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The maternal age-specific live birth prevalence of trisomies 13 and 18 compared to trisomy 21 (Down syndrome)

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Objective To estimate the maternal age-specific live birth prevalence (in the absence of prenatal diagnosis and selective termination) of trisomy 13 (Patau syndrome) and trisomy 18 (Edwards syndrome) and compare it with that of trisomy 21 (Down syndrome).

Methods Records of prenatal and postnatal diagnoses from seven UK regional congenital anomaly registers and two Australian registers covering 4.5 million births included 975 diagnoses of trisomy 13 and 2254 of trisomy 18. Prevalence at birth in the absence of prenatal diagnosis and selective termination was calculated by adjusting for prenatally diagnosed pregnancies that were terminated according to their likelihood of surviving to term.

Results The live birth prevalence in the absence of prenatal screening and selective termination in England and Wales from 1997 to 2004 was 1.4 (95% CI: 1.2–1.6) per 10 000 births for trisomy 13 and 2.3 (95% CI: 2.1–2.5) for trisomy 18. It has increased since 1989–1996, by 13% for trisomy 13 and 25% for trisomy 18. These increases are consistent with those predicted due to increases in maternal age.

Conclusion This study provides the first estimates of maternal age-specific prevalence of trisomies 13 and 18 for women aged 16–45. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS: Patau syndrome; Edwards syndrome; general cytogenetics; prenatal cytogenetics; genetic counselling; Down syndrome; trisomy

INTRODUCTION

Trisomies 13 and 18 are the most common viable autosomal trisomies after Down syndrome (trisomy 21). Trisomy 13 (Patau syndrome) and trisomy 18 (Edwards syndrome) affect multiple systems, have a high risk of foetal death and are usually fatal within the first few weeks of life. At present in England and Wales over 90% of reported cases of both trisomies are diagnosed prenatally, with over 90% of these subsequently terminated (Morris, 2009).

Accurate maternal age-specific estimates for the prevalence of these trisomies at birth or at specific gestational ages are needed when calculating risk reports for use in prenatal screening programmes, and for predicting the impact of changes in the maternal age distribution on the prevalence of each trisomy. Understanding the variation of each trisomy with maternal age is also useful for aetiological research.

Several estimates for the prevalence at birth of each trisomy are based on birth series obtained before the widespread availability of prenatal diagnosis. Owing to the rarity of trisomies 13 and 18, estimates obtained in this way are imprecise as they are based on very few affected births. For example, prevalences of 0.5 per 10 000 births (95% CI: 0.2–1.6 per 10 000 births) for trisomy 13 and 1.2 per 10 000 births (95% CI: 0.6–2.6 per 10 000 births) for trisomy 18 are often used but are based on only three cases of trisomy 13 and seven cases of trisomy 18 (Hook and Hamerton, 1977).

In this article we provide estimates of the maternal age-specific birth prevalence of trisomy 13 and trisomy 18 using cases reported to nine regional congenital anomaly registers from the UK and Australia, covering 4.5 million births. The data include pregnancies that were terminated. Many of these pregnancies would not have survived to term and therefore we use newly available estimates for the risk of natural foetal loss of each trisomy (Morris and Savva, 2008) to estimate the expected birth prevalence in the absence of such interventions. We also compare the prevalence estimates with those of Down syndrome (trisomy 21).

MATERIALS AND METHODS

Congenital anomaly registers

All records of cases of trisomy 13 and trisomy 18 were received from the following nine regional congenital anomaly registers, the first seven of which are members of the British Isles Network of Congenital Anomaly Registers (BINOCAR) and the last two

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from Australia: Northern Congenital Anomaly Survey (NorCAS); North Thames West Congenital Malformation Register; South West Congenital Anomaly Register; East Midlands and South Yorkshire Congenital Anomaly Register (EMSYCAR); Congenital Anomaly Register and Information Service (CARIS) of Wales; Congenital Anomaly Register for Oxfordshire, Bedfordshire and Berkshire (CAROBB); Wessex Antenatally Detected Anomalies Register (WANDA); Victorian Birth Defects Register; Birth Defects Registry of Western Australia.

