International Trends of Down Syndrome 1993–2004: Births in Relation to Maternal Age and Terminations of Pregnancies

Guido Cocchi,[1] Silvia Gualdi,[1] Caroline Bower,[2] Jane Halliday,[3] Björn Jonsson,[4] Åsa Myrelid,[4] Pierpaolo Mastroiacovo,[5] Emmanuelle Amar,[6] Marian K. Bakker,[7] Andrea Correa,[8] Berenice Doray,[9] Kari Klungsør Melve,[10] Babak Koshnood,[11] Daniella Landau,[12] Osvaldo M. Mutchinick,[13] Anna Pierini,[14] Anukka Ritvanen,[15] Vera Ruddock,[16] Giocchino Scarano,[17] Barbara Sibbald,[18] Antonin Sípek,[19] Romano Tenconi,[20] Dave Tucker,[21] and Göran Annerén[4]*

[1]Istituto Clinico di Pediatria Preventiva e Neonatologia and the Emilia-Romagna Registry of Congenital Malformations, Bologna, Italy
[2]Western Australian Birth Defects Registry, Perth, Australia
[3]Murdoch Children's Research Institute, Victoria, Australia
[4]Swedish Birth Defect Registry, National Board of Health and Welfare, Stockholm and Department of Genetics and Pathology, Uppsala University, Uppsala, Sweden
[5]Centre of the International Clearinghouse for Birth Defects and Research, Rome, Italy
[6]Central-East France Register of Congenital Malformations, Lyon, France
[7]EUROCAT Northern Netherlands, Department of Genetics, University Medical Centre, Groningen, the Netherlands
[8]Metropolitan Atlanta Congenital Defects Program, Atlanta, GA
[9]Strasbourg Prospective Study of Congenital Malformations, Strasbourg, France
[10]Medical Birth Registry of Norway, Norwegian Institute of Public Heath and Department of Health and Primary Heath Care, University of Bergen, Bergen, Norway
[11]Paris Registry of Congenital Malformations, Paris, France
[12]Israel Birth Defects Surveillance Program, Beer-Sheva, Israel
[13]Department of Genetics, Mexican Registry and Epidemiological Surveillance of Congenital Malformations, National Institute of Medical Science and Nutrition Salvador Zubrirán, Mexico City, Mexico
[14]Tuscany Registry of Congenital Defects, Epidemiologiy Unit, IFC-CNR, Pisa, Italy
[15]Register of Congenital Malformations, National Institute for Health and Welfare, Helsinki, Finland
[16]National Congenital Anomaly System of England and Wales, London, England
[17]Birth Defects Registry of Campania, Benevento, Italy
[18]Alberta Congenital Anomalies Surveillance System, Alberta Health & Wellness and Department of Clinical Genetics, Alberta Children's Hospital, Calgary, AB, Canada
[19]National Register of Congenital Anomalies of the Czech Republic, Department of Medical Genetics, Thomayer University Hospital, Prague, Czech Republic
[20]North East Italy Registry of Congenital Malformations, Padova, Italy
[21]CARIS—Welsh Congenital Anomaly Register, Swansea, Wales, UK

Received 5 November 2009; Revised 12 February 2010; Accepted 16 February 2010

BACKGROUND: The aim of this study was to examine trends of Down syndrome (DS) in relation to maternal age and termination of pregnancies (ToP) in 20 registries of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR). **METHODS:** Trends of births with DS (live-born and stillborn), ToP with DS, and maternal age (percentage of mothers older than 35 years) were examined by year over a 12-year period (1993–2004). The total mean number of births covered was 1550,000 annually. **RESULTS:** The mean percentage of mothers older than 35 years of age increased from 10.9% in 1993 to 18.8% in 2004. However, a variation among the different registers from 4–8% to 20–25% of mothers >35 years of age was found. The total mean prevalence of DS (still births, live births, and ToP) increased from 13.1 to 18.2/10,000 births between 1993 and 2004. The total mean prevalence of DS births remained stable at 8.3/10,000 births, balanced by a great increase of ToP. In the registers from France, Italy, and the Czech Republic, a decrease of DS births and a great increase of ToP was observed. The number of DS births remained high or even

*Correspondence to: Göran Annerén, Department of Genetics and Pathology, Uppsala University, S-751 85 Uppsala, Sweden.
E-mail: goran.anneren@genpat. uu.se

Published online 2 April 2010 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/bdra.20666

increased in Canada Alberta, and Norway during the study period. **CONCLUSIONS:** Although an increase in older mothers was observed in most registers, the prevalence of DS births remained stable in most registers as a result of increasing use of prenatal diagnostic procedures and ToP with DS. *Birth Defects Research (Part A) 88:474–479, 2010.* © 2010 Wiley-Liss, Inc.

