

Estimates of live birth prevalence of children with Down syndrome in the period 1991–2015 in the Netherlands

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Abstract

Background In Western countries, increasing maternal age has led to more pregnancies with a child with Down syndrome (DS). However, prenatal screening programs, diagnostic testing and termination of pregnancy influence the actual DS live birth (LB) prevalence as well. The aim of this study is to examine these factors in the Netherlands for the period 1991–2015. In our study, we establish a baseline for DS LB prevalence before non-invasive prenatal testing will be made available to all pregnant women in the Netherlands in 2017.

Methods Full nationwide data from the Dutch cytogenetic laboratories were used to evaluate the actual DS LB prevalence. In addition, nonselective DS prevalence, which is the DS LB prevalence that would be expected in absence of termination of

pregnancies, was estimated on the basis of maternal age distribution in the general population.

Results Because of an increase in maternal age, nonselective DS prevalence increased from around 15.6 [95% confidence interval (CI) 13.9–17.4] per 10 000 LBs in 1991 (311 children in total) to around 22.6 (95% CI 20.3–24.9) per 10 000 in 2015 (385), the increase levelling off in recent years. Actual LB prevalence rose from around 11.6 (95% CI 10.9–12.2) per 10 000 in 1991 (230 children) to an estimated peak of 15.9 (95% CI 15.6–16.2) per 10 000 in 2002 (322), gradually decreasing since to 11.1 (95% CI 10.8–11.5) per 10 000 in 2015 (190). Reduction of DS LBs resulting from elective terminations had been fairly constant between 1995 and 2002 at around 28% and rose afterwards from 35% in 2003 to around 50% in 2015.

Conclusions In spite of expansion of antenatal screening in the Netherlands in the 1990s and early 2000s, actual DS LB prevalence increased during this period. However, after 2002, this trend reversed, probably because of informing all pregnant women

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about prenatal testing since 2004 and the implementation of a national screening program in 2007.

Keywords birth prevalence, Down syndrome, epidemiology, first trimester prenatal screening, maternal age, NIPT

Introduction

In the Netherlands, the average age of women giving birth has steadily increased from around 27 years in the late 1970s to around 31 years in the period 2010–2015 (CBS, 2016a). As chromosomal aneuploidies are more prevalent in children born to older women, this increase in maternal age is to be expected to result in more pregnancies with a child with Down syndrome (DS).

Prenatal diagnosis and screening policies for Down syndrome

In the Netherlands, the cytogenetic examination of amniocentesis and chorion villus sampling was made available for women aged 36 years and over in the 1970s. In the mid-1980s, the alpha-fetoprotein measurement in amniotic fluid for the detection of neural tube defects was introduced, followed in the early 1990s by the second trimester serum screening and in the early 2000s by the first trimester combined test (ftCT). However, there was no national policy for offering these tests and no reimbursement (Crombag *et al.*, 2014). According to the Population Screening Act of 1996, counsellors were not allowed to actively bring screening tests to the attention of expectant women, unless there was an increased risk for fetal aneuploidy (for instance, advanced maternal age). However, women could request screening on their own initiative (Janssens & Beumer, 2001). In 2004, the government allowed informing all expectant women about prenatal screening tests (Crombag *et al.*, 2014). In 2007, a national screening program was implemented. For women aged 36 years and over, the costs of the ftCT were reimbursed (Schoonen, 2011). The costs for invasive testing were reimbursed in all cases.

In comparison with many other European countries, the uptake of screening with the ftCT has been relatively low in the Netherlands (<30%, versus England 74%, and Denmark >90%) (Crombag *et al.*, 2014). Although in all three countries there is an opt-in

system, Danish stakeholders (health professionals and parents) recognise that in their country, pregnant women probably experience prenatal screening as an opt-out system, as in the Danish context, almost all pregnant women participate in screening. In addition, it is a free test offered by the government, and this could be perceived as a recommendation (Crombag *et al.*, 2014). In the Netherlands, in contrast, women are explicitly asked if they want information on screening for DS before information is provided, and charging a fee for screening might convey the message that it is a deliberate choice. However, according to Crombag *et al.* (2016a), charging a fee only for younger women might have conveyed another, unjustly reassuring message, that is, that for younger women, screening is not needed. This might explain some of the difference between the Netherlands and England. In the Netherlands, uptake is much lower in younger than in older women (Schiljee & Schielen, 2013); this considerably lowers the total uptake of screening, as nowadays, around 80% of all Dutch women giving birth are younger than 35 years (CBS, 2016b, c). However, a low uptake in younger women will have a more modest effect on the total reduction of DS live births (LBs) resulting from termination of pregnancies (TOPs), as older women have a much higher chance of a pregnancy with a child with DS (Morris *et al.*, 2003).

