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Maternal age in the epidemiology of common autosomal trisomies

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What is already known about this topic

- Birth prevalence of each common autosomal trisomy increases with maternal age
- Each trisomy has high intra-uterine fatality
- Down syndrome fetal loss rates increase with maternal age

What does this study add

- A review of all published estimates of prevalence at term and during pregnancy
- Confirms flattening of the Down syndrome birth prevalence curve at extremely high maternal ages
- Dismisses the claimed relatively high Down syndrome birth prevalence at extremely low ages
- Shows that Patau syndrome birth prevelance increases with maternal age less rapidly than Down syndrome

Abstract

The birth prevalence rate of each common autosomal trisomy generally increases with advancing maternal age and there is a substantial fetal loss rate between late first trimester and term. The literature is reviewed in order to provide the best estimates of these rates, taking account where possible of biases due to prenatal diagnosis and selective termination of pregnancy. There is an almost exponential increase in Down syndrome birth prevalence between ages 15 and 45 but at older ages the curve flattens. There is no evidence of the claimed relatively high birth prevalence at extremely low ages. Gestation-specific intra-uterine fetal loss rates are estimated by follow-up of women declining termination of pregnancy after prenatal diagnosis, comparison of observed rates with those expected from birth prevalence and comparison of age-specific curves developed for prenatal diagnosis and birth. Down syndrome fetal loss rates reduce with gestation and increase with maternal age. Edwards and Patau syndrome birth prevalence is approximately 1/8 and 1/13 that of Down syndrome overall, although the ratio differs according to maternal age, particularly for Patau syndrome where it reduces steadily from 1/9 to 1/19. Fetal loss rates are higher for Edwards and Patau syndromes than for Down syndrome.

Keywords: epidemiology; autosomal trisomy; maternal age; gestation; fetal losses

In this review we consider the common autosomal trisomies, defined as an extra copy of chromosome 21, 18 or 13 (Down, Edwards and Patau syndromes) whose birth prevalence increases with maternal age. Among the common sex chromosome abnormalities birth prevalence is not universally associated with age: 47,XXY and 47,XXX increase, 47,XYY is unaltered and monosomy X (Turner syndrome) declines [1]. For each type of trisomy maternal age-specific prevalence rates are estimated at birth and according to gestational age. Claims are examined that in women aged 45 of more prevalence does not continue to increase and in those aged 15 or less prevalence is relatively high.

Down syndrome – early studies of adults and children

The discovery of a maternal age effect was made by Lionel Penrose. This arose from his study of 1280 residents of the Royal Eastern Counties Institution in Colchester, England, and their families [2]. Penrose belief that mental abnormality had a biological rather than social aetiology was confirmed by the survey. It yielded clear evidence to support a number of salient features of mental abnormality: an excess of males, heterogeneity of expression and continuum between normal and intellectual impairment. This seminal work led to more focussed investigation including a study of 63 residents with Down syndrome where Penrose observed an association with increased maternal and paternal ages. In a more detailed study with a larger population he was able to show, using regression analysis, that the primary effect was maternal age [3].

Down syndrome – maternal age-specific birth prevalence rates

Methodology

The only unequivocal estimates of age-specific prevalence are available from studies carried out before invasive prenatal diagnosis for aneuploidy became clinically established. Prenatal diagnosis and subsequent termination of affected pregnancies will necessarily reduce birth prevalence and this will not be uniform across all maternal ages. When advanced maternal age was the only indication for prenatal diagnosis it was still possible to estimate prevalence at younger ages, say, less than 35. When maternal

serum and, later, ultrasound marker screening became widespread the problem became exacerbated. Screening combined information on the marker profile and maternal age calculate a personalised DS risk which was used to select those at high enough risk to warrant the costs and hazards of prenatal diagnosis. Consequently, the proportion of affected pregnancies diagnosed and terminated varied according to maternal age. During this phase it was possible to estimate birth prevalence from the observed numbers of affected births and affected terminations but required assumptions to be made about *intra-uterine* viability. Where possible, the best estimate of prevalence is based on the meta-analysis of individual studies, ideally fitting a simple curve to the data.

Early studies and four meta-analyses

In the late 1980s a meta-analysis was carried out using data from all eight studies published at that time [4]. This included with a total of 4528 DS births and more than 5 million unaffected births. The studies were from Australia (1960-77), Belgium (1971-8), Canada (1961-70), Sweden (1968-70), USA (Massachusetts (1958-65), New York (1968-74), Ohio (1970-9)) and Wales (1968-76). Five used multiple sources to identify DS births including birth certificates, hospital and mental health institution records, cytogenetic laboratories, special schools and sheltered workshops. Two studies, in New York and Ohio, used only birth certificates but were adjusted for under-ascertainment, increasing the number of cases 2.66- and 2.74-fold respectively, based on a comparison of cytogenetic records and birth certificates. The last study was based solely on newborn examinations by an obstetrician and paediatrician. For each year of age from 15 to 50 data were pooled by taking the average birth prevalence rate across the studies weighted by the number of births. A three parameter, additive-exponential regression equation was used of the form, $y=a+\exp(b+cx)$, where y is prevalence and x is age. A single regression was performed over the entire age range.