Key words: Down syndrome; birth prevalence; termination of pregnancies; maternal age; international trends

INTRODUCTION

The incidence of Down syndrome (DS) at conception is highly dependent on maternal age (Lindsten et al., 1981; Hecht and Hook, 1996; Olsen et al., 1996; Bray and Wright, 1998). Carothers and co-workers (1999) concluded, based on data from 49 population groups, that variation between population groups was small, after accounting for maternal age. The majority of observed differences in the prevalence of births with DS between populations are thus likely to be due to variations in maternal age distributions, maternal age-specific pregnancy rates, and the use of prenatal diagnosis and the termination of affected pregnancies.

The International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) is an international organization of population- and hospital-based registers for surveillance and research of birth defects (Botto et al., 2006). We assessed the impact of changes in maternal age and the use of prenatal diagnostic procedures and elective terminations on the prevalence of DS at birth. Data for this study came from the ICBDSR for the period 1993–2004, which comprises 20 registries in nine European countries and five non-European countries.

MATERIALS AND METHODS

Data were provided by 20 birth defects registers (Table 1) from 14 countries (Australia, Canada, Czech Republic, England, Finland, France, Israel, Italy, Mexico, the Netherlands, Norway, Sweden, USA, Wales). Six registers (Czech Republic, England, Finland, Norway, Sweden, and Wales) covered all births in the nation, and the other 14 registers covered all births from a defined region in their country. France and Italy reported data from three and four different regions, respectively.

The following data were obtained from each registry by year 1993–2004: total number of births, percentage of mothers older than 35 years of age at delivery, number of children (live-born and stillborn) with DS per 10,000 births, number of terminations of pregnancies (ToP) with DS per 10,000 births, and total number of live-born, stillborn, and ToP with DS per 10,000 births. The overall means and percentages are presented as weighted means according to number of births per country (Table 1).

Mean gestational age in weeks at termination for DS in mothers >35 years of age in 2002 was available for 16 of the registers (Table 2).

Table 1
Mean Number of Births; Percentage of Mothers Older than 35 Years; Mean Number of DS/10,000 Births; Mean Number of Terminated Pregnancies with DS (ToP)/10,000 Births; Total Number of DS (Liveborn + Stillborn + ToP)/10,000 Births for the Period 1993–2004

Country/registry	No. Births	Maternal age >35 years, %	Newborn DS	Terminations	Total DS
Australia: Western	25,306	14.95	11.46	11.97	23.43
Australia: Victoria	63,210	17.71	11.35	13.09	24.45
Canada: Alberta	38,019	14.41	13.68	4.11	18.58
Czech Republic	96,158	5.8	6.19	8.81	15.00
England	636,816	14.61	5.63	5.23	10.85
Finland	59,425	17.38	12.08	11.63	23.63
France: Central-East	103,964	15.37	7.39	12.62	20.01
France: Paris	38,878	24.37	7.25	27.09	34.34
France: Strasbourg	13,437	13.3	6.1	13.88	19.89
Italy: Campania	50,574	13.98	6.91	6.11	13.02
Italy: Emilia-Romagna	25,603	18.82	7.88	11.23	19.11
Italy: North-East	55,376	22.83	8.58	7.09	15.67
Italy: Tuscany	24,002	21.52	6.73	9.71	16.48
Israel	20,880	16.36	5.73	3.71	9.43
Mexico	38,508	6.23	11.9	0	11.9
Norway	59,321	13.88	12.45	3.73	17.15
Netherlands: Northern	19,766	14.81	10.64	4.83	15.47
Sweden	98,220	16.04	13.07	9.07	22.12
USA: Atlanta	46,248	14.94	12.66	3.95	16.61
Wales	31,634	13.6	9.72	9.82	19.57
All, 1993	1,554,529	10.89	8.29	4.78	13.08
All, 2004	1,564,501	18.77	8.32	9.92	18.24

Table 2
Mean Gestation Age (Number of Weeks ± Standard Deviation) at Time of Termination of Pregnancies with DS in Women Older than 35 Years of Age in 16 Different Registries in 2002

