that use of this approach necessarily introduces a large uncertainty into the derived rates.

Nevertheless, rates obtained in this manner, imperfect though the adjustment may be, have been appreciably higher than in many studies which ascertained a greater proportion of cases but in which an adjustment for completeness of reporting was not possible.[13] Only one study provides data making it possible to infer that ascertainment has been essentially complete.[14]

Other studies, excluding those limited to birth certificates, are likely to underestimate rates because an adjustment for incomplete ascertainment cannot be made.

Accuracy of diagnosis. Unless all clinical diagnoses are confirmed cytogenetically, some non-DS cases may be included in error.

Even presumably astute clinicians may on rare occasions make a diagnosis later contradicted by cytogenetic study.[15] Birth certificate reports abstracted by clerks from hospital records in the USA include 5 to 10% false positives.[16] About half of these are readily detectable clerical errors in transcribing or coding diagnoses. The remainder result from mistaken medical judgements before newborn discharge from the hospital. These may well have been altered subsequently but not corrected on the original files. From these studies, a figure of 5 to 10% appears to be a plausible upper limit for the level of false positive diagnoses in the absence of cytogenetic confirmation.

The figure is unlikely to exceed 2-3% for studies using hospital newborn discharge records. In general, where diagnostic information is incomplete, any bias from false positive diagnoses is likely to be more than outweighed by underascertainment of cases.

Extent of prenatal screening. In many developed countries, prenatal diagnosis and selective termination of DS were introduced in the mid-1970s, and became widespread in the early 1980s. In some jurisdictions this has had a significant impact on observed livebirth prevalence rates.[17 18] Adjustment must then be made for the numbers of electively terminated fetuses that would naturally have survived to birth.[19] This requires that the numbers of prenatal terminations be reported separately from those of affected births.

Definition of base population. Ideally, rates should apply to the entire population, or to well defined subgroups, living within a specified geographical area. In practice, many studies are based on observations of births in maternity hospitals. In parts of the world where only a minority of mothers give birth in hospital, such rates may be biased by the very factors that determine where a baby is born. Most of these, such as social class, educational background, proximity, or convenience of transport etc, are not known to be associated with DS rates and are therefore probably of little consequence. However, an obvious potential source of overascertainment arises if mothers with complicated pregnancies are preferentially referred to centres of excellence in obstetrics.

Accuracy of reported ages and other demographic information. Accurate reporting of ages is required for the mothers both of affected cases and of unaffected births in the general population. Because of the relatively small numbers of births at the lower and upper extremes of maternal age, inaccuracies may lead to significant biases in these age groups.[20] Also, incorrect reporting of the place of birth may lead to cases being wrongly included in or excluded from the study population.

Methods

AGE ADJUSTED INDICES

Carothers[8] reviewed three different methods for constructing maternal age adjusted indices and concluded that the most suitable for congenital abnormality rates involved indirect standardisation, analogous to the standardised mortality ratio (SMR). This index, referred to as BIISMA ("Birth Index Indirectly Standardised for Maternal Age"), compares the total number of DS births with the number expected if the maternal age specific rates derived from a reference population are applied to the study population. It is given by:

$$BIISMA = \frac{b}{\Sigma R_i n_i}$$

where b is the number of DS births, and n_i the total number of births at maternal age i, in the study population and R_i is the reference rate at maternal age i.

Carothers[8] pointed out that, under the assumption that the maternal age specific rates in the study population are a fixed multiple of the reference rates, BIISMA has the lowest standard error of the three indices considered, and is the easiest to adjust for underascertainment and for the effects of prenatal diagnosis. As can be seen from the formula, it requires only the maternal age distribution of all births, and the total number of DS births, in the study population. It does of course depend on the reference rates R_i, but this is of little relevance when comparing indices among themselves. In the small number of studies in which the maternal age distribution of all livebirths in the study population was not given, an alternative index, denoted BINSMA ("Birth Index Inversely Standardised for Maternal Age"), was used instead. It is given by:

$$BINSMA = \frac{1}{n}\Sigma\frac{b_i}{R_i}$$

where n is the total number of births, and b_i the number of DS births at maternal age i, in the study population.

Carothers[8] noted that, where sufficient data were available to compute both indices, they had closely similar values. We confine analysis to livebirths because of generally inadequate data on, and ambiguous definition of, stillbirths.[15]

DATA SOURCES

From a search of the Science Citation Index and of the reference lists of earlier studies on DS prevalence, we have included, to the best of our knowledge, all published studies in which there were sufficient data to compute either index, and for which at least 10 000 total births were reported. Smaller studies would have been unlikely to include more than about 15 DS cases, and would have given estimates with such large standard errors as to be of little use.