The BINOCAR registers from which we received data cover roughly one-third of the population of England and Wales, and the records we received covered roughly 2.5 million births from 1989 to 2004. The two Australian registers covered a total of 1.9 million births from 1980 to 2003.

The ascertainment of chromosomal anomalies in the Victorian register was estimated to be 94% between 1982 and 1985 (Lumley *et al*., 1988), and close to 100% in 1992 (Kilkenny *et al*., 1995) and between 1999 and 2002 (Riley *et al*., 2004). Using capture–recapture methods, ascertainment of chromosomal anomalies by the Western Australian register for terminations of pregnancy between 1980 and 1997 was estimated to be 99.1%(Bower *et al*., 2001).

Ascertainment of Down syndrome cases by BINOCAR registers was estimated to be 95% in 1989–2004 using capture–recapture methods (Savva and Morris, 2009), and we assumed the ascertainment of trisomy 13 and trisomy 18 was similar.

All of these registers perform active case finding and use multiple sources of ascertainment. Each register collects information on all congenital anomalies occurring in live births, miscarriages and stillbirths, and in foetuses terminated after prenatal diagnosis of an anomaly. Miscarriages and stillbirths were excluded from the analysis because they do not contribute to the live birth prevalence. Table 1 summarises the data received from the registers.

Case definition

We included all cases where a full trisomy of chromosomes 13 or 18 or a translocation introducing a third copy of either chromosome was mentioned. Mosaic genotypes were included. There were no reports of trisomies 13 and 18 occurring simultaneously in our dataset.

Table 1—Pregnancy outcomes for cases of trisomy 13 and 18

	Trisomy 13		Trisomy 18	
Pregnancy outcome	Number	(%)	Number	(%)
Live birth	215	(22.1)	447	(19.8)
foetal loss	149	(15.3)	313	(13.9)
Termination	558	(57.2)	1334	(59.2)
Unknown	53	(5.4)	160	(7.1)
Total	975	(100)	2254	(100)

Denominators

The Australian registers provided the number of births by year and maternal age in the areas covered by each register. Birth statistics, provided by the Office for National Statistics, for regions in England and Wales were supplied in five year maternal age bands (personal communication). We imputed the number of births per single year of maternal age for each region using these figures and the single year maternal age distribution for births nationally.

Analysis

Adjusting for foetal loss

A large proportion of trisomy 13 and 18 pregnancies do not survive to term (Snijders *et al*., 1994; Won *et al*., 2005; Morris and Savva, 2008). Therefore, not all terminated cases would have survived to birth had termination not occurred. In order to calculate the live birth prevalence in the absence of prenatal diagnosis and subsequent termination, we estimated the number of terminated cases that would have survived to birth had termination not occurred, by applying a probability of survival to each terminated case. These probabilities depended on trisomy, gestational age at termination and the sex of the foetus, and the only complete set of estimates are published in an earlier article (Morris and Savva, 2008). In the earlier study five regional congenital anomaly registers in England and Wales provided details on the outcomes of 198 pregnancies prenatally diagnosed with trisomy 13 and 538 pregnancies prenatally diagnosed with trisomy 18. For each pregnancy, the time from prenatal diagnosis until birth, miscarriage or termination occurred was calculated, and these times were analysed using Kaplan–Meier survival functions. Between 12 weeks' gestation and term an estimated 49% (95% CI: 29–73%) of pregnancies diagnosed with trisomy 13 and 72% (61–81%) of pregnancies diagnosed with trisomy 18 ended in a miscarriage or stillbirth. Therefore, in this current study, if two trisomy 13 pregnancies are terminated at 12 weeks, then one would expect approximately one birth to occur if these two pregnancies had not been terminated, as only 49% of these pregnancies survive till birth. Therefore in this analysis these two terminations would be given a weight of 0.49 and the total number of weighted terminations is summed to determine how many births would have survived to birth had termination not occurred.

