Revised estimates of the maternal age specific live birth prevalence of Down's syndrome

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Objectives: To revise the estimates of maternal age specific live birth prevalence of Down's syndrome in the absence of antenatal screening and selective termination using newly available data.

Setting and Design: Data were used from the National Down Syndrome Cytogenetic Register (NDSCR), which contains information on nearly all antenatally or postnatally diagnosed cases of Down's syndrome in which a karyotype was confirmed between 1989 and 1998 in England and Wales. It is the largest single series of data on the prevalence of Down's syndrome.

Results and conclusion: The prevalence does not continue increasing at an increasing rate with age above age 45 as has been previously assumed. Above this age the rate of increase declines with increasing age. The overall age pattern is sigmoidal. A new logit logistic model is proposed which fits the data well. The risk of a Down's syndrome live birth is given by:
risk=1/(1+exp(7.330–4.211/(1+exp(–0.282×(age–37.23))))).

T he National Down Syndrome Cytogenetic Register (NDSCR) is the largest single series of data on the prevalence of Down's syndrome, particularly on mothers aged over 45. The most widely used estimates of maternal age related risk calculated by Cuckle *et al* are derived by combining smaller series of data from different countries over the period 1958 to 1978.[1] We used the NDSCR data from 1989 to 1998 to revise the maternal age related risk of a Down's syndrome birth.

METHODS

The National Down Syndrome Cytogenetic Register (NDSCR)

The NDSCR collects reports from all regional cytogenetic laboratories in England and Wales of antenatally or postnatally referred cases found to have a Down's syndrome karyotype. The methods of data collection and processing have been described previously.[2][3] In brief, with the collaboration of the Association of Clinical Cytogeneticists and their members, a form completed by the laboratory is received by the Register for diagnoses of Down's syndrome, including data on the cytogenetic findings, diagnostic test performed and date, maternal age or date of birth, outcome of the pregnancy, and date and gestational age at testing and delivery. For most cases the referring physician receives a copy of the form and most add any missing relevant clinical information. Checks are made for possible duplicates, and further validation is possible by exchanging information with the Office for National Statistics, which receives notifications of births, although both sets of data are anonymous. Births or terminations of pregnancy to mothers resident outside England and Wales are excluded, as are any miscarriages or stillbirths, which had not been antenatally diagnosed. Twin pregnancies (and higher) are considered as two (or more) cases. Data are now available for 11 683 cases karyotyped within the years 1989–98. The total number of births to women in England and Wales from 1990 to 1998 was obtained from the Office for National Statistics.

Statistical analysis

Adjustment for underreporting of births

We have estimated that the NDSCR comprised all but about 6% of births with Down's syndrome in England and Wales.[2][3] Therefore the number of births was increased by 6% to allow for those not included.

Adjustment for fetal loss

Of the 5276 affected pregnancies diagnosed antenatally, 4337 (82%) were known to have been terminated. A proportion of these pregnancies would have aborted spontaneously or resulted in a stillbirth if left to continue to term. We have estimated that, between the time of chorionic villus sampling and term, 43%, and between the time of amniocentesis and term, 23% of the affected pregnancies ended in a miscarriage or stillbirth.[4] Therefore it was assumed that a live birth would have occurred in 57% of the 731 pregnancies terminated before 14 weeks of gestation, and 77% of the 3606 pregnancies terminated at 14 weeks of gestation or later.

Adjustment for unknown outcome

Of the 5276 affected pregnancies diagnosed antenatally, 341 (6%) had unknown outcomes. They were treated in the same way as the terminated pregnancies. It was assumed that a live birth would have occurred in 57% of the 179 pregnancies diagnosed before 14 weeks of gestation, and 77% of the 162 pregnancies diagnosed at 14 weeks of gestation or later.

Adjustment for missing maternal age

Maternal age was missing for 2.6% of pregnancies, 0.3% with an antenatal diagnosis and 4.5% with a postnatal diagnosis. The age distribution of these women with antenatal diagnosis was assumed to be the same as that of the women of known ages with an antenatal diagnosis, and similarly for the women with a postnatal diagnosis.

