ORIGINAL ARTICLE

Weight correction of MoM values: which method?

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Background: Adjusting maternal serum markers for maternal weight is considered to be a standard practice when screening for pregnancies associated with Down's syndrome. The choice of model for taking maternal weight into account is, however, rarely explicitly evaluated.

Method: The relationship between the maternal serum markers α fetoprotein (AFP), human chorionic gonadotropin (HCG) and unconjugated oestriol (uE3), determined with the Beckman Coulter access reagents and maternal weight was investigated in a cohort of 752 Belgian women being screened for pregnancy associated with Down's syndrome. Two different models (the log-linear equation and the linear-reciprocal equation) were used to determine the relationship between the serum markers and maternal weight.

Results: A significant relationship between $\log_{10}$ multiples of median (MoM) values and weight (kg) was obtained for all markers, and the log-linear model had higher coefficients of determination (r^2) when compared with the linear-reciprocal model. Weight correction with either method achieved the optimum effect that the correction factor for a woman with a population median weight of 65.5 kg was not significantly different from 1. Simulated weight-corrected MoM values with the two approaches were compared and variation was estimated. The mean difference between the weight-corrected MoM values calculated by the two methods was 7.8% (SD 4.3%) for AFP, 14.0% (4.4%) for HCG and 5.9% (3.2%) for uE3. This resulted in a difference in risk estimate of 1.66–5.34% for Down's syndrome owing to weight correction algorithm differences in women of median weight.

Conclusion: The log-linear weight correction approach was shown to be marginally more effective by a goodness-of-fit analysis. Differences in weight-corrected MoM values estimated with the two approaches are highly significant ($p < 0.0001$, Wilcoxon's paired sample test), but the effect on risk calculation was not significant. It was observed that the changes in risk became significant the more the MoM correction factors deviated from 1.

It was shown in 1981 that the maternal serum α fetoprotein (AFP) concentration is influenced by maternal weight during the second trimester.¹ Later, this was also shown for serum human chorionic gonadotropin (HCG) and unconjugated oestriol (uE3) concentrations.² Heavier women tend to have lower levels and lighter women have higher marker levels, which may affect their relative tendency to be selected as "high risk". Two statistical models in the recent literature describe this inverse relationship between maternal weight and serum analytes: the log-linear model and the linear-reciprocal model.³ Both models are empirically derived and are generally chosen by a goodness-of-fit analysis. Because weight adjustment is simple it has become common practice in prenatal screening programmes.³ The improvement, however, is relatively small (0–1%);^{4,5} nevertheless, the weight correction is justified on the grounds of simplicity and equity (ie, as p_{Downs} is not related to p_{Weight} , the effect of weight needs to be removed).^{2,6}

The National Health Service Down's screening programme for England⁷ recommends that the weight correction should be centred on the median weight for the screened population, in such a way that a woman of median weight has no adjustment (or a very small adjustment) made to her marker values. As different populations may have different demographic properties, it is advised that testing labs should derive and verify their own weight correction equations. The UK screening programme prescribes minimum workloads for screening laboratories such that laboratories can operate independently only if their workload is in excess of 5000 cases per year; for 1000–5000 cases, it is essential to be part of a network pooling data; and no laboratory is permitted to carry out screening if workload is below 1000 cases per year. The effect of data pooling has not yet been investigated. In

Abbreviations: AFP, α fetoprotein; HCG, human chorionic gonadotropin; MoM, multiples of median; uE3, unconjugated oestriol

Table 1 Median AFP, HCG and uE3 values and 95% confidence interval for gestational weeks 14–19

Gestational weeks	AFP in IU/ml (95% CI)	HCG in IU/ml (95% CI)	uE3 in nmol/l (95% CI)
14	23.7 (21.4 to 25.8)	39.0 (30.0 to 43.6)	2.29 (1.99 to 2.41)
15	24.8 (24.0 to 25.9)	31.0 (29.0 to 33.0)	2.67 (2.58 to 2.85)
16	30.5 (27.6 to 31.8)	27.0 (24.1 to 30.0)	3.80 (3.62 to 4.00)
17	36.0 (32.6 to 39.7)	20.5 (18.3 to 24.4)	4.68 (4.38 to 5.09)
18	41.5 (36.8 to 44.8)	16.1 (12.0 to 19.6)	6.00 (4.99 to 6.85)
19	45.3 (40.1 to 50.3)	14.6 (11.3 to 23.0)	7.05 (6.41 to 8.46)

AFP, α fetoprotein; HCG, human chorionic gonadotropin; uE3, unconjugated oestriol.