Missing data

Maternal age was missing in 39 cases of trisomy 13 (4.7%) and 64 cases of trisomy 18 (3.3%). We assumed that cases with missing maternal age for each specific outcome had the same maternal age distribution as cases with the same outcome. Pregnancy outcome was not recorded in 53 cases of trisomy 13 (5.4%) and 160 cases of trisomy 18 (7.1%). Of these 213 cases, in 169 it was known that the pregnancy was either terminated or ended

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in stillbirth. Here we assumed that if the outcome was before 30 weeks (107 cases) the pregnancy had been terminated, otherwise the pregnancy ended in a stillbirth (62 cases). From the distribution of gestational ages this assumption is reasonable. The 46 remaining cases with unknown pregnancy outcome (1.4%) were assumed to have the same distribution of pregnancy outcome as those with a similar gestational age whose outcome was recorded.

The gestational age at the end of pregnancy was missing in 53 (9.3%) of the terminated trisomy 13 cases and 131 (9.8%) of the terminated trisomy 18 cases. For 61 of these 183 cases, the gestational age at diagnosis was reported and it was assumed that the termination occurred one week later (the median time that terminations occurred after diagnosis). In the remaining 122 cases, we assumed the same distribution of gestation as in terminated cases, where gestational age was known. Sensitivity analyses were conducted for all these assumptions.

Modelling maternal age-specific prevalence

Counts of cases weighted to adjust for natural foetal loss, under-ascertainment and missing data were used with live birth denominators described above to model the maternal age-specific prevalence of each trisomy.

A logit-logistic regression model was used for the maternal age-specific prevalence. This model has been previously used to quantify the maternal age-specific prevalence of Down syndrome (Morris *et al.*, 2002), and has the form:

$$\text{prevalence} = \frac{1}{\left[1 + \exp\left(\alpha - \frac{\beta}{1 + e^{-\gamma(\text{age}-\delta)}}\right)\right]}$$

where the parameters α, β, γ, and δ are estimated for each trisomy separately. The maximum likelihood function, *ml*, was used to fit the logit-logistic model using Stata 9.0.

Estimating the prevalence in England and Wales

In order to estimate the effect of increasing maternal ages in England and Wales we applied the age-specific prevalences obtained above to the national numbers of live births in England and Wales according to maternal age.

RESULTS

Figure 1 plots the observed maternal age-specific live birth prevalence with 95% confidence intervals compared with the modelled prevalence for trisomies 13, 18 and, for comparison purposes, Down syndrome (reproduced using data from an earlier publication) (Morris *et al.*, 2002). The appendix (Appendices A and B)