What is the effect of ethnicity? The percentage of women from non-Western ethnic origin giving birth to a child has risen from 10% in 1985 to 20% in 2015 (CBS, 2017). In the 1990s and 2000s, mothers with a non-Western ethnic origin were relatively more often young mothers, which leads to a lower chance of DS LBs (absent elective terminations). However, these maternal age differences between non-Western migrants and the Dutch autochthonous population have diminished over time (CBS, 2017). In addition, as of 2009, in comparison with the 28%-uptake rate of ftCT in women from autochthonous Dutch origin, uptake rates were 15%, 15% and 8% in women from Turkish, Aruban/Antillean and North African ethnic origin, respectively (Fransen *et al.*, 2010). Thus, the changing ethnic profile of the Netherlands will moderate uptake of ftCT to some extent. However, in comparison with the UK and Denmark, uptake is remarkably low in the autochthonous Dutch population as well.

Recently, another screening method for DS was introduced: non-invasive prenatal testing (NIPT). In

the Netherlands, in April 2014, an evaluation study of NIPT was initiated: The Trial by Dutch laboratories for Evaluation of Non-invasive Prenatal Testing (TRIDENT). Inclusion was possible if the ftCT shows an increased chance ($>1:200$) for DS (or Edward or Patau syndrome) or for medical reasons (previous child with a trisomy 13, 18 or 21 or if one of the parents is a Robertsonian translocation carrier). The age criterion is no longer considered to be a valid reason, neither for invasive testing without a preceding ftCT nor for the NIPT. The costs of the ftCT are not reimbursed, but the costs of NIPT and invasive testing are. Recently, the Dutch government decided that as of 2017, NIPT should be allowed as the first test, without a preceding ftCT. For NIPT, a fee comparable with that for the ftCT will be charged.

With the planned introduction of NIPT in April 2017, an increased uptake of screening is expected, as women declining the ftCT for test-related reasons may tend to accept NIPT (Crombag *et al.*, 2016b). However, in the Dutch context, there is a considerable number of women who consider DS not to be a reason for TOP, and these may be more likely to decline NIPT (Bakker *et al.*, 2012; Crombag *et al.*, 2016b). On the other hand, women can choose for NIPT without having the intention to terminate the pregnancy. The TRIDENT study shows that out of the women choosing for NIPT after a positive ftCT result, 58% had the intention to terminate the pregnancy for DS (van Schendel *et al.*, 2016).

Focusing on NIPT, the Health Council (2013) warns for a potential negative impact of screening on the social position of individuals with DS. According to the Health Council, the biggest risk of NIPT is routinisation, accompanied by subtle pressure to participate in screening. If such routinisation and social pressure would occur, a strong increase in the number of DS-related TOPs, and a decrease in number of LBs of children with DS, might be expected to follow the introduction of NIPT. In order to evaluate whether introduction of NIPT actually leads to such strong changes, a baseline should be established.

The aim of this study

In this study, we explored the LB prevalence of children with DS. We followed an adaptation of the method of de Graaf *et al.* (2011a). However, in contrast to this previous study, all eight cytogenetic centres

participated in the present study, and in addition, the range of years is extended up to 2015. To evaluate the net effect of screening policies on DS LB prevalence, as a background, we also assessed nonselective prevalence, which is the DS LB prevalence that would be expected in absence of TOPs. This latter estimate is needed to evaluate to what extent the number of DS LBs is reduced by TOPs. In estimating actual and nonselective DS LB rates, we establish a baseline situation before NIPT will be made available to all pregnant women in the Netherlands in 2017.

Method

In the Netherlands, there are four professional registers recording births of children with DS notably one regional and three national registries (Supplementary Material S5 and the Discussion section). There are indications that both the national registry by midwives and obstetricians and the national registry by paediatricians suffer from substantial under-ascertainment (de Graaf, 2011a; Weijerman *et al.*, 2008). We expect a higher ascertainment in data based on cytogenetic examinations. The National Cytogenetic Network (LOC) of the Dutch Society for Clinical Genetic Laboratory Diagnostics has been collecting postnatal diagnostic data on DS from the Dutch cytogenetic centres from 1991 to 2012. The Working Party on Prenatal Diagnosis, WPDT, of the Dutch Society of Obstetrics and Gynaecology and the Dutch Association of Clinical Geneticists, has collected prenatal data from the cytogenetic centres since 1991. In this study, we used combined data of LOC and WPDT.