The reference rates R_i were taken from the "Derived rates" column of table II of the paper by Hecht and Hook,[1] based on studies judged to have "near complete" ascertainment. Where indices were computed by five year maternal age groups, population data from England and Wales 1980 were used to apportion livebirths within each five year age group so as to determine the appropriate risk.[21] When combined with the data from Hecht and Hook,[1] these gave rate estimates for the age groups 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, and 45-49 years of, respectively, 0.60, 0.71, 0.91, 1.54, 4.24, 16.22, and 53.3 per 1000 livebirths. These estimates are little affected by the choice of reference population since they depend only on the relative numbers of livebirths within each five year age group. The relevant formulae, and the conditions under which they produce unbiased estimates, are given by Carothers.[8]

The main category of study included here comprises those that made use of multiple sources of ascertainment or comprehensive cytogenetic registers or both in an attempt to identify all DS cases born, or diagnosed prenatally where relevant, in a well defined population. Such studies were confined to "developed" countries having relatively reliable record keeping within the health care system. A second major category comprises those based on maternities in particular hospitals. This is the only source of relevant data from parts of the world with less developed health care systems, though it also includes some studies from Europe and North America.

In addition there were a few surveys of DS cases living in a specified area, and two reviews of diagnostic information recorded on birth certificates. Such studies are clearly vulnerable to the possibility of underascertainment, though in some cases it is possible to adjust for this at the cost of introducing greater sampling variation (see above).

Finally, there were two complete cytogenetic surveys of all consecutive births in specified hospitals.[22 23] Because these involved relatively small numbers, but otherwise used identical methods and referred to populations with a similar ethnic background, they were combined for the purpose of the present analysis. The above categorisation of studies is summarised in table 1.

STATISTICAL METHODS

Wherever possible, the indices have been computed for the age range 15-44 years. Higher and lower ages were excluded because they are often reported inaccurately (or not at all), and because the small absolute numbers of cases may have a disproportionate effect on the standard errors or biases of estimation or both. To allow for the possibility that the rates in each study population may not be the same multiple of those in the reference data at all maternal ages, we have also, where possible, computed separate indices for the age ranges 15-34 and 35-44. Where prenatal diagnosis has had a significant impact on crude livebirth prevalence rates, we adjusted the indices according to the formulae given by Carothers,[8] using a multiplier (s) of 0.7 to allow for the proportion of electively aborted fetuses that would have survived naturally to term.[19]

In some studies, the numbers of pre- and postnatal cases were not reported separately, and for these it was therefore possible to compute the index only for the 15-34 age group in which we presumed that prenatal diagnosis had a negligible effect.

The majority of published studies report maternal ages only in quinquennial age groups, and for these the five year indices were computed by the formulae given by Carothers.[8] Where single year maternal age data were available, both the one year and five year indices were calculated.

Two different classes of variation between estimated rates may be distinguished. First, there is "random" sampling variation arising from the finite size of the reported samples. Its magnitude can be estimated for each data set by standard formulae.[8] The remaining "non-random" variation consists of several components as discussed above, including the "real" variation in which we are interested.

We can derive an upper limit for the latter by jointly estimating the non-random components. Our approach has been to derive the "James-Stein" estimator for each index. A very readable account of the method is given by Efron and Morris.[24] The basic idea is to replace each index, y say, by a value, z, given by the equation $z=y-f\ (y-\bar{y})$, where $\bar{y}$ is the global mean of all the $y-$ values and f is a constant known as the "shrinkage factor".

If f is equal to zero, then the $z-$ and $y-$ values are identical. If f is 1, then the $y-$ values are replaced by the global mean. The essential feature of the James-Stein method is that the factor f is directly proportional to the sampling variation in y by the formula:

$$f = Min\left[1, \frac{(k-3)\sigma^2}{\Sigma\ (y-\bar{y})^2}\right]$$

where σ^2 is the random sampling variation of y

and k is the number of indices being estimated. Thus, if y is poorly estimated then σ^2 is large, f is close to unity, and the effect is to "shrink" y towards the global mean. Conversely, if y is accurately estimated then σ^2 is small, f is close to zero, and the effect is to leave y almost unchanged. James and Stein showed that, provided that $k>3$, this procedure leads to a set of estimates that have lower expected mean squared error than the original ones and that therefore give better estimates of their non-random variation.

Results

A total of 36 studies, covering 49 population groupings, satisfied the inclusion criteria. Approximately 35 further studies gave raw estimates of livebirth prevalence of DS, but either based on fewer than 10 000 total births or lacking sufficient information to allow adjustment for maternal age. Comparison of one year and five year indices in 17 groupings where both could be calculated showed that on average the five year index exceeded the one year index by only 0.006 (SE 0.011).

Table 1 Summary of studies included in this report. The indices listed are those based on five year maternal age groups. Unless otherwise indicated in the 'Notes' column, they are of the indirectly standardised type (BIISMA). Also listed at the foot of the table, though not analysed in the text, are four studies that had data in common with more extensive data sets listed in the upper part of the table