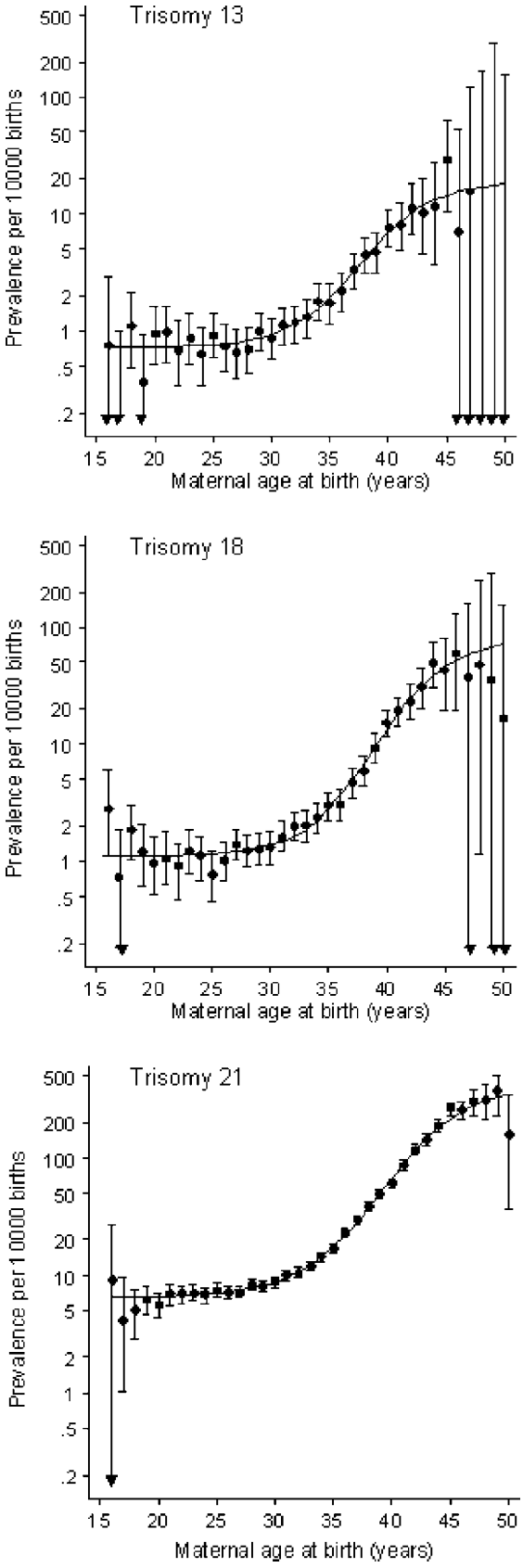

Figure 1—The observed and modelled prevalence of trisomies 13, 18 and 21 with 95% confidence intervals of the observed data according to maternal age (Trisomy 21 included for comparison purposes, data from Morris *et al.*, 2002)

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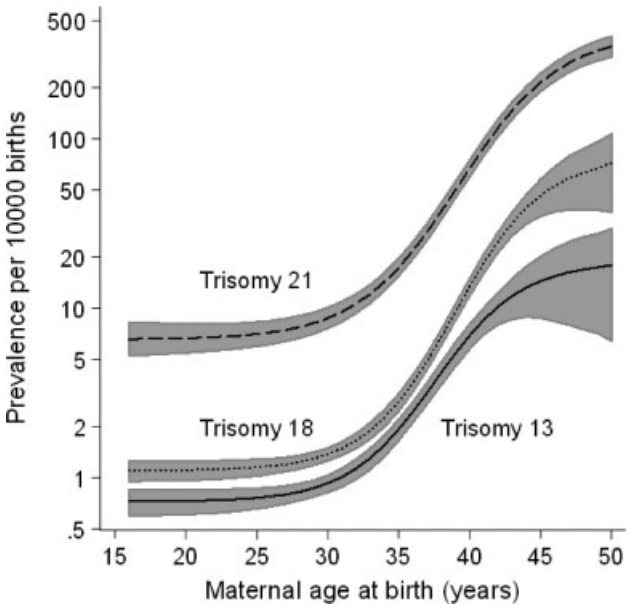

Figure 2—The modelled prevalence of trisomies 13, 18 and 21 with 95% confidence intervals for the modelled prevalence according to maternal age (Trisomy 21 included for comparison purposes, data from Morris *et al*., 2002)

provides the data used to plot these figures. The log-logistic model for prevalence fits each trisomy well, which is demonstrated in Figure 1, as all the points for mothers between the ages of 20 and 44 lie extremely close to the predicted lines. For mothers outside this age range there is some deviation from the line due to sampling variation, having a greater effect because of the smaller numbers of mothers in each single year of age.

The prevalence of each trisomy is roughly constant until age 30, and then increases exponentially before beginning to level off again at age 45. Figure 2 compares the maternal age-specific live birth prevalence of trisomies 13, 18 and 21 all on the same graph. The shape of each prevalence curve is similar. The prevalence of trisomy 13 rises more slowly with maternal age than either trisomy 18 or trisomy 21, which show a similar increase.

The formulae for the prevalence of trisomies 13, 18 and, for comparison, 21 with maternal age (measured in completed years) are:

$$\text{prevalence of trisomy 13} = \frac{1}{\left[1+\exp\left(9.53-\frac{3.25}{1+e^{-0.332(\text{age}-37.5)}}\right)\right]}$$

$$\text{prevalence of trisomy 18} = \frac{1}{\left[1+\exp\left(9.11-\frac{4.27}{1+e^{-0.324(\text{age}-38.9)}}\right)\right]}$$

$$\text{prevalence of trisomy 21} = \frac{1}{\left[1+\exp\left(7.33-\frac{4.21}{1+e^{-0.282(\text{age}-37.2)}}\right)\right]}$$