The annual figures of the LOC contain diagnoses of newborn children as well as adults. Especially in the early 1990s, some large organisations for people with developmental disabilities decided to let all their adult inhabitants be karyotyped, as karyotyping was not regular in their youth. To correct for these extra adult diagnoses, like de Graaf *et al.* (2011a), we approached the cytogenetic centres directly for more detailed information.

Nonselective Down syndrome prevalence

Nonselective DS prevalence is the DS LB prevalence that would have occurred in absence of TOPs. We estimated nonselective prevalence on the basis of maternal age distribution in general population.

Researchers have developed slightly different models for the relation between maternal age and the chance for a DS LB in absence of elective terminations (Morris *et al.* 2003). We have applied the most recent model. This model was developed by Morris *et al.* (2002) using data from the National Down Syndrome Cytogenetic Register. Data on maternal age at birth in the Netherlands were derived from the National Office for Statistics (CBS, 2016b). The method is described in Supplementary Material S1 (see also Table S1).

Postnatal diagnoses

The cytogenetic centres reported the number of postnatal diagnoses of DS by calendar year and year of birth. From 2001 onwards, we have full nationwide data on postnatal diagnoses of newborn children with DS. For preceding years without full data, we extrapolated on the basis of the available data, following the approach and assumptions of de Graaf *et al.* (2011a), that is, estimating the number of postnatal diagnoses in children by applying the annual child/adult ratios obtained from the participating centres to the nationwide data on postnatal diagnoses from the LOC. See Supplementary Material S3 and Table S3 for details.

Prenatal diagnoses

For the period 1991–2013, data on the annual number of prenatal diagnoses of DS (differentiated into TOPs and no-TOPs) were collected from the annual reports of the WPDT (1991–2013). In addition, the eight cytogenetic centres reported directly the number of prenatal diagnoses in 2014 and 2015.

Adjusted total Down syndrome prevalence

For 1991–2015, we calculated the total number of postnatal and prenatal diagnoses. This total number can be directly compared with the estimates of nonselective numbers of DS births, if adjusted for the natural fetal loss that would have occurred between the moment of prenatal diagnosis and the expected date of delivery in absence of TOPs. If there is a high ascertainment of DS diagnoses, the nonselective number of DS births and this adjusted total number of DS births should be highly similar. On the basis of a study of Savva, Morris, Mutton and Alberman (2006) who followed up pregnancies with children with DS,

de Graaf *et al.* (2011b) estimated natural fetal loss.

Following the same method, we estimated this natural fetal loss for our samples to be around 29% (see Supplementary Material S4 and Table S4 for a full explanation). So of every 100 prenatal DS diagnoses, around 71 would have been an LB in absence of TOPs. Thus, we estimate the adjusted total DS prevalence by (postnatal DS diagnoses + $(0.714 \times (\text{prenatal diagnoses from the preceding year} + \text{prenatal diagnoses from the current year})/2)$). As the first year with information on prenatal diagnoses in this article is 1991, the first year for which we could estimate adjusted total DS prevalence is 1992. The derived adjusted total DS prevalence was compared with the nonselective DS prevalence to evaluate the ascertainment of our empirical data (Fig. 1).

Live births after a prenatal diagnosis

The annual WPDT reports contain information on the number of prenatal diagnoses followed by a TOP versus prenatal diagnoses not followed by a TOP. Following the same method as described previously, in this case with the numbers of no-TOPs by category of referral as input, we estimated that out of these no-TOPs, ~72.5% probably will have been an LB (Supplementary Material S5 and Table S5). However, this method probably leads to an overestimation of LBs after a prenatal diagnosis, as it is possible that the outcome of the pregnancy is not known in 100% of the cases (and unknown outcomes, among which there might be a few TOPs, will be allocated to the category no-TOPs), and as some natural losses will have occurred between the moment of referral for chorion villus sampling or amniocentesis and the time of prenatal diagnosis. Three centres directly reported the results of the follow-up in more detail (Supplementary Material S5). In their sample, 51% of the no-TOPs were LBs, a smaller percentage than the ~72.5% indeed. It is important to realise that the effect of changing this parameter on the estimates of actual LBs is very small, because only a very limited number of prenatal diagnoses will not be followed by a TOP (see Supplementary Material S5 and the Discussion section).