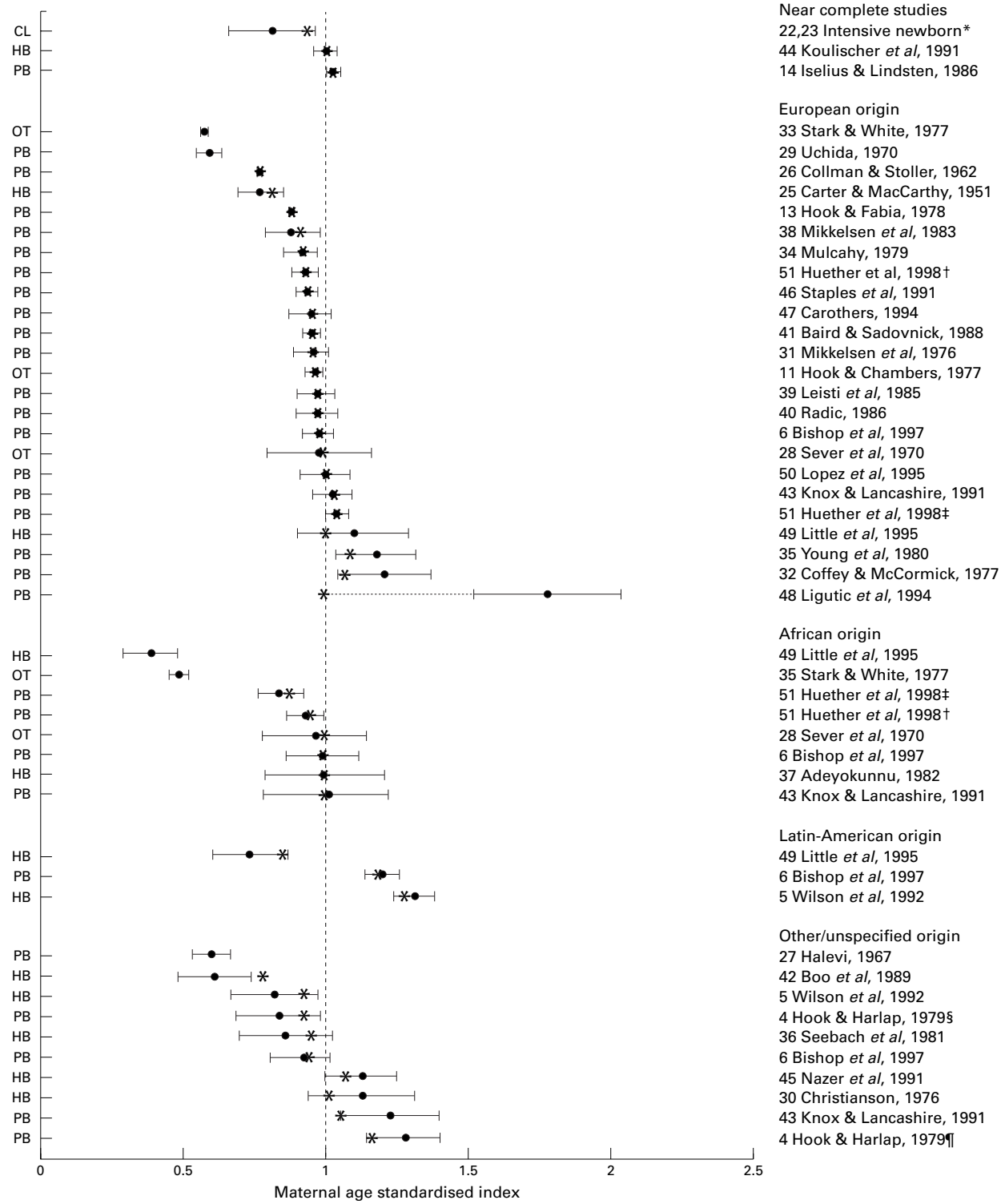
Study	*Ref*	*Location*	*Period*	*Race**	*Cat†*	*Index (SE) Mat age < 35*	*Index (SE) Mat age >= 35*	*Index (SE) All mat ages*	*J-S est‡*	*Notes§*
Carter & MacCarthy, 1951	25	London, UK	1943-1949	EU	HB	0.65 (0.11)	0.85 (0.11)	0.76 (0.08)	0.80	
Collman & Stoller, 1962	26	Victoria, Aus	1942-1957	EU	PB	0.82 (0.04)	0.71 (0.03)	0.76 (0.02)	0.76	
Halevi, 1967	27	Israel	1959-1960	JW	PB	0.63 (0.09)	0.56 (0.09)	0.59 (0.06)	-	
Sever *et al*, 1970	28	USA	1958-1965	AF	OT	0.67 (0.19)	1.41 (0.35)	0.96 (0.18)	0.98	1
Sever *et al*, 1970	28	USA	1958-1965	EU	OT	1.26 (0.27)	0.57 (0.21)	0.97 (0.18)	0.98	1
Uchida,1970	29	Manitoba	1960-1967	EU	PB			0.58 (0.04)	-	2
Jacobs *et al*, 1974	22	Edinburgh	1967-1972	EU	CL	0.84 (0.20)	0.74 (0.25)	0.80 (0.15)	0.92	3
Hamerton *et al*, 1975	23	Winnipeg	1970-1973	EU	CL					3
Christianson, 1976	30	Oakland, CA	1959-1967	MX	HB	1.06 (0.27)	1.17 (0.25)	1.12 (0.18)	1.00	
Mikkelsen *et al*, 1976	31	Copenhagen	1960-1971	EU	PB	1.01 (0.08)	0.80 (0.10)	0.94 (0.06)	0.95	
Coffey & McCormick, 1977	32	E Ireland	1974-1975	EU	PB			1.20 (0.16)	1.05	4
Hook & Chambers, 1977	11	NYS excl NYC	1963-1974	EU	OT	0.96 (0.04)	0.93 (0.05)	0.95 (0.03)	0.95	5
Stark & White, 1977	33	Lower Michigan	1950-1964	EU	OT	0.57 (0.02)	0.56 (0.02)	0.56 (0.01)	-	5
Stark & White, 1977	33	Lower Michigan	1950-1964	AF	OT	0.54 (0.05)	0.40 (0.05)	0.48 (0.03)	-	5
Hook & Fabia, 1978	13	Mass, USA	1958-1965	EU	PB	0.88 (0.04)	0.85 (0.03)	0.86 (0.03)	0.87	
Hook & Harlap, 1979	4	W Jerusalem	1964-1975	JN	PB	1.25 (0.19)	1.29 (0.17)	1.27 (0.13)	1.15	
Hook & Harlap, 1979	4	W Jerusalem	1964-1975	JE	PB	0.94 (0.21)	0.69 (0.19)	0.83 (0.14)	0.91	
Mulcahy, 1979	34	W Australia	1966-1976	EU	PB	0.84 (0.07)	1.02 (0.11)	0.90 (0.06)	0.91	
Young *et al*, 1980	35	S Wales	1968-1976	EU	PB	1.14 (0.17)	1.22 (0.24)	1.17 (0.14)	1.07	
Seebach *et al*, 1981	36	Valparaiso, Chile	1973-1977	MX	HB	0.93 (0.23)	0.77 (0.22)	0.86 (0.16)	0.94	6
Adeyokunnu, 1982	37	Ibadan, Nigeria	1972-1980	AF	HB			0.99 (0.21)	0.98	4
Mikkelsen *et al*, 1983	38	Denmark	1979-1980	EU	PB	0.86 (0.10)	1.15 (0.19)	0.88 (0.10)	0.90	4
Leisti *et al*, 1985	39	N Finland	1965-1979	EU	PB	0.94 (0.09)	0.98 (0.09)	0.96 (0.06)	0.96	
Iselius & Lindsten, 1986	14	Sweden	1968-1982	EU	PB	1.02 (0.03)	1.00 (0.04)	1.01 (0.02)	1.01	
Radic, 1986	40	E Ireland	1979-1983	EU	PB	0.97 (0.10)	0.95 (0.10)	0.96 (0.07)	0.96	
Baird & Sadovnick, 1988	41	Br Columbia	1964-1983	EU	PB	0.93 (0.04)	0.96 (0.06)	0.94 (0.03)	0.94	