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Abbreviations: NDSCR, National Down Syndrome Cytogenetic Register

Table 1 Number of cases of Down's syndrome and the total number of live births in England and Wales from 1990–8

Maternal age at birth	Down's syndrome live births	Down's syndrome terminations		Down's syndrome diagnosis with missing outcomes		Predicted Down's syndrome live births in the absence of selective terminations		Total Office of National Statistics live births
		Before 14 weeks gestation	At 14 weeks or later	Before 14 weeks gestation	At 14 weeks or later	Total*	Total adjusted for missing ages†	
	A	B	C	D	E	F	G	
11	0	0	0	0	0	0	0	3
12	0	0	0	0	0	0	0	20
13	0	0	0	0	0	0.0	0.0	251
14	1	0	1	0	0	1.8	1.9	2084
15	4	0	0	0	0	4.2	4.4	10710
16	13	0	5	0	0	17.6	18.4	36962
17	44	1	3	0	0	49.5	51.3	82120
18	53	1	11	0	3	67.5	70.1	125464
19	87	3	20	2	1	111.2	115.6	166520
20	112	5	11	0	1	130.8	133.9	196330
21	117	4	31	0	5	154.0	161.3	224272
22	136	5	28	1	0	169.1	176.5	257213
23	174	4	28	0	0	208.3	215.0	291048
24	180	6	41	1	0	226.4	235.1	328543
25	199	6	51	2	1	255.5	267.3	366930
26	255	6	64	1	1	324.3	336.4	399695
27	257	4	65	2	2	327.4	337.4	419911
28	260	9	97	2	3	358.9	372.3	427195
29	304	17	86	2	7	404.7	421.1	421456
30	309	7	88	3	2	402.5	416.1	401356
31	290	23	118	3	5	416.9	433.6	362512
32	302	20	129	7	3	437.2	454.3	319277
33	292	26	140	9	6	441.9	455.3	269974
34	319	27	183	8	9	505.9	528.0	225050
35	299	34	219	16	7	519.5	529.3	181787
36	273	41	272	13	9	536.5	558.3	143249
37	226	52	308	13	17	526.9	536.0	108798
38	190	57	304	13	6	480.0	491.7	80177
39	197	59	304	27	14	502.7	513.4	58687
40	156	83	301	14	10	460.1	470.1	39828
41	124	59	238	9	17	366.6	372.6	26054
42	98	59	184	8	13	293.8	297.0	15984
43	83	55	143	8	4	237.1	245.4	9221
44	49	22	65	7	8	124.7	124.7	4945
45	26	21	32	3	1	66.7	69.3	2277
46	13	9	17	1	0	32.6	33.2	1073
47	9	4	10	1	0	20.1	20.4	535
48	3	0	1	1	0	4.5	4.7	293
49	0	1	2	0	0	2.1	2.1	185
50	3	0	0	0	0	3.2	3.2	147
51	1	0	0	0	0	1.1	1.1	103
52	1	0	0	0	0	1.1	1.1	69
53	0	0	0	0	0	0.0	0.0	42
54	0	0	0	0	0	0.0	0.0	49
55	0	0	0	0	0	0.0	0.0	51
Missingages	257	1	6	2	7	284.1	0.0	
Total	5716	731	3606	179	162	9479	9479.0	6008450

*F=1.06×A+0.57×(B+D)+0.77×(C+E)
†Missing ages assigned according to proportions of available ages with prenatal and postnatal diagnosis.

Modelling maternal age related risk

Dates of birth were assigned to antenatally diagnosed cases in which the pregnancies were terminated, by assuming that the birth would have occurred in the 38th week of gestation, the modal gestation at birth in those registered. The number of live births with Down's syndrome that occurred, plus the estimated number that would have occurred if the antenatally diagnosed cases had not been terminated was compared with the number of live births occurring in England and Wales from 1990–8 by year of maternal age to obtain the estimated live birth prevalence. Exact binomial 95% confidence intervals (95% CIs) were calculated with STATA.[5] The maternal age related risk and 95% CI was modelled by fitting a logit logistic curve in STATA as suggested by Professors P Royston and S Evans (personal communication, see acknowledgements).

Maximum likelihood estimation was used to fit the curve by specifying the formulae to calculate the log likelihood for each observation and maximising the total of these with the ml procedure in STATA.