To evaluate which of these two scenarios (72.5% or 51% LBs among the no-TOPs) is more plausible, we have conducted an additional analysis. Since 2013, one of the questions to parents of children with DS that

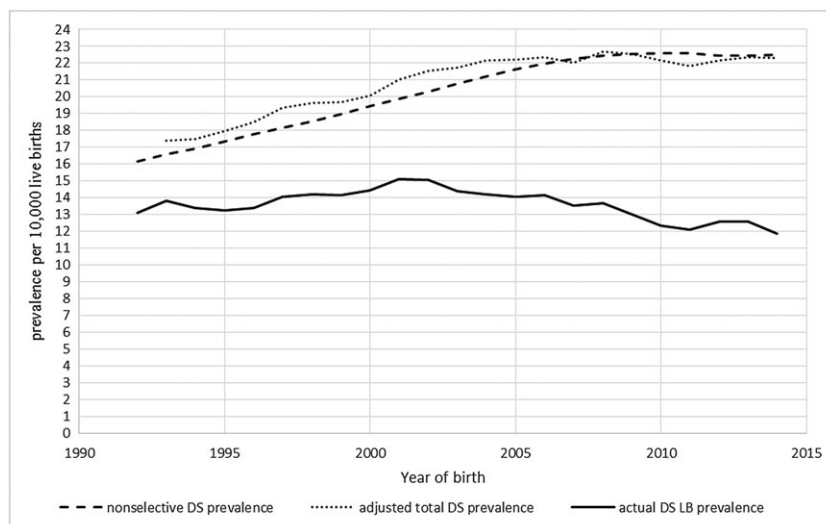


Figure 1 Estimates of nonselective DS prevalence, adjusted total DS prevalence and actual DS LB prevalence in the Netherlands, 3-year running averages*.

*Nonselective DS prevalence is the DS LB prevalence that would be expected in absence of TOPs – estimated on the basis of maternal age in general population; adjusted total DS prevalence is as follows: (observed postnatal DS diagnoses + ~ 0.72 observed prenatal DS diagnoses)/total of LBs in general population $\times 10\,000$; actual DS LB prevalence is the estimate of the actual number of DS LBs/total of LBs in general population $\times 10\,000$. DS, Down syndrome; LB, live birth; TOP, termination of pregnancy.

approach the Dutch Down Syndrome Foundation by phone is whether the diagnosis DS was delivered before or after birth. Secondly, in 2009 and again in 2016 (in 2016, only targeting children born later than 2009), the Foundation has conducted a questionnaire among parents of children with DS in which this question was included. We combined all these data (Supplementary Materials S5 and S6). Out of a total of 1211 LBs of children with DS, born between 1980 and 2015 and represented in these data, 77 were diagnosed prenatally. However, the percentage that was diagnosed prenatally was much lower in the earlier years (around 1% in the 1980s) than in more recent years (around 11% in 2015). In regard to the proportion of DS LBs that were prenatally diagnosed, the 51% scenario had the best match with the proportion found in the data of the Dutch Down Syndrome Foundation (Table S5). Therefore, we have followed this scenario in constructing our final estimates (Supplementary Materials S5 and S6).

Finally, combining these data, we estimated the trends in actual DS LB prevalence and in the net reduction of LBs resulting of TOPs (Table 1, Fig. 1 and Supplementary Material S6).

Results

Nonselective DS prevalence has risen from around 15.6 per 10 000 LBs in 1991 (an estimated 311

children in total) to around 22.6 per 10 000 in 2015 (385). Actual DS LB prevalence rose from around 11.6 per 10 000 in 1991 (230 children) to an estimated peak of 15.9 per 10 000 in 2002 (322). After 2002, DS LB prevalence has gradually decreased to around 11.1 per 10 000 in 2015 (190). The reduction of DS LBs resulting from TOPs was estimated at around 22% in the period 1991–1994, but has risen gradually since to an estimated 50% in 2015. These estimates are presented in Table 1. Figure 1 depicts our estimates of nonselective DS prevalence, adjusted total DS prevalence and actual DS LB prevalence as 3-year running averages.