Monitoring registers	Gestational week (Mean ± SD)
Australia: Victoria	16.91 ± 1.72
Canada: Alberta	18.63 ± 2.33
Czech Republic	19.41 ± 1.85
Finland	18.00 ± 1.36
France: Central-East	19.68 ± 2.96
France: Paris	21.25 ± 4.75
France: Strasbourg	22.67 ± 5.39
Israel: IBDMS	21.50 ± 1.38
Italy: BDRCam	20.39 ± 2.34
Italy: IMER	21.43 ± 1.29
Italy: North-East	19.31 ± 1.60
Italy: Tuscany	18.94 ± 1.12
Netherlands: Northern	18.25 ± 0.96
Sweden	17.19 ± 1.48
USA: Atlanta	20.00 ± 3.61
Wales	18.53 ± 2.23

RESULTS

Maternal Age

The percentage of delivering mothers >35 years of age increased in most registers included in the study (Figs. 1 and 4). The percentage of mothers older than 35 years of age increased from 10.8% in 1993 to 18.8% in 2004. The overall percentage for each register is presented in Table 1. The lowest percentage of older mothers was observed in the Czech Republic (5.8% over the study period, ranging from 4.3% in 1993 to 8.1% in 2004). Mexico had a similar low percentage of older mothers (6.2%), which did not change during the study period. The greatest increase in mothers >35 years of age was observed in Italy (all four registers combined), where the percentage increased from 14.5 to 22.7% during the study period. A similar increase was observed in France, and the Paris region reported the highest percentage of mothers older than 35 years of age (28.7% in 2004). Similar increases in maternal age were reported from the two Australian registers with 12.9% of the mothers >35 years of age in 1993 compared to 22.4% 2004. There was a much smaller increase (14.8 to 16.5%, in 1993 and 2004, respectively) in the percentage of mothers >35 years of age in the mean of the two registers in North America (Canada Alberta and USA Atlanta) compared to the European and Australian registers.

Births with DS

Overall, the mean birth rate with DS remained stable (8.3/10,000 births) during the study period (Figs. 2 and 4). There were, however, differences between registers. A marked decrease in DS births was observed in registers from France and Italy, whereas Canada Alberta, Israel, and Norway reported an increase in DS births.

ToP with DS

The mean rate of ToP with DS increased from 4.8/10,000 births in 1993 to 9.9/10,000 births in 2004 (Fig. 4). The greatest increase was observed in France, especially in the Paris region (14.8/10,000 in 1993 to 35.7/10,000 in 2004). In the two North American registers (Canada Alberta and USA Atlanta) the rates of ToP with DS were low (Fig. 5), and little change was observed during the study period (3.5 and 3.1/10,000 births in 1993 and 2004, respectively). The ToP rate in Norway was low compared to that of the other Nordic countries. The mean gestational ages at ToP because of DS in mothers >35 years of age are presented in Table 2 and range from 16.91 week in Victoria (Australia) to 22.67 weeks in Strasbourg (France).

Total Prevalence of DS

The total mean prevalence of DS (live and stillbirths and terminations of pregnancies) increased from 13.1/10,000 births in 1993 to 18.2/10,000 births in 2004. In 1993 in the European and Australian registers almost two-thirds of all DS pregnancies resulted in a birth, but in 2004 an opposite trend was seen with two-thirds of DS

