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Correct estimation of parameters for ultrasound nuchal translucency screening

The indirect method used by Wald and Hackshaw (1997) to derive parameters for first-trimester nuchal translucency (NT) screening for Down's syndrome makes unacceptable assumptions. It is only invalid to combine different series, as they do, if sources of variability are known to be comparable. The parameters for Down's syndrome were obtained by extracting 86 values from a figure in a publication (Pandya *et al*., 1995) on the Fetal Medicine Foundation multi-centre study co-ordinated by King's College Hospital. The parameters for unaffected pregnancies were obtained from an unpublished study of 561 women (Schuchter *et al*., 1998). However, no evidence is presented to show that the two series are compatible and potential differences due to the screening technique are likely. This is further compounded when they attempt to correct the bias inherent in intervention studies by applying a simple correction factor.

In a prospective intervention trial, diagnosed cases of Down's syndrome are a biased subset of all cases and have a skewed distribution of NT values. This is because most of those with increased NT values but only a few with normal values will have prenatal diagnosis and selective termination of pregnancy. Since a large proportion of Down's syndrome pregnancies end in miscarriage and are undiagnosed, the diagnosed cases include a disproportionate number with increased NT. The correction factor method used by Wald and Hackshaw in an attempt to overcome this assumes, without proof, that bias only affects the mean value and not the shape of the distribution.

We have derived correct parameters *directly* from the results of the Fetal Medicine Foundation study. The NT and crown–rump length (CRL) measurements were analysed for 95 476 singleton unaffected pregnancies and 326 with Down's syndrome screened before the end of 1996. All results were expressed as multiples of the median (MOM) value for each crown–rump length derived from the unaffected pregnancies. From regression analysis on the observed medians the best fitting equation was $\log_{10}NT = -0{\cdot}3599 + 0{\cdot}0127CRL - 0{\cdot}000058CRL^2$. Among the cases, 8 miscarried, 258 were terminated, 127 in the first trimester of pregnancy and 131 in the second, and 60 survived until the third trimester, including two intra-uterine and one neonatal death.

We overcame bias directly by selecting a 'potentially viable' subset of Down's syndrome pregnancies. This comprised all third-trimester survivors together with, chosen at random, half of those terminated in the first trimester and two-thirds of those terminated in the second. These proportions are the approximate survival rates

Table I—Centiles of NT (in MoMs) for unaffected and Down's syndrome pregnancies: comparison of values observed (O) and expected (E) from log-Gaussian distributions

	Unaffected		Down's syndrome		Viable subset	
Centile	O	E	O	E	O	E
1	0·50	0·53	0·69	0·66	0·64	0·57
5	0·62	0·63	0·93	0·95	0·86	0·83
10	0·69	0·70	1·10	1·15	1·01	1·01
25	0·82	0·83	1·51	1·59	1·34	1·40
Median	1·00	1·00	2·27	2·27	2·02	2·02
75	1·19	1·20	3·23	3·25	3·01	2·91
90	1·40	1·42	4·32	4·49	4·05	4·04
95	1·57	1·58	4·75	5·45	4·60	4·92
99	2·19	1·90	6·42	7·83	6·41	7·11

found by comparing the prevalence observed at first-trimester chorionic villus sampling with expected birth prevalence (Snijders *et al.*, 1994; Macintosh *et al.*, 1995) and in women refusing termination after second-trimester amniocentesis (Hook *et al.*, 1989, 1995).

Table I shows selected centiles of NT, in MOMs, for unaffected pregnancies, the complete series of 326 pregnancies with Down's syndrome and in the potentially viable subset of 211 pregnancies. Correction for bias resulted in a 12 per cent decrease in the median NT for Down's syndrome from 2·27 to 2·02 MOM. The table compares the observed values with those expected from log-Gaussian frequency distributions with $\log_{10}$ means derived from the observed medians and $\log_{10}$ standard deviations from the 10th–90th centile range divided by 2·563. In unaffected pregnancies the distribution fits the data well and in the Down's syndrome subset the fit is reasonable over a wide range. So our best estimates of the parameters required for risk calculation (mean and standard deviation) are: 0·305 and 0·235 for Down's syndrome; 0·000 and 0·120 for unaffected pregnancies.

The parameters derived in this way can be used by those carrying out routine first-trimester NT screening provided that ultrasound staff are certified, and subject to external quality control by an external agency like the Fetal Medicine Foundation (Royal College of Obstetricians and Gynaecologists, 1997). In this case, standard statistical modelling methods will predict the screening performance based on the maternal age distribution for England and Wales in 1991–1995 (Office of Population Censuses and Surveys, 1993–1997). If the NT was used to calculate the risk of Down's syndrome for each woman and a risk cut-off chosen to yield a 5 per cent false-positive rate, the expected Down's syndrome detection rate would be 73 per cent. Using the incorrect parameters of Wald and Hackshaw it would only be 62 per cent, considerably lower and no greater than the detection rate observed with 2–3 marker second-trimester serum screening (Cuckle, 1996).

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Authors' reply

We are pleased that Nicolaides *et al.* (1998) acknowledge three important points in our paper (Wald and Hackshaw, 1997), namely:

(i) the need to adjust for ascertainment bias in deriving estimates of screening performance. Their estimate of the correction for this is virtually identical to ours (12 per cent versus 13 per cent, see Table I);

(ii) the value of expressing nuchal translucency measurement in multiples of the median (MOMs);

(iii) that the distribution of nuchal translucency should be expressed on a log scale.

As a result of these three points, much of the disagreement over the performance of nuchal translucency measurement in screening for Down's syndrome based on the data in the multicentre study co-ordinated by Nicolaides and his team has been resolved.

Nicolaides *et al.* (1998) assert that it is 'invalid to combine different series' because of possible incompatibility between the data from Vienna (Schuchter *et al.*, 1998) and those from London (Pandya *et al.*, 1995), but give no specific reasons for this opinion. We would agree if we had used the Vienna medians to derive the MOMs for the London cases, but this was not done; nuchal translucency measurements were converted into MOMs using each centre's *own* unaffected median values. This allows for systematic differences in measurement between the Vienna and the London data sets in the same way as the use of MOMs in serum screening for Down's syndrome. The problem of incompatibility therefore does not arise.

We do not believe that we made 'unacceptable assumptions' in our analysis. The only material difference in results between our analysis and theirs is the estimate of the standard deviation of nuchal translucency in unaffected pregnancies (0·1717 versus 0·120; see Table I); otherwise the results are remarkably similar, and each set validates the other. This is illustrated by the fact that if they use our estimate of the standard deviation of nuchal translucency in unaffected pregnancies but otherwise keep everything unchanged, the predicted estimate of screening performance would be a 62 per cent detection rate for a 5 per cent false-positive rate almost identical to our estimate of 63 per cent.

In estimating the standard deviation of nuchal translucency in unaffected pregnancies we used the 50th–98th centile rather than the 10th–90th (which yielded an estimate of 0·1349 $\log_{10}$ MOM) as there was some positive skewness after log transformation (Schuchter *et al.*, 1998). Part of the difference between the two estimates of the standard deviation in nuchal translucency may arise because informal averaging may have taken place in the