The second meta-analysis used the same eight studies [5]. Pooling was by summation of the birth prevalence numerators and denominators at ages 15 to 50. Two different additive-exponential regression equations were fitted: three parameter, and five parameters with a cubic exponential component. Separate

analyses were carried out for the two series that the authors regarded as most complete – from Belgium and Sweden - and restricting maternal age range in four ways (15-49, 20-49, 15-45, 20-45). Unlike the first meta-analysis, four terminations of pregnancy following prenatal diagnosis of Down syndrome at amniocentesis in the Wales study were reduced by 30% to allow for fetal loss (see 'Down syndrome – *intra-uterine* viability' below).

The third meta-analysis comprised five studies [6]. This included the two 'most complete' studies from the second meta-analysis replaced by a study in Belgium which extended the series to 1971-90 and complemented by a more recent study in Sweden (1971-77). The study in Australia was also replaced by a more extended series 1960-89 although data from 1960-4 were not included because of concerns about completeness. The fifth 'Intensive Newborn' study combined data from studies in Winnipeg and Edinburgh where all neonates had cytogenetic tests. Pooling was by summation at each maternal age, 16 to 49. Three, five and six parameter additive-exponential regression equations were used, the latter having a quartic exponential component. A separate analysis was carried out after excluding the Australia study. A total of 110 terminations of Down syndrome pregnancies diagnosed following amniocentesis were reduced by 30%.

The fourth meta-analysis included nine studies, all but two of those in the first meta-analysis (New York and Wales), making the replacements (Australia and Belgium) and additions (Sweden and Intensive Newborn) from the third meta-analysis, together with a study of Down syndrome births from a different part of Australia (1987-91), in women aged 36 or more [7]. Pooling was by the use of a weighting factor which estimated the proportional under-ascertainment in each study. The regression analysis simultaneously estimated the curve parameters and this proportion over the maternal age range 16 to 50. A three parameter logistic regression equation was used of the form, $y=a+(1-a)/(1+\exp(-b-cx))$, where a is between 0 and 1. A separate analysis was carried out after excluding the Canada study. The numbers of terminated pregnancies were reduced by 30%.

<u>National Down Syndrome Cytogenetic Register (NDSCR)</u>

NDSCR receives reports of cases with a DS karyotype from all clinical cytogenetic in England and Wales; this is the largest national consecutive series of such cases [8]. The register used data on 11,683 DS cases reported in 1989-98 to estimate maternal age-specific prevalence rates, more than double the total number included in a meta-analysis [9]. Prevalences were calculated at maternal age 11 to 55 from the number of births according to age in England and Wales in 1990-98 obtained from the Office of National Statistics. Unlike the early studies this series was strongly biased by prenatal diagnosis which accounted for 5276 cases (45%) of which 82% were known to have been terminated. In order to allow for this, after all cases were increased by 6% to allow for under-ascertainment, the number of terminated cases was reduced by 43% if prenatal diagnosis followed chorionic villus sampling (CVS) and by 23% if it followed amniocentesis. For terminated cases the maternal age was calculated assuming that the pregnancy would have delivered at 38 weeks gestation, the modal value for DS births in the study. A four parameter logistic regression curve was fitted to the data including all maternal ages with the form, $y=1/(1-\exp(a+b/(1+\exp(c+d*age))))$. Separate analyses were carried out for births in 1989-93 and 1994-8 but there were no material differences.

Comparison between curves

Over the 15-40 year age range there is little difference between each of the 19 regression curves from the four meta-analyses or the NDSCR regression curve (Table 1). At age 45 differences emerge with estimated prevalence ranging from 27.8/1000 to 43.0/1000 but at age 50 there is an almost 5-fold range of values from 38.5/1000 to 188/1000. The curves that yield the lowest values at older ages are either additive-exponential with higher order parameters or logistic.

Table 2 shows the observed age-specific prevalence rates for each single year of age between 45 and 49 or more in ten studies included in the four meta-analyses, in NDSCR and 87 cases from twelve of the congenital malformations registries belonging to the European network EUROCAT [11]. For Australia and Belgium the studies in the second meta-analysis replacing those in the first meta-analysis were used,

except that the 1960-4 data from Australia was not excluded. The study from Wales did not include data in this maternal age range.

The tabulated maternal age-specific birth prevalence rates are higher at all ages in the meta-analyses than in the NDSCR and EUROCAT data but all series combined indicates a flattening within this age range. This could be, at least in part, due to bias. One possibility is that there the observation is an artefact due to errors in the recording of maternal age. Pregnancy at such advanced reproductive ages is relatively uncommon and a proportion of those recorded as aged over 45 may in fact be younger and have a lower DS prevalence. One group of pregnancies where age might be under-recorded are those achieved by assisted reproductive technology (ART) using either a donor oocyte or an autologous frozen embryo transfer. The recorded age should be that of the donor or the woman at the time of storage rather than the literal maternal age. However, most of the pregnancies included in Table 2 occured before 1990, when ART was not very common, and this is unlikely to have contributed to the overall result.