RESULTS

Table 1 shows the effect of all the adjustments to the data. Figure 1 shows the estimated prevalence estimates of live births with increasing maternal age with their 95% CIs. There were only 12 births with Down's syndrome out of a total of 939 births to women above age 47 from 1990–8, which is indicated by the very wide 95% CIs. Similarly there were only two Down's syndrome births for the women under the age of 15. Table 2 and figure 2 show the logit logistic curve fitted to the
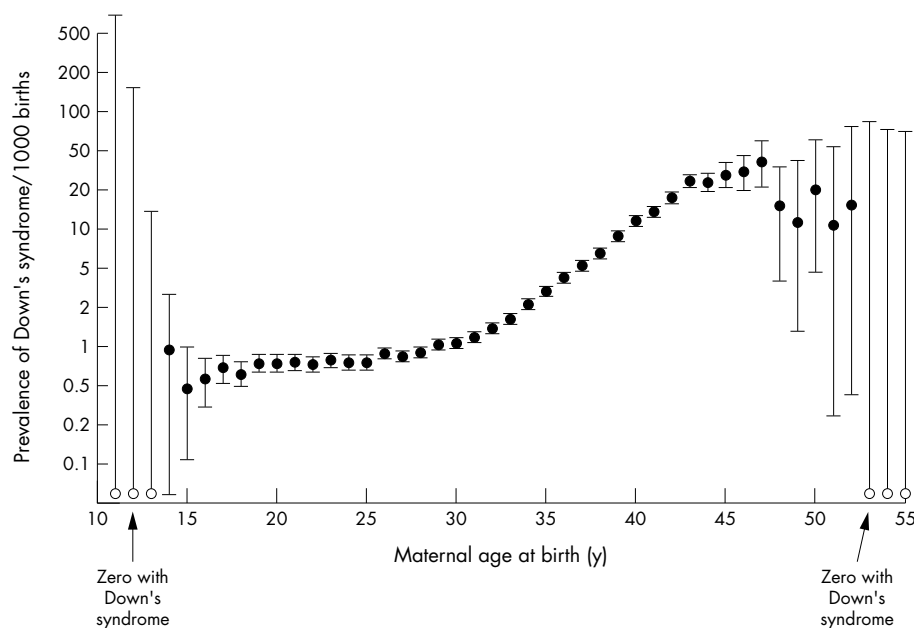
Figure 1   Estimated prevalence (95% CI) of births with Down's syndrome in the absence of antenatal screening in England and Wales 1990–8.

Table 2   Observed and predicted odds of Down's syndrome live birth by maternal age

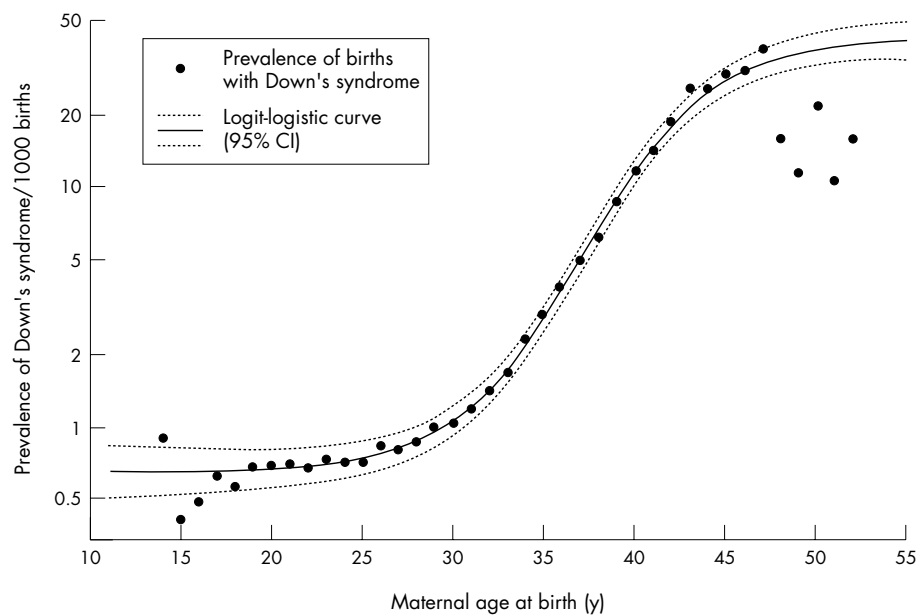| Maternal age at birth	Observed odds	Predicted odds	Lower 95% CI for predicted odds	Upper 95% CI for predicted odds	Estimated odds from exponential curve
11	1:–	1:1521	1:1186	1:1951	1:1589
12	1:–	1:1520	1:1194	1:1935	1:1587
13	1:–	1:1518	1:1201	1:1918	1:1585
14	1:1108	1:1516	1:1208	1:1902	1:1582
15	1:2434	1:1513	1:1215	1:1884	1:1578
16	1:2013	1:1509	1:1220	1:1866	1:1572
17	1:1599	1:1504	1:1225	1:1847	1:1565
18	1:1789	1:1497	1:1227	1:1826	1:1556
19	1:1440	1:1488	1:1228	1:1802	1:1544
20	1:1441	1:1476	1:1227	1:1776	1:1528
21	1:1409	1:1461	1:1222	1:1746	1:1507
22	1:1465	1:1441	1:1213	1:1711	1:1481
23	1:1346	1:1415	1:1198	1:1670	1:1447
24	1:1396	1:1381	1:1177	1:1621	1:1404
25	1:1383	1:1339	1:1147	1:1562	1:1351
26	1:1187	1:1285	1:1107	1:1491	1:1286
27	1:1235	1:1219	1:1056	1:1407	1:1208
28	1:1147	1:1139	1:992	1:1309	1:1119
29	1:1002	1:1045	1:914	1:1195	1:1018
30	1:959	1:937	1:823	1:1067	1:909
31	1:837	1:819	1:722	1:929	1:796
32	1:702	1:695	1:614	1:786	1:683
33	1:589	1:571	1:506	1:644	1:574
34	1:430	1:455	1:404	1:512	1:474
35	1:338	1:352	1:313	1:395	1:384
36	1:259	1:266	1:237	1:299	1:307
37	1:201	1:199	1:177	1:223	1:242
38	1:162	1:148	1:132	1:166	1:189
39	1:113	1:111	1:99	1:125	1:146
40	1:84	1:85	1:75	1:95	1:112
41	1:69	1:67	1:59	1:75	1:85
42	1:52	1:54	1:48	1:61	1:65
43	1:37	1:45	1:40	1:51	1:49
44	1:38	1:39	1:34	1:44	1:37
45	1:32	1:35	1:30	1:39	1:28
46	1:31	1:31	1:27	1:36	1:21
47	1:25	1:29	1:25	1:34	1:15
48	1:62	1:27	1:24	1:32	1:11
49	1:86	1:26	1:23	1:31	1:8
50	1:44	1:25	1:22	1:30	1:6
51	1:92	1:25	1:21	1:29	1:4
52	1:62	1:24	1:20	1:29	1:3
53	1:–	1:24	1:20	1:28	1:2
54	1:–	1:23	1:20	1:28	1:1
55	1:–	1:23	1:19	1:28	1:1