Table 2 Belgian population statistics for unaffected (Cohort of 748 data) pregnancies.				
Weight (kg)	n	AFP	HCG	uE3
<49	33	1.39	1.18	1.09
50–59	184	1.12	1.00	1.07
60–69	259	1.01	1.12	1.00
70–79	157	0.96	0.91	1.01
80–89	54	0.81	0.94	0.93
90–99	37	0.76	0.88	0.90
>100	28	0.66	0.83	0.83
All weights	752	0.99	1.00	1.01

AFP, α fetoprotein; HCG, human chorionic gonadotropin; uE3, unconjugated oestriol.

Belgium, screening laboratory workloads are often below the 1000 case cut-off and it is therefore necessary to pool data and identify parameters that are suitable for several laboratories.

We studied the relationship between serum markers and weight in 752 pregnant Belgian women and examined the central correction value to check whether a woman of median weight has a weight correction value close to 1.

METHODS

The study was carried out at six Belgian laboratories: Centraal Laboratorium Hasselt, Hasselt; Labo MCT, Tessenderlo; Centre Hospitalier Notre Dame-Reine Fabiola, Charleroi; Centraal Laboratorium St-Vincentius Ziekenhuis, Deinze; Laboratory Van Poucke, Kortrijk; CH Jolimont-Lobbes Site Jolimont, Haine-Saint-Paul.

A dataset of 862 requests derived from women being screened for pregnancy associated with Down's syndrome was examined. Gestational ages were estimated by ultrasound scanning (crown-to-rump length and biparietal diameter) or by last menstrual period dates if scan dates were unavailable. Data from women without maternal age or weight were excluded (table 1).

The Beckman Coulter access reagents for AFP, HCG and uE3 (catalogue numbers 33210, 33500 and 33570 with their corresponding calibrators) were used on the Beckman Coulter Access base, Access2 and Unicell DxI analysers to measure mid-trimester AFP, HCG and uE3 results. Fresh maternal serum samples were used to determine median values of the three serum markers for each completed gestational week. A subset of 752 results for AFP, HCG and uE3 was used to study the weight dependency and to estimate the weight correction equations. All assay results were expressed as multiples of median (MoM) to correct for gestational age.⁸ Finally, to check whether the two models produce similar MoM values, 50 representative MoM values for the three serum markers were selected. These were linked

Figure 1 Distribution of maternal weight of 752 Belgian women during the second trimester of pregnancy and weight distribution normalised by the reciprocal (Kolmogorov–Smirnov $p=0.818$). Normal distribution is superimposed on the histogram. The vertical lines represent the number of cases that should lie in the corresponding histogram class if the distribution is normal.

with 50 random maternal weights: an arithmetic mean maternal weight (reciprocal transformation) of 0.0153 (65.36) kg and an SD (1/weight) of 0.0028 was used. The difference between MoM values corrected with the log–linear weight model and the reciprocal weight model was then evaluated.

Data analysis was carried out with MedCalc for Windows software V.7.4.1.2, BIOMstat statistical software for biologists for Windows V.3.4, Microsoft Excel 2002, data analysis tool add-in and RiskCalc V.1.3a, a Down's risk calculation package.