There are also possible biological explanations. In older women, the Down syndrome fetal loss rate following prenatal diagnosis is relatively high (discussed below) but losses are likely to be even higher before prenatal diagnosis. Specifically, with the approach of menopause the number of available oocytes declines leading to fewer recognized pregnancies and the number of ~~trisomy 21~~abnormal oocytes (resulting in trisomic conceptions) may decline even more than ~~disomic~~ normal oocytes (resulting in non-trisomic conceptions). Double and triple aneuploidy with trisomy 21 and another autosomal trisomy or monosomy X are more common at advanced ages [8] and are excluded from DS prevalence rates.

Even if bias has substantially contribed to the flattening of the maternal age-specific curve, it would be reasonable to use a single birth prevalence estimate for all women aged 45 or more. Since the 95% confidence intervals (CIs) on the age-specific estimates in this range largely overlap, the number of cases and pregnancies can be combined. This yields an overall prevalence of 34.1 per 1000 (454/13,304) with 95% CI 31.2-37.3. The age-specific and overall estimates are shown together with the 95% CIs in Figure 1.

Table 3 shows the observed age-specific prevalence rates for each single year of age between 15 or less and 19 in nine studies included in the four meta-analyses and in the NDSCR. There are no substantial differences at any age in this range between prevalence in the meta-analyses and NDSCR and the rates are consistent with a baseline low prevalence as assumed with the use of an additive exponential curve.

The results are inconsistent with the suggestion that the prevalence of Down syndrome is relatively high at extremely young ages [21]. This was found in a USA register of malformations, the National Cleft Lip and Palate Intelligence Service during 1961-6, which included 4925 Down syndrome births obtained from birth certificates. A representative 1% sample of unaffected controls was obtained from the same referral areas as the cases and no adjustment was made for under-ascertainment. The prevalence in those aged under 15 was, after allowing for the sample control proportion, 0.682 per 1000 (3/44; 95% CI 0.235-1.82) compared with the rate at age 15-19 of 0.208 per 1000 (239/11,502; 95% CI 0.183-0.236). It is noteworthy though that prevalence was low at all ages in the 15-45 range indicating considerable under-ascretainment of Down syndrome which might have not been present in the youngest group.

Down syndrome – *intra-uterine* viability

Three approaches have been used to estimate the DS fetal loss rate between CVS or amniocentesis and term. These are (1) follow-up of individuals declining an offer of termination of pregnancy after prenatal diagnosis, (2) comparison of observed number of cases at the time of prenatal diagnosis to the number expected from the maternal age-specific prevalence curves at birth, and (3) comparison of age-specific curves developed for the time of prenatal diagnosis with those at birth. The estimates for approaches (1) and (2) are shown in Table 4.

Declining termination

The combined results from three amniocentesis series including a total of 110 cases in women having prenatal diagnosis for advanced age observed a 29% fetal loss rate [22]. However, such direct follow-up is potentially biased since some miscarriages will have occurred in women who did intend to have a pregnancy

termination, thus inflating the rate. Actuarial survival analysis rather than direct follow-up has been carried out for NDSCR data [23]. Not only does this overcome the bias but it is more data efficient since all cases contribute to the estimate, not just those in which pregnancy termination was refused. During the period 1989-96, among a total of 2035 cases diagnosed by amniocentesis carried out at 16-18 weeks gestation the estimated loss rate was 24%. There were also 441 cases diagnosed by CVS carried out at 11-13 weeks and the fetal loss rate was 31%. During this period, of the DS cases diagnosed prenatally in England and Wales the indication for invasive testing was advanced age in 40%, serum screening in 34% and ultrasound screening in 20%, the remainder because of family history and third trimester ultrasound [24]. The state-wide California screening program reported the direct follow-up of 392 pregnancies detected by screening and declining termination; the fetal loss rate was only 10% [25]. However, the authors suggested that the low rate may be due to some miscarriages having been classified as terminations of pregnancy. The screening program relies on reporting by obstetrical practioners and it is possible that some women who originally chose to continue the pregnancy changed their mind without informing the provider.

Prenatal diagnoses and number expected from birth prevalence

A number of studies have used this approach in women having prenatal diagnosis because of advanced age. In one study three series, two of them previously published, were combined yielding estimated loss rates after CVS and amniocentesis of 54% and 33% respectively [26]. In another study from the same group, two different previously published series were combined with an estimated rate after amniocentesis of 31% [27]. The group later considerably extended one of the original series and reanalysed the data to allow for the increase in maternal age between prenatal diagnosis and term [28]. This yielded much lower loss rates after CVS, 32% and after amniocentesis, 22%. Another study included five series, three of which were included in the above analyses, and found loss rates of 54% and 32% after CVS and amniocentesis [29]. One of the studies of DS births according to maternal age over 36 in Australia which was included in one of the meta-analyses also included data on prenatal diagnoses [20]. A statistical model was fitted and the estimated fetal

loss rates were much lower than the other studies – 31% and 18% after CVS and amniocentesis, but the numbers of cases were small and the upper 90% confidence limits were 52% and 38% respectively. Finally, modelling was also used on the combined data in older women from series included some of the studies of births (five), amniocentesis (three) and CVS (six) [30]. Again the estimated loss rates were low at 39% and 12%.