Boo *et al*, 1989	42	Kuala Lumpur	1986-1987	ML	HB	0.37 (0.14)	0.86 (0.22)	0.60 (0.13)	0.77	
Knox & Lancashire, 1991	43	Birmingham, UK	1964-1984	EU	PB	1.02 (0.07)			1.01	7
Knox & Lancashire, 1991	43	Birmingham, UK	1964-1984	AI	PB	1.22 (0.17)			1.04	7
Knox & Lancashire, 1991	43	Birmingham, UK	1964-1984	AF	PB	1.00 (0.22)			0.98	7
Koulischer *et al*, 1991	44	S Belgium	1971-1990	EU	HB	0.96 (0.05)	1.05 (0.07)	0.99 (0.04)	0.99	8
Nazer *et al*, 1991	45	Chile	1977-1989	MX	HB	1.27 (0.18)	0.95 (0.16)	1.12 (0.12)	1.06	6
Staples *et al*, 1991	46	S Australia	1965-1989	EU	PB	0.93 (0.05)	0.93 (0.07)	0.93 (0.04)	0.93	
Wilson *et al*, 1992	5	Los Angeles	1974-1988	LA	HB	1.26 (0.09)	1.37 (0.12)	1.30 (0.07)	1.26	
Wilson *et al*, 1992	5	Los Angeles	1974-1988	AE	HB	0.87 (0.19)	0.71 (0.24)	0.81 (0.15)	0.91	
Carothers, 1994	47	Scotland	1989-1990	EU	PB	0.87 (0.09)	1.07 (0.14)	0.93 (0.08)	0.94	
Ligutic *et al*, 1994	48	Croatia, 3 cities	1983-1988	EU	PB	1.77 (0.26)			0.98	7
Little *et al*, 1995	49	Dallas, TX	1980-1989	AF	HB	0.37 (0.10)	0.40 (0.23)	0.38 (0.10)	-	
Little *et al*, 1995	49	Dallas, TX	1980-1989	LA	HB	0.62 (0.14)	1.17 (0.37)	0.73 (0.13)	0.84	
Little *et al*, 1995	49	Dallas, TX	1980-1989	EU	HB	0.81 (0.19)	2.32 (0.65)	1.09 (0.19)	0.99	
Lopez *et al*, 1995	50	Glasgow, UK	1980-1990	EU	PB	0.99 (0.09)			0.99	7
Bishop *et al*, 1997	6	California	1990-1991	AM	PB	0.79 (0.16)	1.00 (0.14)	0.91 (0.10)	0.93	
Bishop *et al*, 1997	6	California	1990-1991	AF	PB	0.89 (0.16)	1.14 (0.22)	0.98 (0.13)	0.98	
Bishop *et al*, 1997	6	California	1990-1991	LA	PB	1.23 (0.08)	1.13 (0.09)	1.19 (0.06)	1.17	
Bishop *et al*, 1997	6	California	1990-1991	EU	PB	0.85 (0.08)	1.09 (0.08)	0.96 (0.06)	0.97	
Huether *et al*, 1998	51	Atlanta	1970-1989	EU	PB	0.93 (0.06)	0.88 (0.08)	0.92 (0.05)	0.92	
Huether *et al*, 1998	51	Atlanta	1970-1989	AF	PB	0.96 (0.08)	0.81 (0.11)	0.92 (0.06)	0.93	9
Huether *et al*, 1998	51	SW Ohio	1970-1989	EU	PB	1.00 (0.05)	1.12 (0.08)	1.03 (0.04)	1.03	
Huether *et al*, 1998	51	SW Ohio	1970-1989	AF	PB	0.90 (0.10)	0.66 (0.13)	0.84 (0.08)	0.86	9
Hook & Lindsjo, 1978	52	Sweden	1968-1970	EU	PB	0.99 (0.06)	0.90 (0.07)	0.95 (0.05)	-	10
Trimble & Baird, 1978	53	Br Columbia	1961-1970	EU	PB	0.95 (0.06)	0.85 (0.06)	0.91 (0.04)	-	11
Huether *et al*, 1978	12	Ohio	1970-1979	EU	OT	1.07 (0.05)	1.15 (0.08)	1.09 (0.04)	-	5, 12
Unpublished	-	Sweden	1971-1982	EU	PB	1.03 (0.03)	1.04 (0.04)	1.03 (0.03)	-	13