Figure 2 Fit of logit logistic curve (95% CI) to estimated prevalence of births with Down's syndrome in the absence of antenatal screening in England and Wales 1990–8.

data with the 95% CIs. The curve does not continue increasing exponentially after around the age of 45.

Figure 3 and table 2 show the widely used exponential age related risk curve by Cuckle et al[1] and the proposed logit logistic curve. The risks obtained by the two curves are similar up to the age of 35. From 35 to 44 the logit logistic curve is higher, after the age of 44 the logit logistic curve is considerably lower.

The formulas for the two curves are :

Exponential curve (Cuckle et al):
risk=0.000627+exp (−16.2395+0.286×age))
Proposed logit logistic curve:

risk=1/(1+exp(7.330−4.211/
(1+exp(−0.282×(age−37.23)))))

With the proposed logit logistic curve the predicted number of births with Down's syndrome by single year of maternal age in each calender year was close to the observed numbers for women (χ^2=49; df=43 ; p=0.25). The exponential curve proposed by Cuckle et al is clearly inappropriate for women over 44 years of age.

Separate analyses were performed on births in 1989–93 and 1994–8. There was no evidence of any change in maternal age related risk over time.
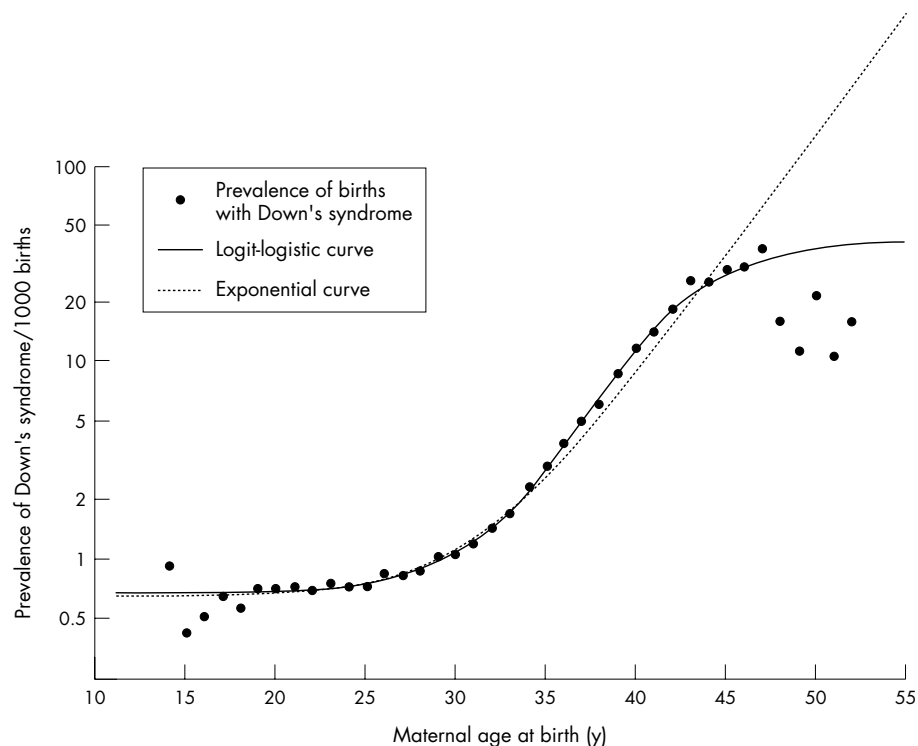