Potential confounding and bias

A problem with these analyses is that the maternal age, serum and ultrasound screening indications for invasive testing are associated with altered *a prior* risk of fetal loss generally and could potentially disproportionately influence fetal losses rates in DS pregnancies which are already vulnerable.

A large population based epidemiological study from Denmark has demonstrated that among pregnancies in general, the probability of miscarriage increases steadily with age from 9% at 20-24 to 75% at 45 or older [31]. Since, karyotype analysis is not routinely carried out on material obtained after miscarriage it is not known if aneuploidy *per se* contributes to the increasing rates.

Fetal demise is associated with abnormal screening marker levels: in the first trimester, low pregnancy associated plasma protein (PAPP)-A, low or high free β-human chorionic gonadotrophin (hCG), very large nuchal translucency (NT) or cystic hygroma; in the second trimester, low α-fetoprotein or unconjugated estriol, high hCG or inhibin-A [32]. The marker profile in women who are referred for invasive testing because of a screen-positive result varies according to maternal age. For example, in young women with a screen-positive Combined tests PAPP-A will be lower, free β-hCG and NT higher than older women with screen-positive results who might have moderate marker profiles and a higher risk just because of relatively advanced age.

Maternal and gestational age-specific rates

Comparison of maternal age-specific prevalence according to gestational age with that at birth has been carried out in two studies. The first study included three series in women aged 36 or more and was discussed above in relation to the overall fetal loss rate [28]. Relative prevalence compared to births was analysed and over this range it was not significantly related to maternal age but reduced with gestation: 1.57 at 9-10, 1.35 at 11-14 and 1.29 at 15-16 week, equivalent to fetal loss rates of 34%, 26% and 22% respectively. The second study was from NDSCR including 5177 prenatally diagnosed cases, more than 10 times larger than the first study and represented the entire maternal age range of 15-50 [33]. A subset of the cases had been included in a previous study of fetal loss which like this also used an actuarial survival analysis [23]. Proportional hazards regression was used to assess any effect on survival of maternal age, stratified by CVS or amniocentesis and gestational age. This showed a statistically significant increase in losses with maternal age from the time of CVS and from amniocentesis: at age 25, 23% and 19%; at 35, 32% and 25%; and at 45, 44% and 33%.

When the first study [28] was combined with three further series of older women [20,27,29], it was confirmed that the fetal loss rate from the time of CVS increased with maternal age but there was no statistically significant comparable increase from the time of amniocentesis [33]. It remains possible that the discrepancy between these studies and NDSCR is due to confounding with screening markers in younger women.

A consequence of an association between DS fetal loss and maternal age is that the estimated maternal age-specific birth prevalence rates in some studies will have been distorted. In studies which included a large numbers of terminated DS pregnancies and the number was reduced by applying a single overall fetal loss rate will have under-estimated prevalence at younger ages and over-estimated it at older ages. It is also possible that the association has contributed to the observed flattening of the birth prevalence curve at advanced maternal ages. However, this is unlikely to explain all the effect since the rate of increase in fetal losses with age is much less than the expected exponential increase in births.

Implications for Down syndrome screening

Age-specific prior risk

Screening programs differ in time referred to by the computed risk: term, mid-second trimester, late first trimester or the gestational week of screening. Those computing term risks – the probability of having a DS birth in the absence of detection and termination of pregnancy – use one of the published age-specific birth prevalence curves. However, since the curves were constructed from prevalence at completed years of age, they need to be modified to accurately estimate risk at the estimated date of delivery in years and decimals by subtracting 0.5 years assuming that the prevalence relates to the middle of the year. For the mid-second and late-first trimester referral points either an *overall* fetal loss factor from DS loss rates after amniocentesis or CVS is applied to the term prior risk or a maternal age-specific factor is used.

Monitoring performance

The expected detection and false-positive rates for different multi-marker screening policies can be derived from statistical modelling based on the assumption of multi-variate log Gaussian methods distributions of the multi-marker profile. An observed maternal age distribution can be used, usually a national population whose maternal age structure has been published, or a Gaussian distribution of maternal ages [34].

Deriving the performance of a specific policy in practice is not so straightforward. The observed false-positive rate is reliable but the observed detection rate will necessarily be inflated due to viability bias. One unbiased estimate is derived from the observed numbers of Down syndrome cases: screen detected terminated (n1) or not (n2), missed by screening but terminated subsequently (n3) or born (n4); using the formula (n1*p+n2)/(n1*p+n2+n3*p+n4), where p is the intra-uterine survival rate for Down syndrome at the time of prenatal diagnosis. Another approach is to calculate e which is the expected number of DS births, given the maternal age distribution of screened women and use the formula 1-(n2+n4)/e.

Edwards and Patau syndromes

Birth prevalence

Three studies, one of which combined multiple series, have reported aneuploidy rates following routine karyotyping of consecutive neonates in the era before widespread prenatal diagnosis [35-37]. The total numbers of Down, Edwards and Patau syndrome births were 143, 20 and 7 respectively. Hence the birth prevalence of Edwards syndrome was 1/7 that of Down syndrome and Patau syndrome was 1/20.