Discussion

In spite of expansion of antenatal screening in the Netherlands in the 1990s and early 2000s, actual DS LB prevalence increased during this period. However, after 2002, this trend reversed.

Postponing motherhood has resulted in an increase of nonselective DS prevalence. Interestingly, this increase was fairly constant during the period 1991–2004, but has levelled off since. De Graaf *et al.* (2015) found a similar flattening in the USA after 2004. It appears that the trend of postponing motherhood is slowing down in recent years.

One might expect that the rise of reduction of DS LBs resulting from TOPs up to 2002 (from around

Table 1 Estimates of nonselective DS prevalence, adjusted total DS prevalence, actual DS LB prevalence, DS LBs, prenatal DS diagnoses, reported TOPs and net reduction[†] of DS LBs resulting from TOPs

| Year | Nonselective DS prevalence (per 10 000) | Adjusted total DS prevalence | Actual DS LB prevalence | Number of DS LBs | Prenatal DS diagnoses | Reported TOPs | Net reduction of DS LBs |
|------|---|------------------------------|-------------------------|------------------|-----------------------|---------------|-------------------------|
| 1991 | 15.6 (13.9–17.4) | | <11.6> (10.9–12.2) | <230> (217–242) | 106 | 96 | <26%> (17–36) |
| 1992 | 16.2 (14.4–18.0) | 17.2 (16.4–18.1) | 14.0 (13.5–14.6) | 276 (265–287) | 81 | 74 | 19% (14–24) |
| 1993 | 16.6 (14.8–18.5) | 17.1 (16.3–17.9) | 13.7 (13.2–14.2) | 268 (258–278) | 119 | 108 | 20% (16–25) |
| 1994 | 17.0 (15.1–18.8) | 17.8 (17.0–18.7) | 13.7 (13.2–14.2) | 268 (259–277) | 121 | 112 | 23% (19–28) |
| 1995 | 17.3 (15.4–19.2) | 17.6 (16.6–18.5) | 12.8 (12.2–13.3) | 243 (233–253) | 156 | 137 | 27% (23–33) |
| 1996 | 17.8 (15.9–19.8) | 18.5 (17.5–19.4) | 13.3 (12.8–13.7) | 252 (243–261) | 149 | 127 | 28% (24–33) |
| 1997 | 18.1 (16.2–20.1) | 19.4 (18.5–20.3) | 14.2 (13.8–14.6) | 273 (266–280) | 165 | 145 | 27% (23–31) |
| 1998 | 18.5 (16.6–20.4) | 20.1 (19.2–21.0) | 14.7 (14.3–15.1) | 293 (286–300) | 166 | 148 | 27% (24–31) |
| 1999 | 19.0 (17.0–20.9) | 19.3 (18.4–20.2) | 13.8 (13.5–14.2) | 277 (270–284) | 164 | 149 | 28% (25–32) |
| 2000 | 19.4 (17.5–21.4) | 19.6 (18.7–20.5) | 14.0 (13.7–14.3) | 290 (284–296) | 189 | 162 | 28% (25–32) |
| 2001 | 20.0 (18.0–22.0) | 21.3 (20.4–22.2) | 15.4 (15.2–15.7) | 313 (307–319) | 175 | 154 | 27% (24–31) |
| 2002 | 20.3 (18.3–22.3) | 22.1 (21.2–23.1) | 15.9 (15.6–16.2) | 322 (316–328) | 210 | 184 | 28% (25–32) |
| 2003 | 20.7 (18.7–22.8) | 21.8 (20.3–22.2) | 13.9 (13.6–14.1) | 278 (273–283) | 231 | 217 | 35% (32–39) |
| 2004 | 21.3 (19.2–23.4) | 21.8 (20.7–22.9) | 13.5 (13.2–13.7) | 261 (255–267) | 253 | 225 | 38% (36–42) |
| 2005 | 21.7 (19.5–23.9) | 23.4 (22.3–24.5) | 15.3 (14.9–15.7) | 287 (279–295) | 232 | 184 | 35% (31–38) |
| 2006 | 22.0 (19.8–24.2) | 21.4 (20.3–22.6) | 13.5 (13.1–13.9) | 250 (242–258) | 244 | 201 | 37% (33–40) |
| 2007 | 22.3 (20.1–24.5) | 22.2 (21.1–23.4) | 13.7 (13.3–14.2) | 249 (241–257) | 251 | 206 | 38% (34–42) |
| 2008 | 22.4 (20.2–24.6) | 22.4 (21.2–23.6) | 13.3 (12.9–13.8) | 246 (238–254) | 281 | 240 | 41% (37–44) |
| 2009 | 22.6 (20.4–24.8) | 23.4 (22.3–24.6) | 14.0 (13.6–14.3) | 258 (251–265) | 261 | 233 | 41% (38–44) |
| 2010 | 22.7 (20.4–24.9) | 21.8 (20.6–23.1) | 11.8 (11.4–12.2) | 218 (211–225) | 307 | 266 | 46% (43–50) |
| 2011 | 22.6 (20.4–24.8) | 21.3 (20.0–22.5) | 11.2 (10.8–11.6) | 202 (194–210) | 255 | 217 | 47% (44–51) |
| 2012 | 22.4 (20.2–24.7) | 22.3 (21.1–23.6) | 13.2 (12.8–13.7) | 233 (225–241) | 258 | 205 | 41% (36–44) |
| 2013 | 22.4 (20.1–24.6) | 22.9 (21.6–24.1) | 13.4 (12.9–13.8) | 229 (221–237) | 265 | 224 | 42% (37–45) |
| 2014 | 22.6 (20.3–24.8) | 21.8 (20.5–23.1) | <11.1> (10.8–11.5) | <195> (189–201) | 321 | <273> | <49%> (44–53) |
| 2015 | 22.6 (20.3–24.9) | 22.3 (20.9–23.6) | <11.1> (10.8–11.5) | <190> (184–196) | 277 | <235> | <50%> (46–54) |