Figure 3 Estimated prevalence of births with Down's syndrome (95% CI) in the absence of antenatal screening in England and Wales 1990–8: comparison of logit logistic curve with exponential curve.

Table 3 Sensitivity analysis: predicted odds of a Down's syndrome birth by maternal age

Changes made to assumptions used in proposed model	Mother of 20	Mother of 35	Mother of 50
No changes	1:1476	1:352	1:25
Assuming that there is no underreporting of live births	1:1553	1:364	1:26
Assuming that all unknown outcomes result in a live birth	1:1474	1:347	1:25
Excluding all women with missing ages from the analysis	1:1532	1:363	1:26

DISCUSSION

Data from the NDSCR provide evidence that the rate of births with Down's syndrome per 1000 live births does not continue increasing exponentially after the age of 45 as had previously been assumed. The proposed model attenuates the increase in risk after age 45 and fits the data better for older women than the exponential curve.

In this paper the new model has been compared only with the most widely used exponential age related risk curve by Cuckle *et al*.[1] There are several alternative models which have subsequently been proposed.[6–8] These three models also all continue increasing exponentially up to the age of 50 and are therefore not appropriate for this set of data.

In our analyses we had several assumptions, none of which materially altered our results. Firstly, there is underreporting of live births with Down's syndrome by 6%. As live births account for about 55% of all records in the NDSCR, this means that our numbers are increased by about 3% to correct for this. We assume that the underreporting of live births is not related to the age of the woman. The sensitivity analysis in table 3 shows that this assumption is not critical as indicated by the estimated prevalence of live births for women of three different ages (20, 35, and 50 years). Secondly, we assume that a proportion of pregnancies diagnosed antenatally would have aborted spontaneously or resulted in a stillbirth if they had not been terminated. We used the estimates that, between the time of chorionic villus sampling and term, 43%, and between the time of amniocentesis and term, 23% of the affected pregnancies ended in a miscarriage or stillbirth.[4] If these estimates were incorrect by say 5% (that is, the two proportions should be 38% and 18% or 48% and 28% respectively—an unlikely scenario) this would decrease or increase the numbers of births by only 2%. Thirdly, the data contained 6% of pregnancies with Down's syndrome diagnosed prenatally, but with a missing outcome. These were treated in the same way as terminated pregnancies, but table 3 shows the effect of assuming that they all resulted in a live birth. Finally 2.6% of women had no age recorded and we assumed that their ages were typical of those in the sample. Table 3 shows that even if we excluded all these women from the analysis it has little effect.

The logit logistic curve fits the data better than an exponential curve and therefore the revised estimates are more accurate for the estimation of the risk for individual women. However, in screening programmes for Down's syndrome, it is a minor issue. Modelling the expected detection rates for the triple test gives a 71.1% detection rate for a 5% false positive rate for the proposed risk curve compared with a 71.2% detection rate for the original risk curve.

Figure 1 seems to show that the prevalence of a birth with Down's syndrome decreases above the age of 47. There are several possible explanations for this. Firstly, the numbers of births with Down's syndrome is small, so it may be due to chance (the upper 95% CIs are level). Secondly, rates of miscarriage are higher in women over the age of 45,[9] and it may be that these older women are aborting the affected fetuses before diagnosis occurs. Thirdly, it is difficult to be able to conceive above the age of 45 and it may be that there is something different about these women that reduces their risk of having a pregnancy with Down's syndrome. Finally, it may be due to a few women misreporting their ages. This can have a surprisingly large effect. For example, if one 52 year old mother who has a birth with Down's syndrome had her age recorded as 42, the rates for 52 year olds would change to 30/1000 births from 16/1000, whereas the rates for 42 year olds would only change to 18.5/1000 from 18.6/1000. There is therefore good evidence to indicate that the risk for women over 45 does not continue increasing exponentially, but no good evidence that it actually decreases. It would be desirable to obtain independent corroboration of our risks. Although it is not therefore critical for screening programmes to alter their risk estimation algorithm, doing so will improve the accuracy of risk estimation in older women.

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