Maternal age-specific rates

These rates can be derived from a large study of these trisomies in nine regional multi-source congenital abnormality register, seven members of the British Isles Network of Congenital Anomaly Registers (BINOCAR) and two in Australia [38]. There were a total of 2254 with Edwards syndrome and 975 with Patau syndrome of which 59% and 57% respectively ended in termination of pregnancy. To allow for fetal losses, rates were applied according to trisomy, gestation and gender which had been derived in another BINOCAR study discussed below [39]. Logistic regression was carried out on the observed age-specific prevalences. Based on the regression curves the overall prevalence was for Edwards syndrome 1/8 of that for Down syndrome based on the NDSCR regression curve [10] and for Pat~~u~~au syndrome the overall prevalence was 1/13 of Down syndrome. For both Edwards and Patau syndrome the curves showed a flattening after age 45. Table 5 shows the regressed prevalences for selected maternal ages between 20 and 45 and Figure 2 shows the regression curves. Edwards syndrome prevalence relative to Down syndrome varied with age; Patau syndrome prevalence relative to Down syndrome reduced steadily with age, halving between 20 and 45.

Intra-uterine viability

The frequency of autosomal trisomies in spontaneous abortions indicates that viability is considerably lower for Edwards and Patau syndromes compared with Down syndrome. In a meta-analysis the total numbers of Down, Edwards and Patau syndrome miscarriages were 121, 46 and 35 respectively, prevalence ratios of 1/3 and 1/4 which are 2-4 fold higher than at birth [40].

Table 6 shows the estimated Edwards and Patau syndromes fetal loss rates in women declining termination of pregnancy and based on comparison of observed cases with those expected from maternal age-specific birth prevalence.

Two large studies have reported fetal loss rates in women who decline termination of pregnancy following amniocentesis. One study, including three series, reported fetal loss rates for Edwards and Patau syndromes of 68% (27/40) and 40% (4/10) respectively [22]. A study from the state-wide California screening program followed-up 106 Edwards syndrome and reported only 34 fetal deaths (32%) [25]. The same study found a relatively low fetal loss rate for DS pregnancies, possibly due to misclassification of some miscarriages as terminations of pregnancy (see above). Combining data from five small studies in women refusing termination after prenatal diagnosis the loss rate for Edwards syndrome was 70% (30/43) and for Patau syndrome 37% (20/54) [41-45].

Only one study estimated Edwards and Patau syndrome fetal loss rates by comparing the number of prenatal diagnoses, in older women, with that expected from birth prevalence rates [27]. The estimated loss rates for Edwards syndrome from the time of CVS and amniocentesis were 87% and 77%; for Patau syndrome 82% and 69% respectively. However, the expected number was calculated *indirectly* from the overall relative prevalence compared with Down syndrome based on routine karyotyping of consecutive neonates [35]. Hence, in addition to being based on small numbers of Edwards and Patau syndrome neonates, it makes the assumption that relative incidence is unrelated to maternal age.

More reliable loss rates are provided by a study from five members of BINOCAR which included 475 Edwards and 175 Patau syndrome cases diagnosed prenatally and followed-up [39]. Actuarial survival analysis estimated that for Edwards syndrome the loss rates from 12 and 18 weeks were 72% and 65%; for Patau syndrome 49% and 42% respectively. A similar study, but much larger study from NDSCR provides gestational age-specific fetal loss rates for each syndrome [46]. The actuarial survival rates from 12 and 18 weeks were for 4088 Edwards syndrome cases, 70% and 65%; for 1471 Patau syndrome cases 50% and 43% respectively.

Early small studies reported that the Edwards syndrome fetal loss rate was higher in males than females [22]. This was confirmed by the large BINOCAR study with loss rates from 12 weeks of 79% and 67%, and from amniocentesis, 85% and 64%, respectively [39], and by the NDSCR study [46]. However, none of these gender effects was statistically significant.

Origins of aneuploidy

The rapid increase in prevalence of the common autosomal trisomies over much of the maternal age range has generated a number of aetiological hypotheses. *Production line* - oocytes formed in late fetal life are more susceptible to mal-segregation and the order in which they eventually ovulate mirrors that in which they were produced [47]. *Ageing oocyte* - disturbances during stages of oogenesis, particularly meiotic arrest, are responsible [48]. *Relaxed selection* - the propensity for selection against trisomy, whereby affected fetuses are miscarried, decreases in older mothers [49]. *Premature reproductive ageing* - physiological ageing, for example depletion of the oocyte pool by accelerated atresia, is more important than chronological age *per se* [50].

Other aneuploidies of meiotic origin are also associated with advancing maternal age. However, the shapes of the curve may differ; for some such as trisomy 16 this is because of a greater propensity for mal-segregation [51] whilst some are more susceptible to early fetal loss due to greater imbalance [52]. In contrast, mitotic errors are largely not associated with age [53]. This might explain why the Patau syndrome prevalence relative to Down syndrome reduced steadily with age since a larger proportion of the former are mosaic.