Prevalence in England and Wales

Table 2 shows the increase in the estimated live birth prevalence after adjusting the number of terminations for foetal loss in England and Wales in 1989–1996 compared with 1997–2004, and the predicted live birth prevalence using the age-specific prevalences and the age distribution of births in these time periods. It shows that observed increases are similar to those expected due to increases in maternal age alone. The modelled prevalences for Down syndrome are given for comparison purposes, and they show that the prevalence of trisomy 13 is around 7% of that of Down syndrome and the prevalence of trisomy 18 is around 12%. The increase in Down syndrome appears larger than that of the other trisomies as the association with maternal age is slightly stronger. Similarly the increase for trisomy 13 appears the smallest as the association with maternal age is the weakest. The study lacks power to demonstrate that the increases in the three trisomies are statistically, significantly different.

DISCUSSION

This study is the largest of its kind and provides the first estimates of maternal age-specific prevalence of trisomies 13 and 18 for women aged 16–45. It demonstrates that observed increases in the prevalence of these trisomies from 1989 to 2004 are likely to be

Table 2—Observed and modelled live birth prevalences in England and Wales from 1989 to 2004 for trisomy 13 and trisomy 18 (Modelled live birth prevalence for trisomy 21 included for comparison purposes, data from Morris *et al*., 2002)

	Trisomy 13 (95% CI)		Trisomy 18 (95% CI)		Down syndrome
Live birth prevalence	Observed	Modelled	Observed	Modelled	Modelled
1989–1996[a]	1.20 (0.98–1.47)	1.20 (1.02–1.38)	1.81 (1.53–2.13)	1.93 (1.70–2.16)	15.3 —
1997–2004[a]	1.36 (1.20–1.55)	1.43 (1.21–1.65)	2.27 (2.05–2.50)	2.37 (2.08–2.66)	19.4 —
Increase	13%	19%	25%	23%	27%

[a] Adjusted for prenatal diagnosis and selective termination.

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attributable to changes in the maternal age distribution during this time period.

Trisomy 13 and trisomy 18 pregnancies have extremely high foetal loss rates and, therefore, the prevalence at birth is much lower than at other gestational ages. The utility of independently screening for trisomy 18 in the population is questionable, while no screening protocols have yet been established for trisomy 13. If either anomaly is to be included as an 'add-on' in trisomy 21 screening, estimates of the prevalence at birth and at other specific gestational ages will be essential to audit and compare different prenatal foetal anomaly screening programmes. These can be calculated by using an earlier article that gives the foetal loss rate according to gestational age (Morris and Savva, 2008). For example between 12 weeks' gestation and term an estimated 49% of pregnancies diagnosed with trisomy 13 and 72% of pregnancies diagnosed with trisomy 18 end in a miscarriage or stillbirth. Therefore, the prevalence at 12 weeks' gestation of trisomy 13 is the live birth prevalence divided by (1−0.49) and similarly for trisomy 18, the prevalence at 12 weeks' gestation is the live birth prevalence divided by (1−0.72)

Strengths and weaknesses of the study

Trisomies 13 and 18 are rare and the precision of our estimates was made possible by the use of several congenital anomaly registers with known high level ascertainment covering a large population over a long time period.

We adjusted for the effects of prenatal diagnosis and termination by weighting cases that had been terminated according to their probability of survival. There is uncertainty associated with these probabilities, which is not taken into account in this analysis.

There was a moderate amount of missing data, particularly for pregnancy outcome and gestation at outcome. Sensitivity analysis of the missing data assumptions was performed and found not to significantly affect our results.

Comparison with previous studies

Three studies (Hook and Hamerton, 1977; Maeda *et al*., 1991; Nielson and Wohlert, 1991) estimated the live birth prevalence using series of births before prenatal screening became widely available. These studies covered a total of 107 000 births, including 6 cases of trisomy 13 (including one termination) and 23 cases of trisomy 18 (including three terminations). These lead to estimates of 0.6 (CI: 0.2−1.2) cases of trisomy 13, and 2.2 (CI: 1.0−2.7) cases of trisomy 18 per 10 000 births. Our estimates for the live birth prevalences given the maternal age structure in 1989 are 1.3 (CI: 1.2−1.5) and 2.0 (CI: 1.8−2.3) per 10 000 births respectively. The prevalence estimates for trisomy 18 are reasonably consistent, whilst the estimates for trisomy 13 are imprecise due to being based on only six cases.