Table 3 Regression parameters for least-squares regression of $\log_{10}$ MoM against weight			
	AFP	HCG	uE3
A	0.3007 (0.3890)	0.1889 (0.2026)	0.1339 (0.01442)
B	–0.0045 (–0.0053)	–0.0029 (–0.00288)	–0.0020 (–0.0010)
95% CI for B	–0.0052 to –0.0037	–0.0039 to –0.0018	–0.0027 to –0.0012
r^2	0.1459	0.0328	0.0391
r	–0.3819 (–0.3315)	–0.1812 (–0.1563)	–0.1976 (–0.0758)
n	752	752	752
p	<0.0001	<0.0001	<0.0001
95% CI for r	–0.4414 to –0.3191	–0.2495 to –0.1112	–0.2654 to –0.1279

AFP, α fetoprotein; HCG, human chorionic gonadotropin; uE3, unconjugated oestriol. Values in parentheses are statistics published from Reynolds *et al* (1991).⁶

Table 4 Correlation between multiples of the median (MoM) values (n=752)

	$\log_{10}$ AFP	$\log_{10}$ HCG	$\log_{10}$ uE3
Mean (SD)	-0.0026 (0.164)	-0.0057 (0.2217)	-0.0007 (0.1407)
Correlation			
$\log_{10}$ AFP	1		
$\log_{10}$ HCG	0.2214	1	
$\log_{10}$ uE3	0.2528	0.0519	1
p	AFP v HCG ($p < 0.0001$)	AFP v uE3 ($p < 0.0001$)	HCG v uE3 ($p = 0.1552$)
95% CI	0.1523 to 0.2883	0.1847 to 0.3185	-0.0197 to 0.1229

AFP, α fetoprotein; HCG, human chorionic gonadotropin; uE3, unconjugated oestriol. **Figure 2** (A) Log-linear correlation of weight with $\log_{10}$ of multiples of median (MoMs) for the analytes α fetoprotein (AFP), human chorionic gonadotropin (HCG) and unconjugated oestriol (uE3). The two curves parallel to the regression lines represent the 95% prediction interval of the regression curve. (B) Reciprocal correlation of weight with $\log_{10}$ of MoMs for the analytes AFP, HCG and uE3. The two curves parallel to the regression lines represent the 95% prediction interval of the regression curve.

Figure 3 Relationship between maternal weight and maternal screening markers in the second trimester. The maternal weight (kg) is on the horizontal axis and the maternal serum analytes (expressed as MoMs) on the vertical axis. For each analyte, the uninterrupted line represents the reciprocal model. The dashed line shows the log-linear model. The horizontal line is the no correction line. The equations fitted are weighted by the square number of the data points per weight-class. The vertical bars are 95% CI values for the median values. The last two medians are based on only 11 and 4 data points. Because this number of data points is very small, the effect of the two last points on the regression coefficients is rather small. AFP, α fetoprotein; HCG, human chorionic gonadotropin; MoM, multiple of median; uE3, unconjugated oestriol.

RESULTS

Descriptive data

Table 1 shows the median AFP, HCG and uE3 values and 95% confidence intervals (CI) for gestational weeks 14–19. These medians are slightly different from the regressed median

Table 5 Weight correction for the three markers for a woman of median weight

Marker	Weight (kg)	Correction	L1	L2
AFP	65.5	1.021	0.995	1.046
HCG	65.5	1.004	0.969	1.040
uE3	65.5	1.010	0.985	1.036

AFP, α fetoprotein; HCG, human chorionic gonadotropin; L1, lower confidence limit; L2, higher confidence limit; uE3, unconjugated oestriol.

Table 6 Median MoM values for uncorrected and weight-corrected serum markers

Marker	Uncorrected-median MoM	Weight-corrected median MoM
AFP	0.99282	1.001348
HCG	1.0012455	1.02811417
uE3	1.005003	0.998977619

AFP, α fetoprotein; HCG, human chorionic gonadotropin; MoM, multiples of the median; uE3, unconjugated oestriol.

values reported by us in an earlier paper⁸ (log-linear model) because of the exclusion of data without corresponding maternal weight, but 95% CI of the mentioned medians encompass all regressed medians (table 2, fig 1).

Association between biochemical parameters and weight

The median weight of women in this exercise was 65.5 (SE 0.643) kg and the range was 37–126 kg. Figure 1 shows the weight distribution. The distribution was normalised by transforming the weights into their reciprocal values ($1/\text{weight}$). Table 2 summarises the median serum markers related to the maternal weight. For the three markers, a distinct trend was observed between the MoM values and the weight class. Regression analysis between the $\log_{10}$ values of the markers and weight was carried out by the least squares method. Regression parameters and statistical significance is shown in table 3. Figures 2A and B show the log-linear and linear-reciprocal relationships between weight and MoM.