The proportion of common autosomal trisomies births attributable to maternal age depends on the age distribution. It has been estimated that for England and Wales in 2017 the proportion was about three-quarters [54]. The identification of causal factors in the remaining cases is difficult to establish because of strong confounding by age and gestation.

The reason why some affected pregnancies with common autosomal trisomies are non-viable while others survive to term is not known unknown and a search for differentiating genetic or other factors would

be valuable. It has been suggested that in Edwards and Patau syndromes, the presence of a diploid cell line in the placenta enhances intra-uterine survival although this is not a pre-requisite [55].

Conclusions

Several curves have been developed to describe the increase in Down syndrome birth prevalence with advancing maternal age, based on meta-analysis or by the extensive data from a single national register. The curves do not differ substantially over the range 16-44 with a slow increase only doubling by about age 30, and doubling again by 35 with a much steeper increase therafter. At age 45 or older rates flatten and a single prevalence rate is applicable. There is no evidence that prevalence at age 15 or lower is higher than age 16-19. Edwards syndrome birth prevalence increases at a similar rate to Down syndrome, albeit not uniformly, but for Patau syndrome the increase is shallower. All three common autosomal trisomies have high intrauterine fatality. The fetal loss rate in Down syndrome increases with maternal age and is higher for Edwards syndrome with Patau syndrome having an intermediate rate.

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Table 1 – Estimated Down syndrome birth prevalence (/1000) at selected maternal ages from 20 regression curves

Regression curve*	Maternal age (years)							
	15	20	25	30	35	40	45	50
Meta-analyses								
First [4]								
8 studies, Additive-exponential (3)	0.634	0.654	0.740	1.10	2.60	8.86	35.0	144
Second [5]								
8 studies, Additive-exponential (3)	0.634	0.654	0.740	1.10	2.62	8.97	35.6	147
8 studies, 15-45 age range	0.637	0.656	0.740	1.10	2.60	9.01	36.2	152
8 studies, 15-49 age range	0.632	0.653	0.740	1.10	2.62	8.97	35.6	147
8 studies, 20-45 age range	0.644	0.663	0.745	1.10	2.60	9.01	36.4	153
8 studies, 20-49 age range	0.638	0.659	0.744	1.10	2.61	8.96	35.7	148
2 studies, 15-45 age range	0.594	0.616	0.711	1.12	2.87	10.4	42.7	181
2 studies, 15-49 age range	0.590	0.613	0.711	1.12	2.88	10.3	42.0	177
2 studies, 20-45 age range	0.636	0.655	0.740	1.12	2.81	10.4	44.1	195
2 studies, 20-49 age range	0.630	0.650	0.738	1.13	2.83	10.3	43.0	186
8 studies, Additive-exponential (5)	0.648	0.661	0.740	1.08	2.59	9.26	34.3	99.4
Third [6]								
5 studies, Additive-exponential (3)	0.642	0.666	0.764	1.17	2.87	9.96	39.4	162
5 studies, Additive-exponential (5)	0.664	0.678	0.766	1.14	2.86	10.4	37.0	96.9
5 studies, Additive-exponential (6)	0.588	0.659	0.782	1.16	2.78	10.5	36.9	54.8
4 studies, Additive-exponential (3)	0.661	0.682	0.777	1.18	2.92	10.4	42.5	180
4 studies, Additive-exponential (5)	0.659	0.679	0.781	1.18	2.89	10.5	41.8	145
4 studies, Additive-exponential (6)	0.510	0.655	0.798	1.19	2.81	10.7	41.9	102
Fourth [7]								
8 studies, Logistic (4)	0.688	0.710	0.803	1.20	2.90	10.1	39.6	184
7 studies, Logistic (4)	0.667	0.692	0.794	1.22	2.97	10.2	38.9	142
NDSCR [9,10]								
Logistic (4)	0.660	0.677	0.746	1.06	2.83	11.6	27.8	38.5

*the number of parameters is shown in parenthesis

Table 2 – Observed Down syndrome birth prevalence in single years of maternal ages from age 45 to 49, and older, in 12 studies

Studies	Maternal age (years)				
	45	46	47	48	≥49
Meta-analyses					
New York 1968-74 [12]*	40/1111	27/514	8/183	3/65	5/38
Massachusetts 1958-65 [13]	20/638	9/258	7/103	2/41	0/38
Canada 1971-8 [14]	11/327	-	-	-	-
Sweden 1968-70 [15]	9/161	7/82	1/35	2/19	0/9
Ohio 1970-9 [16]*	16/405	16/188	3/77	0/18	5/20
Sweden 1971-7 [17]	9/217	5/105	0/41	-	-
Belgium 1971-90 [18]	4/112	3/74	1/3	1/6	0/3
Australia (Southern) 1960-89 [19]	9/301	3/170	1/56	1/24	0/12
Intensive newborn 1967-73 [6]	2/19	1/7	1/2	-	-
Australia (Victoria) 1987-91# [20]	0/20	0/23	1/14	0/5	0/4
Total	120/3311	71/1421	23/514	9/178	10/124
Prevalence per 1000 births	36.2	50.0	44.7	50.6	80.6
(95% CI)	(30.4-40.2)	(39.8-62.6)	(30.0-66.2)	(26.8-93.3)	(44.4-142)
Others					
NDSCR [9]**	69/2277	33/1073	20/535	5/293	7/646
EUROCAT [11]	45/1620	21/686	15/303	4/125	2/198
Total	114/3897	54/1759	35/838	9/418	9/844
Prevalence per 1000 births	29.2	30.7	41.8	21.5	10.7
(95% CI)	(24.4-35.0)	(23.6-39.8)	(30.2-57.5)	(11.4-40.4)	(5.62-20.1)
All					
Total	234/7208	125/3180	58/1352	18/596	19/968
Prevalence per 1000 births	32.5	39.3	42.9	30.2	19.6
(95% CI)	(28.6-36.6)	(33.1-46.6)	(33.3-55.1)	(19.2-47.2)	(12.6-30.5)