The rates of diagnosis of trisomies 13 and 18 have been more recently estimated based on the Metropolitan Atlanta Congenital Birth Defects Program (Crider *et al*., 2008), the Hawaii Birth Defects Program (Forrester and Merz, 2002) and the Trent Regional Congenital Anomaly Register (Parker *et al*., 2003). In each case the population being studied had access to prenatal diagnosis services. Data from the Trent Regional Congenital Anomaly Register is incorporated in the current study. In the Atlanta study, Crider *et al*. (2008) recorded 72 diagnoses of trisomy 13 (including 29 live births) and 184 diagnoses of trisomy 18 (including 53 live births). This corresponds to 1.6 (1.2−2.0) diagnoses of trisomy 13 and 4.0 (3.5−4.8) of trisomy 18 per 10 000 births. The observed live birth rates (which ignored all terminations) were 0.6 (0.4−0.9) and 1.2 (0.9−1.5) per 10 000 births respectively. The live birth prevalence that would have occurred in the absence of prenatal diagnosis was not estimated, but must lie between the observed diagnosis rate (which assumes that all terminations would have survived to term) and the observed live birth rate (which ignores all terminations, thereby assuming none would have survived to term), which is consistent with our estimates. The estimates of Forrester and Merz (2002), based on 45 diagnoses of trisomy 13 and 130 of trisomy 18 were very similar, and both are consistent with our population prevalence estimates.

Ferguson-Smith and Yates (1984) estimated the maternal age-specific prevalence of trisomies 13 and 18 using 121 cases of trisomy 18 and 39 cases of trisomy 13 amongst 53 000 amniocentesis offered to women solely because they were over the age of 35. They reported an exponential increase in prevalence with maternal age between 35 and 45 years. We have confirmed this increase, and there is limited evidence (due to a small number of cases) to suggest that the prevalence levels off for older women, as has been demonstrated for Down syndrome (Morris *et al*., 2005).

CONCLUSION

This study provides the first estimates of maternal age-specific prevalence of trisomies 13 and 18 for women aged 16−45. Population prevalences of trisomies 13 and 18 depend on the maternal age structure in the population, with widely used historical estimates underestimating the current prevalence of both trisomies in England and Wales.

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Northern Congenital Anomaly Survey (NorCAS); North Thames West Congenital Malformation Register; South West Congenital Anomaly Register; East Midlands and South Yorkshire Congenital Anomaly Register (EMSYCAR); Congenital Anomaly Register and Information Service (CARIS) of Wales; Congenital Anomaly Register for Oxfordshire, Bedfordshire and Berkshire (CAROBB); Wessex Antenatally Detected Anomalies

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Register (WANDA). We thank the two Australian registers for their data: Victorian Birth Defects Register; Birth Defects Registry of Western Australia.

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Ethics approval

Each of the contributing registers has ethics approval for the routine collection of congenital anomaly records and monitoring the rates of anomalies. Provision of data from Australia was approved by the Ethics Committee of the Women's and Children's Health Service (#980/EW) and the Department of Health Western Australia Human Research Ethic Committee (#200409).

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APPENDIX

Table Appendix A—Observed and modelled live birth prevalence (per 10 000) of each trisomy by maternal age