Values in < > are (partly) based on trend data from preceding or following years.

Values in () are the 95% confidence interval.

DS, Down syndrome; LB, live birth; TOP, termination of pregnancy.

[†]For the period 1992–2015, net reduction is estimated as follows: (adjusted total DS prevalence – actual DS LB prevalence)/adjusted total DS prevalence; for the period 1986–1991, net reduction is estimated as follows: (nonselective DS prevalence – actual DS LB prevalence)/nonselective DS prevalence.

22% in the early 1990s to around 28% in 2002) would lower actual DS LB prevalence. Yet actual DS LB prevalence increased up to 2002. The lowering effect of more DS-related TOPs on actual DS LB prevalence was counterbalanced by an increasing nonselective DS prevalence, that is, more pregnancies with a child with DS. After 2002, actual DS LB prevalence started to decline. Firstly, the increase in nonselective DS prevalence levelled off in recent years. Secondly, in 2004, the Dutch government allowed actively informing all expectant women about first trimester combined prenatal screening. However, some hospitals had already started doing this in 2003. It seems that informing pregnant women – and subsequently establishing a national screening program in 2007 – has led to an increase in reduction of DS LBs, which had been fairly constant between 1995 and 2002 at around 28%, but rose afterwards from an estimate of 35% in 2003 to around 50% in 2015.

Accuracy of ascertainment

As the Dutch official medical guidelines for DS recommend that a diagnosis of DS always should be confirmed by a cytogenetic evaluation (Borstlap *et al.*, 2011), we would expect that in the Netherlands, every baby with clinical features suggesting DS will receive a cytogenetic examination. Our study confirms this assumed high ascertainment of DS by the cytogenetic centres. The estimated adjusted total DS prevalence is very similar to the estimated nonselective prevalence (the first is on average 2% higher for the period 1992–2015), which indicates a high ascertainment. This is in line with the results of the cytogenetic register in England/Wales, the National Down Syndrome Cytogenetic Register, which has a verified high level of ascertainment (Morris *et al.*, 2002; Savva and Morris, 2009). It seems logical that the registrations by cytogenetic centres could be a source of valid prevalence data for other genetic conditions as well. This could be explored in future studies.