* Key to *Race*: AE - mainly a mixture of those of African and of European origin; AF - African origin; AI - Asian (Indian subcontinental origin); AM - Asian (Mongolian origin, ie Chinese, Japanese, Korean etc); EU - European origin; JE - Jewish of European origin; JN - Jewish of non-European origin; JW - Jewish of unspecified origin; LA - Latin-American origin (Mexican or Central American); ML - Malaysian; MX - mixed.

† Key to *Cat*: HB - hospital based; PB - population based; CL - cytogenetic survey of consecutive livebirths; OT - other.

‡ James-Stein estimators based on 43 values (five excluded because of probable underascertainment - see text).

§ Key to *Notes*: (1) Original study based on data from the US Perinatal Collaborative Study of births from 1958 to 1966; the reanalysis presented here is of data made available from the Boston Collaborative Drug Surveillance Program which formed part of the original study. It excluded twin cases and those associated with rubella. (2) Largely based on survey of living cases. (3) Results from Jacobs *et al*[22] and Hamerton *et al*[23] have been combined; note that the latter study included some native Americans. (4) Maternal ages of controls not given, hence BINSMA index used. (5) Largely based on birth certificate data. (6) Racial origins not specified, but probably of mainly European descent. (7) Separate maternal age data on prenatal diagnoses not given, hence only the index for the younger maternal age group was computed. (8) Original study supplemented by additional data, as reported in Hecht and Hook.[1] (9) Populations described as "non-White", but in fact >85% Black. (10) Overlaps with Iselius and Lindsten.[14] (11) Overlaps with Baird and Sadovnick.[41] (12) Overlaps with Huether *et al.*[51] (13) Data of Iselius and Lindsten[14] after removing those of Hook and Lindsjo.[52]



PB Population based
HB Hospital based
CL Cytogenetic survey of consecutive livebirths
OT Other

* Combined data from Jacobs *et al* [22] and Hamerton *et al*.[23]
† Data from Atlanta, GA.
‡ Data from SW Ohio.
§ Jews of European origin.
¶ Jews of non-European origin.

Figure 1 Plot of maternal age standardised indices listed in table 1. Values plotted are those based on maternal ages 15-44 years, where available, and on the younger age group (15-34 years) otherwise. Intervals represent 1 SE. James-Stein estimators are represented by asterisks. "Near complete" studies, all of European origin, are those contributing to the baseline rates estimated by Hecht and Hook.[1]

Similarly, in the 40 cases where indices for both younger and older mothers could be computed, the former exceeded the latter by a mean of only 0.015 (SE 0.014). Since these differences are trivial in relation to other sources of variation, further analysis was confined to the five year indices and to the full (15-44 years) maternal age range.

Principal characteristics of the groupings, together with their five year indices, are summarised in table 1. Indices are presented graphically in fig 1.

GROUPS OF EUROPEAN ANCESTRY

Examination of table 1 and fig 1 shows two exceptionally low indices from groups with a predominantly European ancestral background. These were from the studies of Uchida,[29] which was based on a survey of living DS cases and therefore likely to have missed early neonatal deaths, and of Stark and White,[33] which missed cases not indicated on birth certificates and those not in contact with the institutions surveyed. Both were therefore likely to have been seriously underascertained. The remaining 25 indices varied from 0.76 to 1.77 with a weighted mean of 0.923 (SE 0.009).