*numerators adjusted for under-reporting on birth certificates

**numerators adjusted for under-reporting and terminations of pregnancy

#excluding prenatal diagnoses

CI=confidence interval, based on Wilson score

Table 3 – Observed Down syndrome birth prevalence in single years of maternal ages from age 15 or younger to 19, in 10 studies

Studies	Maternal age years				
	≤15	16	17	18	19
Meta-analyses					
New York 1968-74 [12]*	3/5142	11/12,524	19/27,701	37/51,057	43/80,075
Massachusetts 1958-65 [13]	1/1364	2/3959	10/9848	9/19,632	24/32,687
Canada 1971-8 [14]	-	-	-	15/13,675	16/18,752
Sweden 1968-70 [15]	0/383	1/1979	3/5265	10/9212	4/13,433
Ohio 1970-9 [16]*	5/11,114	14/24,404	30/45,190	33/65,802	63/84,721
Sweden 1971-7 [17]	-	0/3321	3/8883	8/15,891	23/25,262
Belgium 1971-90 [18]	0/797	0/2681	4/5834	5/10,664	9/18,405
Australia (Southern) 1960-89 [19]	1/1611	4/4212	4/9517	6/15,711	13/21,829
Intensive newborn 1967-73 [6]	0/55	0/228	0/457	0/799	1/1013
Total	10/20,464	32/53,308	73/159,695	123/202,443	196/296,177
Prevalence per 1000 births	0.489	0.600	0.457	0.608	0.662
(95% CI)	(0.265-0.899)	(0.425-0.847)	(0.364-0.575)	(0.509-0.725)	(0.575-0.926)
Other					
NDSCR [9]**	6/13,068	18/36,962	51/82,120	70/125,464	116/166,520
Prevalence per 1000 births	0.459	0.487	0.621	0.558	0.697
(95% CI)	(0.210-1.00)	(0.308-0.770)	(0.472-0.816)	(0.442-0.705)	(0.581-0.835)
All					
Total	16/33,532	50/90,270	124/241,815	193/327,907	312/462,697
Prevalence per 1000 births	0.477	0.554	0.513	0.589	0.674
(95% CI)	(0.294-0.775)	(0.420-0.730)	(0.430-0.611)	(0.511-0.678)	(0.604-0.753)

*numerators adjusted for under-reporting on birth certificates

**numerators adjusted for under-reporting and terminations of pregnancy

CI=confidence interval, based on Wilson score

Table 4 – Estimated Down syndrome fetal loss rate (95% CI) from CVS and amniocentesis to birth, in 9 studies

Studies	Indication	CVS	Amniocentesis
Declining termination			
[22]	Maternal age	-	29% (21-38%)
[23]	Mixed	31% (13-64%)	24% (17-34%)
[25]	Screening	-	10% (8.6-14%)
Prenatal diagnoses and expected births			
[26]	Maternal age	54% (48-61%)	33% (30-36%)
[27]	Maternal age	-	27% (25-30%)
[28]	Maternal age	32% (26-38%)	22% (18-27%)
[29]	Maternal age	54% (48-60%)	32% (26-39%)
[20]	Maternal age	31% (22-43%)	18% (11-29%)
[30]	Maternal age	39% (34-43%)	12% (10-14%)

CI=confidence interval, calculated by the authors or based on Wilson score

Table 5 – Estimated Down, Edwards and Patau syndrome birth prevalence at selected maternal ages (/1000 and relative to Down syndrome)*

Disorder	Maternal age (years)					
	20	25	30	35	40	45
Down syndrome (DS)	0.677	0.746	1.06	2.83	11.6	27.8
Edwards syndrome (ES)	0.112	0.116	0.139	0.283	1.36	4.68
Patau syndrome (PS)	0.0733	0.0764	0.0932	0.195	0.698	1.46
ES/DS	1/6	1/6	1/8	1/10	1/9	1/6
PS/DS	1/9	1/10	1/11	1/14	1/17	1/19

*from logistic regression curves: Down syndrome tabulated values [10]; Edwards and Patau syndromes directly from the curves [38]

Table 6 – Estimated Edwards and Patau syndrome fetal loss rates (95% CI), in 10 studies