Correlation between MoM values

The correlation coefficient indicates the degree of association between parameters. The correlation coefficient between the $\log_{10}$ -transformed MoM data is needed as a factor in the formula used to calculate the Down's syndrome risk factor.⁹ Table 4 contains the correlation coefficients observed for unaffected pregnancies and their statistical significance: these values are within the expected range of correlation identified by the UK National Screening Committee for AFP and HCG, but not for uE3.¹⁰

Correction for a woman of median weight

The weight correction should be centred on the median weight for the screened population. This means that a woman of median weight has minimal adjustment made to her markers. Table 5 gives the correction factors for the three markers for a woman weighing 65.5 kg. It can be concluded that the adjustment for a woman of medium weight is nearly 1.0 and that this criterion is fulfilled for the Belgian Access population. Maximum correction for a woman of median weight is 1.021.

Confirmation that correction is acceptable

The following procedure has been proposed by Neveux *et al*¹¹ to check whether the correction formulas perform optimally:

Table 7 Regression parameters for the linear-reciprocal regression of multiples of the median (MoM) values against weight (1/weight): expected median MoM = $B \times (1/\text{weight}) + A$, where weight is in kg

	AFP	HCG	uE3
A	0.2452	0.6189	0.7474
B	54.0555	32.5776	19.8874
r ²	0.1055	0.0275	0.0267
r	0.3248	0.1659	0.1635
p	<0.0001	<0.0001	<0.0001
95% CI for r	0.2593 to 0.3873	0.0955 to 0.2346	0.0931 to 0.2323

AFP, α fetoprotein; HCG, human chorionic gonadotropin; MoM, multiple of median; uE3, unconjugated oestriol.

1. Calculate the median of the MoM values for the serum analytes with and without weight correction
2. Compare the uncorrected medians with the weight-corrected medians of the MoM values
3. The overall pre-correction and post-correction values should be more or less the same and more or less equal to 1.00 MoM.

For our dataset, estimates listed in table 6 are obtained. These results clearly show that the weight correction formulas established in this exercise are appropriate because the changes in observed median MoM are trivial and can be used in prenatal screening.

Goodness-of-fit: linear-reciprocal and log-linear models

Curve fits were generated using all data points rather than a weighted model based on median data. Statistics for the log-linear model are listed in table 3. Table 7 lists the statistics for the reciprocal model. The coefficients of determination (r^2) of the log-linear model are slightly higher than those of the linear-reciprocal model. Therefore, the log-linear model was chosen as the equation to adjust for weight for collaborating Belgian laboratories. The formula for log-linear weight correction by using the parameters A and B described in table 3 is

$$\text{Weight corrected MoM} = \frac{\text{MoM}}{10^{(A + B \times \text{weight})}}$$

From tables 3 and 7 and figs 2A,B and 3, it can be concluded that the correlation obtained for the two different models is statistically similar, with higher r values obtained for the log-linear model.

Effect of weight correction on risk calculation

Median weight-corrected MoM values (95% CI) estimated with the log-linear and the linear-reciprocal equation were for AFP: 0.98 (0.92 to 1.03) and 0.93 (0.88 to 0.97), for HCG: 1.09 (0.81 to 1.39) and 0.97 (0.72 to 1.18) and for uE3: 1.04 (0.89 to 1.14) and 1.00 (0.85 to 1.08), respectively. Mean variation (calculated as $((\text{largest MoM}/\text{smallest MoM}) - 1) \times 100\%$) between the weight-corrected MoM values is 7.8% (SD 4.3%) for AFP, 14.0% (4.4%) for HCG and 5.9% (3.2%) for uE3. A consistent pattern is observed, with the log-linear-corrected MoM values being consistently the highest ones. The differences between the models are highly significant ($p < 0.0001$, Wilcoxon test for paired samples).