The exceptionally high value of 1.77 from a Croation study was associated with a large standard error.[48] The James-Stein method "shrank" this value to less than 1, suggesting that it is a random outlier.

GROUPS OF AFRICAN ANCESTRY

Two indices from the groups with predominantly African (mainly West African) ancestry were exceptionally low. One was from the study of Stark and White[33] referred to above. The other, from Little *et al*,[49] is somewhat puzzling, since the indices obtained from other ethnic groups in the same study were more closely comparable with those obtained elsewhere. Thus we cannot rule out the possibility of a genuinely low rate among Afro-Americans within the community served by the hospitals included in this study. Nevertheless, the index is so far out of line with those obtained from other groups of African ancestry that we are inclined to suspect underascertainment. Excluding these two studies, the range of values obtained from the remaining six groups of African ancestry was from 0.84 to 1.00 with a weighted mean of 0.911 (SE 0.043).

GROUPS OF LATIN-AMERICAN ORIGIN

There were three indices from recent migrant groups living in the USA of central American, mainly Mexican, origin with a range from 0.73 to 1.30 and a weighted mean of 1.180 (SE 0.043). Because the mean is significantly greater than 1, whereas any biases would be expected to be in the direction of lower ascertainment in these groups, this may be considered evidence that they have a higher real rate of DS, as we have discussed elsewhere.[7]

OTHER GROUPS

Indices were obtained from 10 other groups that could not be categorised as above, and in which there were individually insufficient data to enable us to make useful comparisons. One high value from a study of Israeli Jews of non-European origin may indicate a higher real rate in this group, as noted by the original authors.[4] On the other hand, the lowest rate came from Israeli Jews of heterogeneous origin. However, this was an early study based on notifications of congenital abnormalities, and is therefore likely to have been underascertained.[27]

"REAL" VARIATION BETWEEN GROUPS

Excluding the five studies noted above for which there were grounds to suspect serious underascertainment, the mean James-Stein estimator of the remaining 43 values was 0.964 (SD 0.094) with a range from 0.76 to 1.26. The mean values for groups of European, African, Latin-American, and other ancestry were respectively 0.95 (SD 0.07), 0.95 (SD 0.05), 1.09 (SD 0.22), and 0.97 (SD 0.11).

Discussion

If it is legitimate to ignore the five outliers mentioned above, then we can conclude that underlying variation between groups studied to date is no greater than ±25% around the global mean. Furthermore, in view of the many sources of ascertainment variation to which most of these studies are subject, the totality of published data could well be consistent with no real variation at all, and might explain why a search for environmental factors associated with Down syndrome has been so unproductive. Nevertheless, the high rate among those of Mexican or Central American origin in the USA is probably real, and the possibility cannot be excluded of consistent differences in other groups not yet studied extensively.

In fact, the number of ethnic groupings for which there are useful data is rather small. It is not surprising, in view of other health related priorities in the less developed world, that we were able to find little or no usable data from the Indian subcontinent, China, Africa, and Latin America. However, we were also not able to identify any studies satisfying our criteria from several areas with advanced health care systems, in particular Japan and certain Arabic-speaking countries.

Also, the broad racial groupings we have used are necessarily rather crude and may conceal considerable differences. Thus, populations of European origin include not only those from Europe itself, but also some from North America and Australia, those of African origin include both native Africans and Afro-Americans, and those of Latin-American origin include Spanish speaking populations of diverse ethnic origins. Studies of the latter have so far been confined exclusively to residents of the western USA and have not, for example, included any of Puerto Rican origin. Finally, even from parts of the world with well developed health care systems there have been woefully few studies that could be considered relatively free from bias. We would define the necessary requirements for such studies as: complete ascertainment of prenatally diagnosed cases within the jurisdiction of livebirths

under study; extensive ascertainment of livebirths from multiple sources; cytogenetic or detailed phenotypic diagnostic confirmation; reliable data on maternal ages; reliable data on the fate of prenatally diagnosed cases; and a clearly defined reference population.

The only studies approaching this ideal have been from populations of European origin and provided the baseline estimates used in the present analysis.[1 9] There clearly remains a need for unbiased rate estimates from other ethnic groups. The use of indices standardised for maternal age is a simple and easily understood way to compare rates in populations with widely differing maternal age distributions. We suggest that future reports of DS livebirth prevalence should, wherever possible, present data in a form that allows calculation of such an index using the reference rates quoted above, and that also allows adjustment for elective terminations following prenatal diagnosis. The latter will become increasingly essential as prenatal diagnosis of DS becomes more widespread and effective.

We thank Elizabeth Daniels for bibliographical assistance in the early phases of the study, which was supported in part by Grant No LM04996 from the National Library of Medicine, US National Institutes of Health.