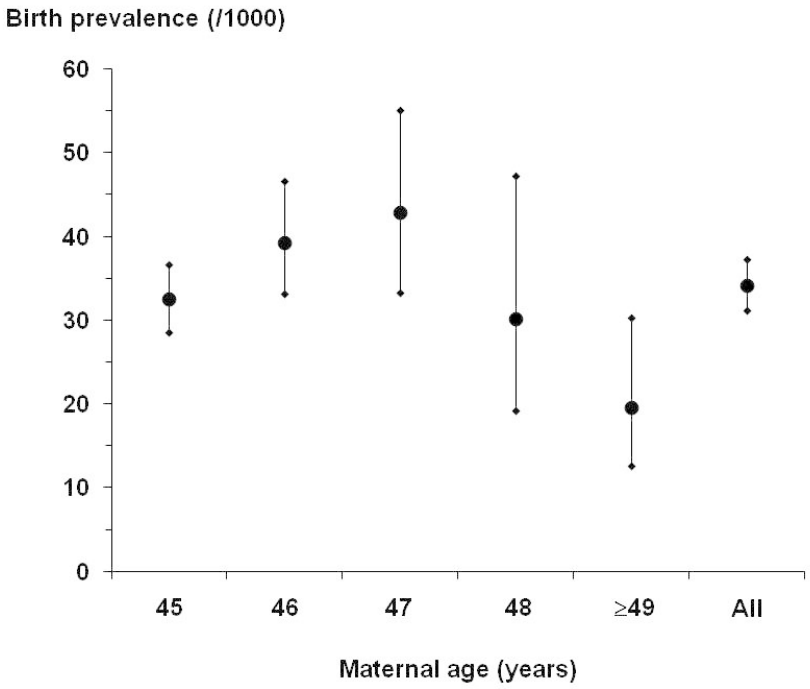
Studies	Diagnosis	Edwards syndrome	Patau syndrome
Declining termination			
[22]	Amniocentesis	68% (52-80%)	40% (17-69%)
[25]	Amniocentesis	32% (24-42%)	-
[41-45]	Prenatal diagnosis	70% (55-81%)	37% (25-50%)
Prenatal diagnoses and expected births			
[26]	CVS	87% (76-93%)	82% (64-93%)
	Amniocentesis	77% (71-82%)	69% (56-78%)
[39]	12 weeks	72% (61-81%)	49% (29-73%)
	18 weeks	65% (59-79%)	42% (18-72%)
[46]	12 weeks	70% (66-75%)	50% (42-59%)
	18 weeks	65% (60-70%)	43% (35-53%)

CI=confidence interval, calculated by the authors or based on Wilson score

Legends to Figures

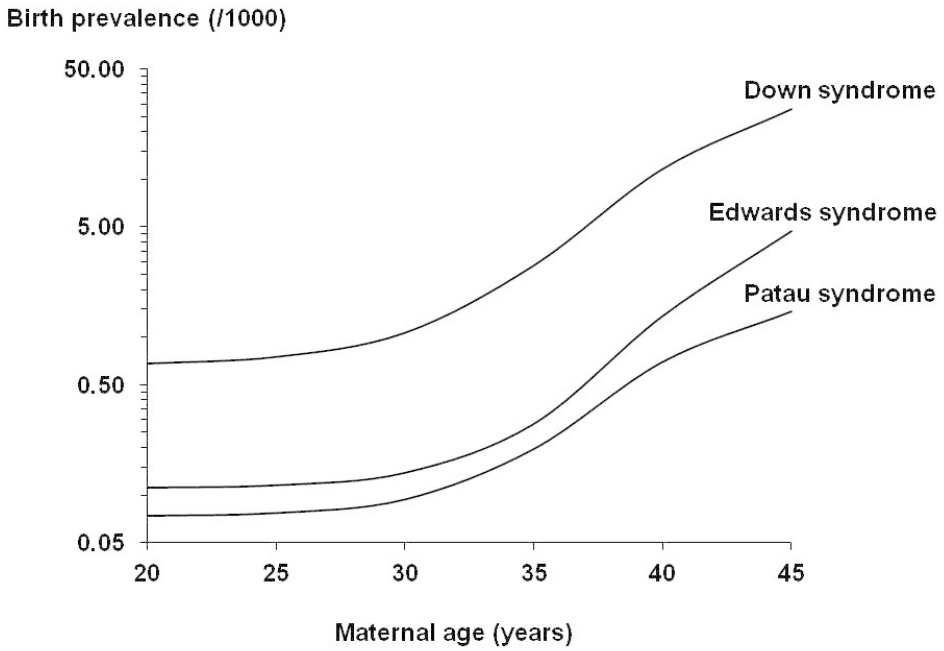
Figure 1 – Observed Down syndrome birth prevalence and 95% confidence interval at maternal age 45 or more from 12 studies combined: [6], [9], [11]-[20]

Figure 2 – Estimated Down, Edwards and Patau syndrome birth prevalence according to maternal ages from logistic regression curves in [10] and [38]



Observed Down syndrome birth prevalence and 95% confidence interval at maternal age 45 or more from 12 studies combined: [6], [9], [11]-[20]

254x190mm (96 x 96 DPI)



Estimated Down, Edwards and Patau syndrome birth prevalence according to maternal ages from logistic regression curves in [10] and [38]

254x190mm (96 x 96 DPI)