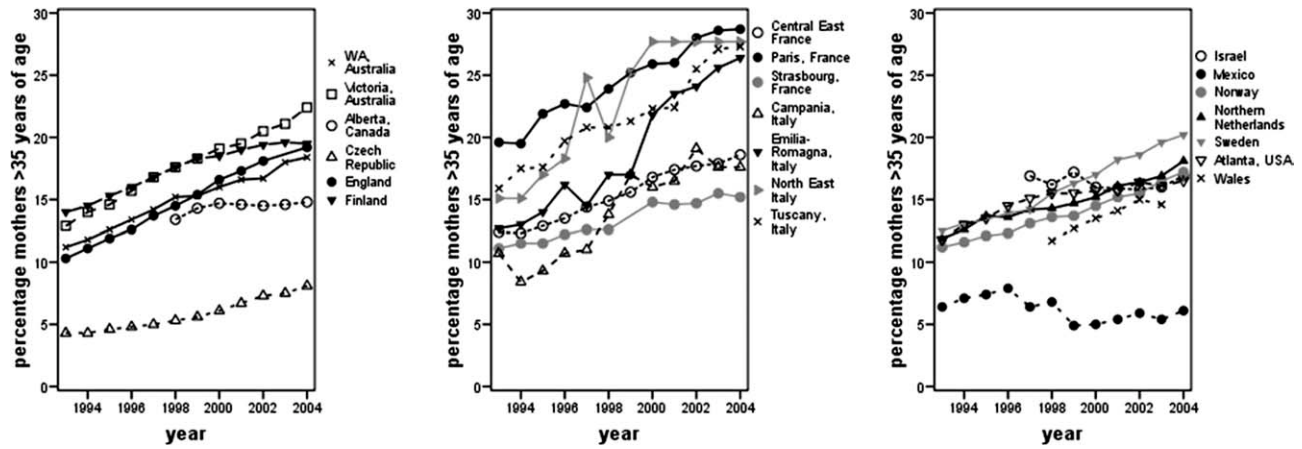

Figure 1. Mean percentages of mothers ≥35 years of age in the registers during the period 1993–2004. A: Australia Western, Australia Victoria, Canada Alberta, Czech Republic, England, Finland. B: France Central East, France Paris, France Strasbourg, Italy Campania, Italy Emilia-Romagna, Italy North East, Italy Tuscany. C: Israel, Mexico, Netherlands Northern, Norway, Sweden, USA Atlanta.

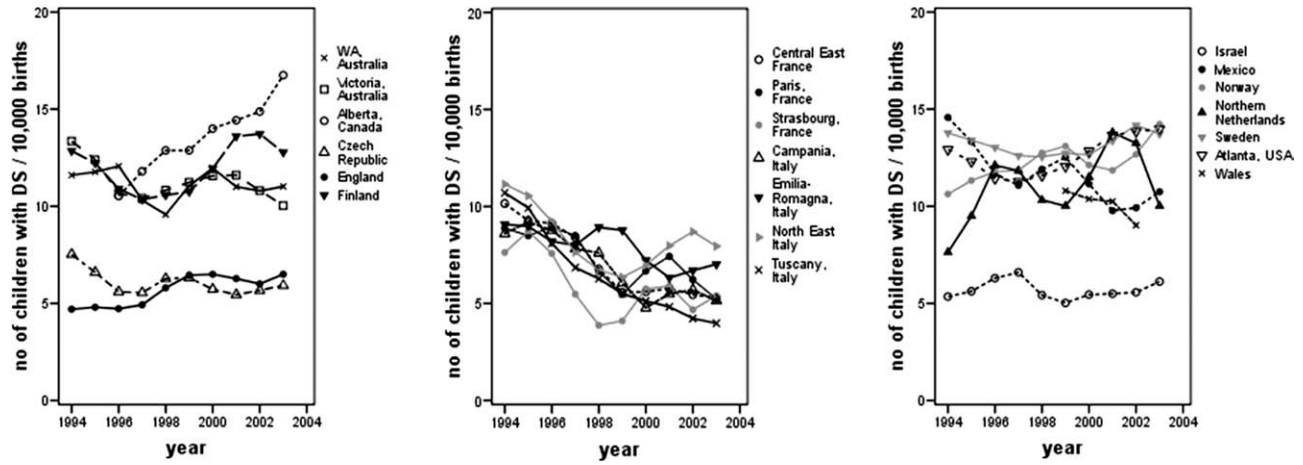

Figure 2. Mean numbers of born children with DS (live-born + stillborn)/10,000 births in the registers during the period 1993–2004. A: Australia Western, Australia Victoria, Canada Alberta, Czech Republic, England, Finland. B: France Central East, France Paris, France Strasbourg, Italy Campania, Italy Emilia-Romagna, Italy North East, Italy Tuscany. C: Israel, Mexico, Netherlands Northern, Norway, Sweden, USA Atlanta.

pregnancies ending in ToP (Fig. 5). In the North American registers about 3/4 of all DS pregnancies resulted in birth of a DS child, with little change over time.

DISCUSSION

We found increases in maternal age at birth for most registers, consistent with the findings of Dolk et al. (2005) for Europe and Bittles et al. (2006) in Australia. This has resulted in an increase in pregnancies with DS, but because of increasing use of different prenatal diagnostic procedures followed by terminations of DS pregnancies, overall there has been no change in births of children with DS. In most registers the increase in DS pregnancies was balanced by an increase in terminations. However, in France (also reported by others, such as Khoshnood et al., 2004, 2008) and Italy, there was a very clear decrease of DS births.