1 Hecht CA, Hook EB. Rates of Down syndrome at livebirth by one-year maternal age intervals in studies with apparent close to complete ascertainment in populations of European origin: a proposed revised rate schedule for use in genetic and prenatal screening. *Am J Med Genet* 1996;**62**:376-85.
2 Cuckle HS. Risk estimation in Down syndrome screening policy and practice. In: Grudzinskas JG, Chard T, Chapman M, Cuckle H, eds. *Screening for Down's syndrome*. Cambridge: Cambridge University Press, 1994:31-46.
3 Reynolds TM. Screening by test combination: a statistical overview. In: Grudzinskas JG, Chard T, Chapman M, Cuckle H, eds. *Screening for Down's syndrome*. Cambridge: Cambridge University Press, 1994:47-72.
4 Hook EB, Harlap S. Differences in maternal age specific rates of Down syndrome between Jews of European origin and North African or Asian origin. *Teratology* 1979;**20**:243-8.
5 Wilson MG, Chan LS, Herbert WS. Birth prevalence of Down syndrome in a predominantly Latino population: a 15-year study. *Teratology* 1992;**45**:285-92.
6 Bishop J, Huether CA, Torfs C, Lorey F, Deddens J. Epidemiologic study of Down syndrome in a racially diverse California population, 1989-1991. *Am J Epidemiol* 1997; **145**:134-47.
7 Hook EB, Carothers AD, Hecht CA. Elevated maternal age specific rates of Down syndrome liveborn offspring of women of Mexican and Central American origin in California. *Am J Hum Genet* (in press).
8 Carothers AD. Methods for maternal age-standardization of the incidence of congenital abnormalities. *Stat Med* 1995;**14**:1797-806.
9 Hecht CA, Hook EB. The imprecision in rates of Down syndrome by 1-year maternal age intervals: a critical analysis of rates used in biochemical screening. *Prenat Diagn* 1994;**14**:729-38.
10 Hook EB, Regal RR. Capture-recapture methods in epidemiology: methods and limitations. *Epidemiol Rev* 1995;**17**:243-64.
11 Hook EB, Chambers GM. Estimated rates of Down syndrome in live births by one year maternal age intervals for mothers aged 20-49 in a New York State study - implications of the risk figures for genetic counselling and cost-benefit analysis of prenatal diagnosis programs. In: Bergsma D, Lowry RB, Trimble BK, Feingold M, eds. *Numerical taxonomy of birth defects and polygenic disorders*. Birth Defects Original Article Series, Vol 13, No 3A. New York: Liss, 1977:123-41.
12 Huether CA, Gummere GR, Hook EB, *et al.* Down's syndrome: percentage reporting on birth certificates and single-year maternal age risk-rates for Ohio 1970-79: comparison with upstate New York data. *Am J Public Health* 1981;**71**:1367-72.
13 Hook EB, Fabia JJ. Frequency of Down syndrome in livebirths by single-year maternal age interval: results of a Massachusetts study. *Teratology* 1978;**17**:223-8.
14 Iselius L, Lindsten J. Changes in the incidence of Down syndrome in Sweden during 1968-1982. *Hum Genet* 1986; **72**:133-9.
15 Hook EB. The epidemiology of Down syndrome. In: Pueschel SM, ed. *Down syndrome. Advances in biomedicine and the behavioral sciences*. Cambridge: Ware Press, 1982:11-88.
16 Johnson KM, Huether CA, Hook EB, *et al.* False positive and negative reporting of Down's syndrome on Ohio and New York birth certificates. *Genet Epidemiol* 1985;**2**:123-31.
17 Kallen B, Knudsen LB. Effect of maternal age distribution and prenatal diagnosis on population rates of Down syndrome - a comparative study of 19 populations. *Hereditas* 1989;**110**:55-60.
18 Hook EB. Down's syndrome epidemiology and biochemical screening. In: Grudzinskas JG, Chard T, Chapman M, Cuckle H, eds. *Screening for Down's syndrome*. Cambridge: Cambridge University Press, 1994:1-18.
19 Hook EB, Topol BB, Cross PK. The natural history of cytogenetically abnormal fetuses detected at midtrimester amniocentesis which are not terminated electively: new data and estimates of the excess and relative risk of late fetal death associated with 47,+21 and some other abnormal karyotypes. *Am J Hum Genet* 1989;**45**:855-61.
20 Hook EB, Cross PK, Regal RR. The frequency of 47,+21, 47,+18 and 47,+13 at the uppermost extremes of maternal ages: results on 56,094 fetuses studied prenatally and comparisons with data on livebirths. *Hum Genet* 1984;**68**:211-20.
21 OPCS. *Birth statistics, series FM1 No 7*. London: HMSO, 1980.
22 Jacobs PA, Melville M, Ratcliffe S, Keay AJ, Syme J. A cytogenetic survey of 11680 newborn infants. *Ann Hum Genet* 1974;**37**:359-76.