		Trisomy 13					Trisomy 18				
Maternal age at birth	Total live Births	Observed cases	Weighted cases	Observed prevalence	Modelled prevalence	(95% CI)	Observed cases	Weighted cases	Observed prevalence	Modelled prevalence	(95% CI)
16	23 398	2	2.0	0.8	0.7	(0.6–0.9)	8	6.8	2.9	1.1	(1.0–1.3)
17	52 403	1	0.8	0.2	0.7	(0.6–0.9)	7	4.6	0.9	1.1	(1.0–1.3)
18	81 040	10	9.9	1.2	0.7	(0.6–0.9)	21	16.4	2.0	1.1	(1.0–1.3)
19	109 518	6	5.2	0.5	0.7	(0.6–0.9)	19	14.6	1.3	1.1	(1.0–1.3)
20	130 066	14	13.9	1.1	0.7	(0.6–0.9)	18	13.2	1.0	1.1	(1.0–1.3)
21	148 733	16	15.9	1.1	0.7	(0.6–0.9)	21	16.7	1.1	1.1	(1.0–1.3)
22	170 316	12	12.3	0.7	0.7	(0.6–0.9)	24	18.0	1.1	1.1	(1.0–1.3)
23	193 265	20	19.4	1.0	0.7	(0.6–0.9)	32	25.1	1.3	1.1	(1.0–1.3)
24	219 022	17	16.1	0.7	0.8	(0.6–0.9)	37	26.3	1.2	1.1	(1.0–1.3)
25	246 496	26	25.7	1.0	0.8	(0.7–0.9)	30	21.2	0.9	1.2	(1.0–1.3)
26	272 139	24	23.2	0.9	0.8	(0.7–0.9)	49	32.7	1.2	1.2	(1.1–1.3)
27	293 391	24	22.8	0.8	0.8	(0.7–0.9)	62	44.1	1.5	1.2	(1.1–1.3)
28	308 040	28	26.1	0.8	0.8	(0.7–0.9)	62	42.1	1.4	1.2	(1.1–1.4)
29	313 831	39	37.2	1.2	0.9	(0.8–1.0)	65	44.3	1.4	1.3	(1.2–1.4)
30	308 781	32	30.7	1.0	0.9	(0.8–1.0)	72	46.0	1.5	1.4	(1.3–1.5)
31	290 824	42	39.5	1.4	1.0	(0.9–1.1)	78	52.4	1.8	1.5	(1.4–1.6)
32	264 557	42	38.0	1.4	1.1	(1.0–1.3)	91	60.2	2.3	1.7	(1.5–1.8)
33	231 440	39	36.5	1.6	1.3	(1.1–1.5)	80	52.7	2.3	1.9	(1.7–2.1)
34	198 106	45	41.9	2.1	1.6	(1.3–1.8)	81	52.1	2.6	2.3	(2.0–2.5)
35	165 778	38	34.7	2.1	1.9	(1.7–2.2)	96	58.0	3.5	2.8	(2.5–3.1)
36	132 674	40	36.0	2.7	2.5	(2.1–2.8)	84	46.5	3.5	3.7	(3.2–4.1)
37	102 555	49	43.2	4.2	3.2	(2.7–3.7)	100	57.1	5.6	4.9	(4.3–5.4)
38	76 737	48	42.9	5.6	4.2	(3.5–4.8)	103	52.8	6.9	6.9	(6.0–7.5)
39	56 149	38	33.8	6.0	5.5	(4.5–6.3)	117	61.5	11.0	9.7	(8.4–10.7)
40	38 304	42	36.8	9.6	7.0	(5.8–8.1)	120	66.8	17.4	13.6	(11.8–15.1)
41	24 718	29	25.1	10.2	8.6	(7.0–10.1)	100	55.8	22.6	18.8	(16.1–21.0)
42	14 964	25	21.7	14.5	10.3	(8.1–12.4)	82	41.5	27.7	25.1	(21.4–28.3)
43	8361	13	11.2	13.4	11.9	(8.7–15.0)	67	32.3	38.6	32.2	(26.8–37.1)
44	4258	7	6.2	14.6	13.4	(8.9–17.7)	51	25.9	60.9	39.6	(31.5–47.2)
45	2067	9	7.7	37.2	14.6	(8.8–20.3)	22	10.4	50.1	46.8	(35.1–58.0)
46	960	1	0.9	9.3	15.6	(8.4–22.7)	13	6.7	69.3	53.3	(37.2–68.8)
47	435	1	0.9	20.6	16.4	(8.0–24.7)	5	2.4	54.2	58.9	(38.3–79.0)
48	222	0	0.0	0.0	17.0	(7.5–26.4)	1	1.1	48.2	63.5	(38.5–88.1)
49	127	0	0.0	0.0	17.4	(7.1–27.7)	2	0.7	56.8	67.2	(38.2–95.8)