In the North American registers (Canada Alberta, Mexico, and USA Atlanta) there was no or very little increase in mean maternal ages, and terminations of pregnancies with DS were performed to a lesser degree than reported from the Australian and European registers (Stiffel et al., 2004). In the USA an increase in children born with DS has been reported (Besser et al., 2007), and in Victoria, Australia, no change in live-birth prevalence has been reported (Collins et al., 2008). In the present study an increase in DS births was observed in Alberta, Canada, Israel, and Norway.

There are great differences in the laws and policies concerning terminations of pregnancies between countries (Dolk et al., 2005). Terminations of pregnancies are allowed to be performed very late in the second trimester

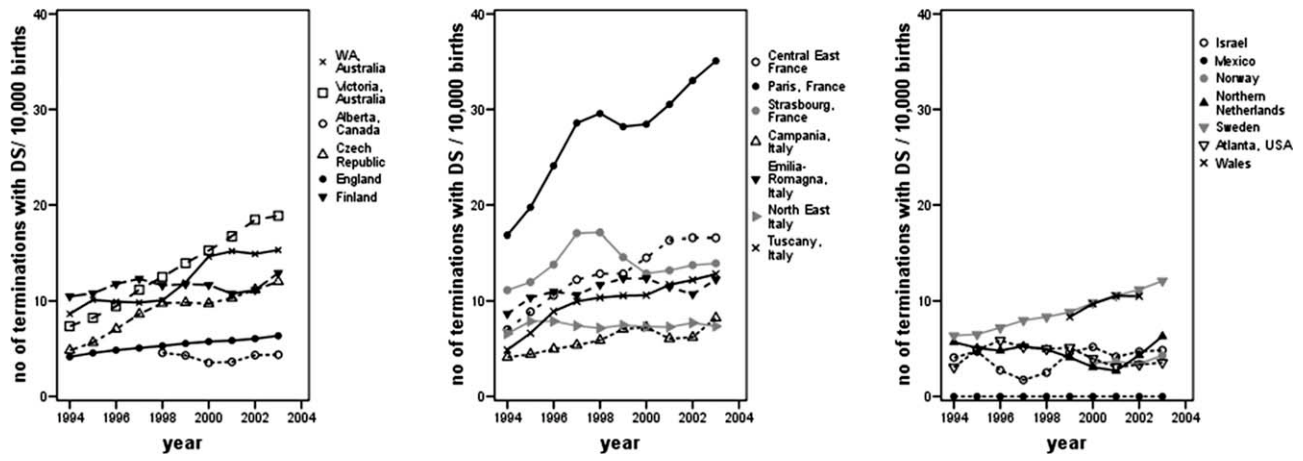

Figure 3. Mean numbers of terminated pregnancies with DS/10,000 births in the registers during the period 1993–2004. A: Australia Western, Australia Victoria, Canada Alberta, Czech Republic, England, Finland. B: France Central East, France Paris, France Strasbourg, Italy Campania, Italy Emilia-Romagna, Italy North East, Italy Tuscany. C: Israel, Mexico, Netherlands Northern, Norway, Sweden, USA Atlanta.

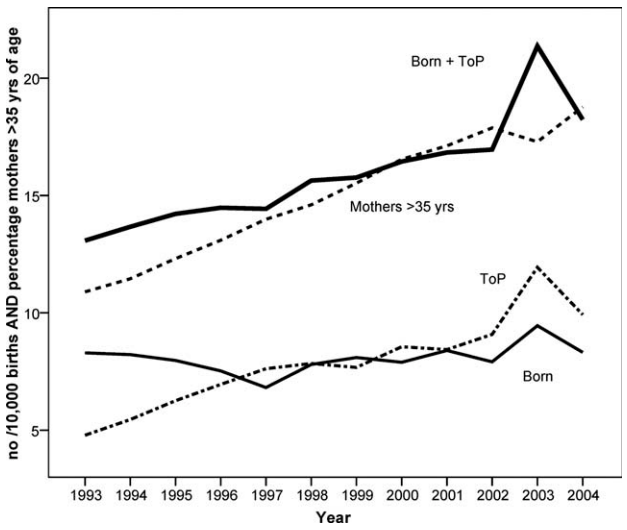

Figure 4. Mean total trends of percentage mothers older than 35 years of age, born children (live-born and stillborn) with DS/10,000 births, termination of pregnancies with DS (ToP)/10,000 births, observed total DS (live-born and stillborn children + ToP)/10,000 births for the period 1993–2004.