The effect of this variation on the final risk estimations was not significant. This is illustrated as follows: it is logical that the most extreme changes in MoM values will occur at the extremes of the weight distribution. For a hypothetical pregnant woman aged 35 years, with Cuckle's population parameters,¹² table 8 shows the corrected MoM values and associated Down's risk estimate for three maternal scenarios of weights (35, 65 and 95 kg) and two marker sets representing a "normal" patient and one with basal marker levels close to the median levels for pregnancies associated with Down's syndrome. Clearly, the MoM values corrected for the near-median weight of 65 kg are not different from the basal uncorrected MoM values and the risk estimate is considerably altered by weight correction, especially for extremes of weight. The difference in estimates between log-linear and linear-reciprocal models is relatively small, except in women with a low body weight.

DISCUSSION

A significant association was found among all the three markers and weight. No association has ever been shown

Table 8 Effect of weight correction on risk estimates for a hypothetical 35-year-old woman

		Corrected weight (kg)					
		35		65		95	
	Basal MoM	LL	LR	LL	LR	LL	LR
Normal							
AFP	1.0	0.7191	0.5588	0.9813	0.9287	1.3391	1.2282
HCG	1.0	0.8177	0.6453	0.9991	0.8928	1.2207	1.0397
uE3	1.0	0.8632	0.7601	0.9911	0.9493	1.1379	1.0452
Risk	1627	1109	820	1573	1657	1915	2122
Diff LL v LR		26.05%		-5.34%		-10.9%	
Down's syndrome							
AFP	0.7	0.5034	0.3911	0.6869	0.6501	0.9373	0.8597
HCG	2.0	1.6354	1.2906	1.9982	1.7856	2.4413	2.0794
uE3	0.7	0.6042	0.5321	0.6937	0.6645	0.7965	0.7317
Risk	128	62	36	120	122	200	202
Diff LL v LR		41.93%		-1.66%		-1%	

AFP, α fetoprotein; HCG, human chorionic gonadotropin; LL, log-linear; LR, linear-reciprocal; MoM, multiples of the median; uE3, unconjugated oestriol.

Take-home messages

- A significant association is found between weight and antenatal Down's screening markers but not between weight and a pregnancy associated with Down's syndrome.
- Multiple median values can be significantly affected by weight—the log-linear correction factor to correct for the difference between 65 kg (average weight) and 95 kg is 1.3391—that is, a 34% change.
- Several mechanisms are proposed for the correction of this weight association, but in the population described here the log-linear model was marginally superior to the linear-reciprocal model.
- Weight correction should be applied to all analytes in Down's syndrome screening.
- Evidence shows that weight correction does improve detection rates.

between maternal weight and the incidence of Down's syndrome. The data in table 8 show the effect of weight correction assuming a standard set of basal medians. In routine practice, the "basal" medians are unknown but the maternal weight is known. As we know weight affects risk estimates, but does not affect true risk, it is appropriate to carry out weight correction to remove this influence from the screening programme.

Owing to the limits of the data in this evaluation, the weight correction equations proposed are valid only for the 39–126 kg range. For higher and lower values, the 39–126 kg limits need to be used to calculate the adjustment factor (ie, for a woman weighing 130 kg, a weight of 126 kg should be applied). Furthermore, it is advised that the weight of the pregnant women should be monitored and if the median weight of the women increases or decreases by 2.5 kg, the weight correction formulas need to be updated.

For the Belgian Access population, the log-linear model was chosen to estimate the weight correction factor, because this model yielded higher coefficients of determination when compared with the linear-reciprocal model. This is in contrast with the results of Neveux *et al.*,¹¹ where the reciprocal equation gave the better fit. Additionally, the Friedman, Billings, Ramsey Survey found that for AFP the dynamic range of reciprocal weight correction, 80–350 lb (36–160 kg), was marginally superior to log-linear weight correction for AFP, but other analytes were not tested.³ Both models give a

reasonable fit of the data and either is suitable for use in a screening programme. Therefore, as there is little practical difference between models, whichever model is provided with Down's screening risk calculation software packages is valid.

The most important effects of differences in weight correction, however, are the effects of the different models on detection rates. This cannot be adequately modelled here and will need a large dataset of known positive and negative pregnancies to allow a definitive answer to be generated.

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