Table Appendix B—Comparison of modelled live birth prevalence (per 10,000) of trisomy 13, 18 and 21 according to maternal age (Trisomy 21 included for comparison purposes, data from Morris *et al.*, 2002)

	Trisomy 13		Trisomy 18		Trisomy 21	
Maternal age at birth	Modelled prevalence (95% CI)		Modelled prevalence (95% CI)		Modelled prevalence (95% CI)	
16	0.7	(0.6–0.9)	1.1	(1.0–1.3)	6.6	(8.3–5.3)
17	0.7	(0.6–0.9)	1.1	(1.0–1.3)	6.6	(8.2–5.3)
18	0.7	(0.6–0.9)	1.1	(1.0–1.3)	6.6	(8.2–5.4)
19	0.7	(0.6–0.9)	1.1	(1.0–1.3)	6.6	(8.2–5.4)
20	0.7	(0.6–0.9)	1.1	(1.0–1.3)	6.7	(8.1–5.5)
21	0.7	(0.6–0.9)	1.1	(1.0–1.3)	6.7	(8.1–5.5)
22	0.7	(0.6–0.9)	1.1	(1.0–1.3)	6.8	(8.1–5.6)
23	0.7	(0.6–0.9)	1.1	(1.0–1.3)	6.8	(8.2–5.7)
24	0.8	(0.6–0.9)	1.1	(1.0–1.3)	6.9	(8.2–5.8)
25	0.8	(0.7–0.9)	1.2	(1.0–1.3)	7.1	(8.3–6.0)
26	0.8	(0.7–0.9)	1.2	(1.1–1.3)	7.2	(8.5–6.2)
27	0.8	(0.7–0.9)	1.2	(1.1–1.3)	7.5	(8.7–6.4)
28	0.8	(0.7–0.9)	1.2	(1.1–1.4)	7.8	(9.0–6.7)
29	0.9	(0.8–1.0)	1.3	(1.2–1.4)	8.2	(9.5–7.1)
30	0.9	(0.8–1.0)	1.4	(1.3–1.5)	8.8	(10.1–7.6)
31	1.0	(0.9–1.1)	1.5	(1.4–1.6)	9.6	(10.9–8.4)
32	1.1	(1.0–1.3)	1.7	(1.5–1.8)	10.7	(12.1–9.4)
33	1.3	(1.1–1.5)	1.9	(1.7–2.1)	12.2	(13.8–10.7)
34	1.6	(1.3–1.8)	2.3	(2.0–2.5)	14.4	(16.3–12.7)
35	1.9	(1.7–2.2)	2.8	(2.5–3.1)	17.5	(19.7–15.5)
36	2.5	(2.1–2.8)	3.7	(3.2–4.1)	21.9	(24.7–19.5)
37	3.2	(2.7–3.7)	4.9	(4.3–5.4)	28.3	(31.8–25.2)
38	4.2	(3.5–4.8)	6.9	(6.0–7.5)	37.4	(42.0–33.4)
39	5.5	(4.5–6.3)	9.7	(8.4–10.7)	50.1	(56.2–44.7)
40	7.0	(5.8–8.1)	13.6	(11.8–15.1)	67.2	(75.3–59.9)
41	8.6	(7.0–10.1)	18.8	(16.1–21.0)	89.3	(100.2–79.6)
42	10.3	(8.1–12.4)	25.1	(21.4–28.3)	116.4	(130.7–103.7)
43	11.9	(8.7–15.0)	32.2	(26.8–37.1)	147.7	(166.1–131.3)
44	13.4	(8.9–17.7)	39.6	(31.5–47.2)	181.7	(204.8–161.2)
45	14.6	(8.8–20.3)	46.8	(35.1–58.0)	216.5	(244.5–191.6)
46	15.6	(8.4–22.7)	53.3	(37.2–68.8)	250.1	(283.4–220.7)
47	16.4	(8.0–24.7)	58.9	(38.3–79.0)	281.2	(319.7–247.2)
48	17.0	(7.5–26.4)	63.5	(38.5–88.1)	308.6	(352.2–270.3)
49	17.4	(7.1–27.7)	67.2	(38.2–95.8)	332.1	(380.6–289.6)

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