Our study also confirms that there is under-ascertainment of DS in other national professional registers (the National Perinatal Database, LVR, since 1994 combined with the National Neonatology Registration LNR, as LVR/LNR, and the Dutch Paediatric Surveillance Unit, NSCK; Supplementary Material S2). For instance, on the basis of the

LVR/LNR, for the period 1997–2007, van Gameren *et al.* (2012) estimated an average number of 288 DS births (LB, TOP and natural pregnancy loss combined) per year. We found a mean total of 475 prenatal and postnatal DS diagnoses per year for the same period. This discrepancy cannot be fully accounted for by the fact that the LVR/LNR does not register TOPs before 16 weeks of pregnancy. In the WPDT data for 1997–2007, an annual average of 111 prenatal diagnoses of DS was made after an amniocentesis, of which 93 were reported to have been TOPs. The result of an amniocentesis will not be available before the 16th week of pregnancy. The LVR/LNR registered an average total of only 43 TOPs and natural losses per year for this period. There appears to be some underreporting of LBs in the LVR/LNR as well. We estimated 281 LBs per year for 1997–2007; van Gameren *et al.* (2012) report only 245, which is 13% less.

Limitations of this study

Nevertheless, a limitation should be mentioned. In the WPDT annual reports, the no-TOPs are not differentiated into LBs, natural pregnancy losses and stillbirths, and unknown outcomes. We have estimated the proportion of LBs among the no-TOPs to be around 51% on the basis of more detailed data of only three of the centres. However, our analysis suggests that this leads to a good match with data of the Dutch Down Syndrome Foundation as regards the proportion of DS LBs that were prenatally diagnosed. We suggest that the validity of the cytogenetic data on prenatal diagnoses could be further improved if the pregnancy outcomes were specified into more categories, that is, LB, TOP, natural pregnancy loss and still birth, and unknown outcome. At this moment, the WPDT only specifies total number of prenatal diagnoses and total number of reported TOPs.

However, it is important to note that the difference in estimated total number of DS LBs between the two scenarios (72.5% or 51% LBs among the no-TOPs) is relatively small. For 2015, the first scenario would have led to an estimation of 201 DS LBs compared with 191 in the 95% scenario, a difference of ~5%. For earlier years, differences between these scenarios are even smaller, around 2% or less before 2005.

Down syndrome live birth prevalence and reduction percentage in other countries

In many countries, including England and Wales (Morris and Alberman, 2009), Slovenia (Tul *et al.*, 2007), Australia (Bittles *et al.*, 2007; Collins *et al.*, 2008) and most European Registration Of Congenital Anomalies (EUROCAT) regions (Dolk *et al.*, 2005), the effect of increasing maternal age on DS LB prevalence was counterbalanced by a growing use of pre-natal screening, resulting in a stable, or slightly decreasing, DS LB prevalence since the 1980s. In contrast, in the Netherlands (de Graaf *et al.*, 2011a, b and the current study) and the USA (de Graaf *et al.*, 2015), DS LB prevalence slightly increased since the 1980s. In the USA, this growth in DS LB prevalence continued at least until 2008 (de Graaf *et al.*, 2015). In the Netherlands, however, DS LB prevalence has been slightly decreasing since 2002.

The reduction of DS LBs resulting from TOPs was estimated at 30% in the USA for 2006–2010 (de Graaf *et al.*, 2015), at 55% in Australia as of 2004 (Bittles *et al.*, 2007), at 48% in the UK as of 2008 (Morris and Alberman, 2009), at 49% in Massachusetts for 2006–2010 (de Graaf *et al.*, 2016) and at 47% for Slovenia as of 2005 (Tul *et al.*, 2007).

The reduction rates in the Netherlands used to be more in line with the relatively low rates in the USA as a whole. However, for the period 2011–2015, reduction of DS LBs in the Netherlands has increased to an estimated average of around 46%, with values of around 50% for the two most recent years. It is important to note that this increase in reduction of DS LBs resulting from TOPs is not a sudden result of the introduction of NIPT in April 2014 in the TRIDENT study, but should be considered as a gradual process that started in the 1990s, with a temporary acceleration around 2003, probably related to the new policy of informing all expectant women about prenatal screening tests about that time.

In conclusion, our study has yielded reliable information on the historical development of DS LB prevalence and reduction of DS LBs resulting from TOPs in the Netherlands. These results can be considered a baseline to assess the effects of the planned introduction of NIPT as prenatal screening test available for all pregnant women in the Netherlands in 2017.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

S1: Estimating nonselective DS prevalence

S2: Registries of DS births in the Netherlands

S3: Postnatal DS diagnoses

S4: Prenatal diagnoses and estimating adjusted total DS prevalence

S5: TOPs and estimating prenatally diagnosed DS LBs and actual DS LB prevalence

S6: Estimates of number of DS LBs, actual DS LB prevalence and reduction of DS LBs

S7: References for Supplementary Materials