23 Hamerton JL, Canning N, Ray M, Smith S. A cytogenetic survey of 14,069 newborn infants. *Clin Genet* 1975;**8**:223-43.
24 Efron B, Morris C. Stein's paradox in statistics. *Sci Am* 1977;**236**:119-27.
25 Carter C, MacCarthy D. Incidence of mongolism and its diagnosis in the newborn. *Br J Soc Med* 1951;**5**:83-90.
26 Collman RD, Stoller A. A survey of mongoloid births in Victoria, Australia, 1942-1957. *Am J Public Health* 1962;**52**:813-29.
27 Halevi HS. Congenital malformations in Israel. *Br J Prev Soc Med* 1967;**21**:66-77.
28 Sever JL, Gilkeson MR, Chen TC, Ley AC, Edmonds D. Epidemiology of mongolism in the Collaborative Project. *Ann NY Acad Sci* 1970;**171**:328-40.
29 Uchida IA. Epidemiology of mongolism: the Manitoba study. *Ann NY Acad Sci* 1970;**171**:361-9.
30 Christianson RE. Down syndrome and maternal age. *Lancet* 1976;**ii**:1198.
31 Mikkelsen M, Fischer G, Stene J, Stene E, Petersen E. Incidence study of Down's syndrome in Copenhagen, 1960-1971: with chromosome investigation. *Ann Hum Genet* 1976;**40**:177-82.
32 Coffey VP, McCormick E. Down's syndrome in Eastern Health Board Area of Ireland 1953-1976. *J Irish Med Assoc* 1977;**70**:140-5.
33 Stark CR, White NB. In: Hook EB, Porter IH, eds. *Population cytogenetics - studies in humans*. New York: Academic Press, 1977:275-83.
34 Mulcahy MT. Down's syndrome in Western Australia: cytogenetics and incidence. *Hum Genet* 1979;**48**:67-72.
35 Young D, Williams EM, Newcombe RG. Down syndrome and maternal age in South Glamorgan. *J Med Genet* 1980; **17**:433-6.
36 Seebach C, Fuenzalida P, Fuentes S, Lacassie Y. Down syndrome and maternal age in a Chilean population, 1973-1977. *Pediatr Res* 1981;**15**:180.
37 Adeyokunnu AA. The incidence of Down's syndrome in Nigeria. *J Med Genet* 1982;**19**:277-9.
38 Mikkelsen M, Fischer G, Hansen J, Pilgaard B, Nielsen J. The impact of legal termination of pregnancy and of prenatal diagnosis on the birth prevalence of Down syndrome in Denmark. *Ann Hum Genet* 1983;**47**:123-31.
39 Leisti J, Vahtola L, Linna SL, Herva R, Koksela SL, Vitali M. The incidence of Down syndrome in northern Finland with special reference to maternal age. *Clin Genet* 1985;**27**: 252-7.
40 Radic A. *Surveillance of congenital malformations in the Eastern Health Board region 1979-1983.* Dublin: The Medico-Social Research Board, 1986.
41 Baird PA, Sadovnick AD. Maternal age-specific rates for Down syndrome: changes over time. *Am J Med Genet* 1988;**29**:917-27.
42 Boo NY, Hoe TS, Lye MS, Poon PK, Mahani MC. Maternal age-specific incidence of Down's syndrome in Malaysian neonates. *J Singapore Paediatr Soc* 1989;**31**:138-42.
43 Knox EG, Lancashire RJ. *Epidemiology of congenital malformations*. London: HMSO, 1991.
44 Koulischer L, Gillerot Y, Lefevre M, Lamy M, Mancuso S. Down syndrome: prenatal diagnosis and incidence at birth. A 20-year study in Belgium (1971-1990). *Am J Hum Genet Suppl* 1991;**49**:267.
45 Nazer JHM, Hubner EG, Cifuentes LO, Ramirez RF, Catalan JM, Ruiz GB. Aumento de la incidencia del sindrome de Down y su posible relacion con el incremento de la edad materna. *Rev Med Chile* 1991;**119**:465-71.
46 Staples AJ, Sutherland GR, Haan EA, Clisby S. Epidemiology of Down syndrome in South Australia, 1960-89. *Am J Hum Genet* 1991;**49**:1014-24.
47 Carothers AD. A cytogenetic register of trisomies in Scotland: results of the first 2 years (1989, 1990). *Clin Genet* 1994;**46**:405-9.

48 Ligutic I, Barisic I, Svel I, *et al*. A high rate of Down's syndrome in two regions of Croatia. *Paediatr Perinat Epidemiol* 1994;**8**:120-2.
49 Little BB, Ramin SM, Cambridge BS, *et al*. Risk of chromosome abnormalities, with emphasis on live-born offspring of young mothers. *Am J Hum Genet* 1995;**57**:1178-85.
50 Lopez PM, Stone D, Gilmour H. Epidemiology of Down's syndrome in a Scottish city. *Paediatr Perinat Epidemiol* 1995;**9**:331-40.
51 Huether CA, Ivanovich J, Goodwin BS, *et al*. Single year maternal age-specific risk rate estimates for Down syndrome in live births of Whites and other races from Ohio and Metropolitan Atlanta, 1970-1989. *J Med Genet* 1998;**35**:482-90.
52 Hook EB, Lindsjo A. Down's syndrome in livebirths by single year maternal age interval in a Swedish study: comparison with results from a New York State study. *Am J Hum Genet* 1978;**30**:19-27.
53 Trimble BK, Baird PA. Maternal age and Down syndrome: age-specific incidence rates by single-year intervals. *Am J Med Genet* 1978;**2**:1-5.