in some countries (Czech Republic, France, Israel, and Italy) and not permitted at all in Mexico. These differences, along with different methods of prenatal screening and diagnosis, are reflected by differences in gestational age at the time of terminations of pregnancies with DS (Table 2). In France and Italy, but also in Israel and USA Atlanta, the mean gestational age at terminations was later compared to that of Australia Victoria, Canada Alberta, Finland, Northern Netherlands, and Sweden. The implementation of the measurement of nuchal translucency and maternal serum screening have been an important factor in the reduction in prevalence of DS births in France (de Vigan et al., 2008; Goujard, 2007; Kjaersgaard et al., 2008). In the study period of this investigation (1993–2004) these screening methods were not yet introduced in most of the countries included. In Sweden, for example, only half of pregnant women were offered such screening in 2009, and in some countries amniotic fluid sampling is restricted to older mothers (>37 years of age in Norway).

All these factors have resulted in differences in the prevalence of DS births. Norway with a rather large population of older mothers and with little use of prenatal diagnostic procedures has a high rate of children born with DS (17/10,000 births). France, especially the Paris region, has a high proportion of older mothers, but the use of prenatal procedures and terminations of pregnancies are widely used, which results in one of the lowest prevalence of DS births combined with the highest rate of ToP with DS.

In spite of similar numbers of mothers older than 35 years of age among registers there was a large variation in reported cases with DS among the registers. This raised a suspicion of under-registration. Under-reporting in the England register has previously been shown (Boyd et al., 2005). When this register is excluded from the calculations, the total mean of births + ToP changed from 13.1 to 16.8/10,000 births in 1993 and from 18.2 to 21.5/10,000 births in 2004. In addition, we had data on only the percentage of mothers older than 35 years of age, but not the exact numbers of mothers in each age group. Thus we could not evaluate the correct ascertainment according to the method of Hecht and Hook (1981). In an ongoing study by Leoncini and co-workers using data from present registries for the period 2002–2005, the ascertainment has been calculated using the method of Hecht and Hook (1981). The under-ascertainment varied among registers and was in some registers substantial; it was most likely due to under-reporting of ToP, rather than births with DS (Leoncini, personal communication).

CONCLUSIONS

Maternal age at delivery has increased in almost all parts of the western world. In 1993 about 11% of mothers were older than 35 years of age, and 12 years later it was about 19%. This resulted in a great increase of pregnancies with DS, but because of increasing use of prenatal diagnostics procedures and terminations of pregnancies, the prevalence of DS births remained stable in most registers. There are, however, differences between the European and Australian registers compared to the North American registers, which report fewer terminations of pregnancy with DS and do not show the same increase in maternal age.

ACKNOWLEDGMENTS

This study was supported by grants from the Sävstaholm Foundation, the Medical Faculty of Uppsala University, and the Swedish Research Council.

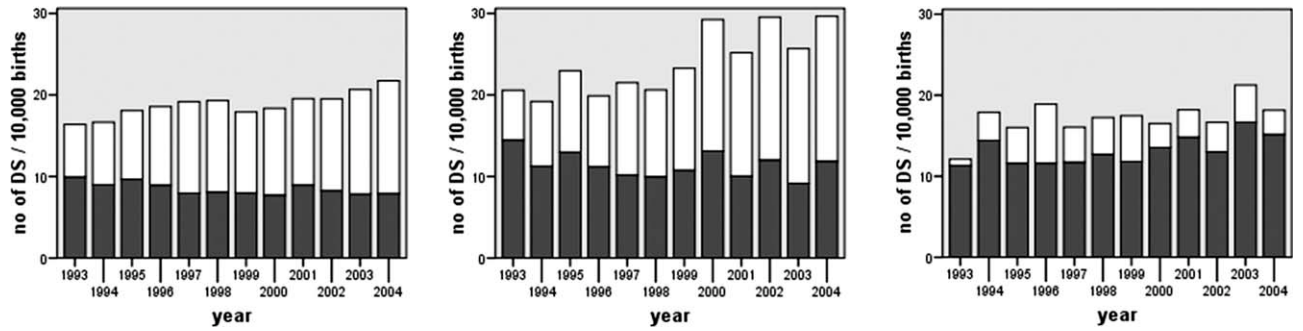

Figure 5. Mean total numbers live-born and stillborn (gray bars) and terminated pregnancies (white bars) with DS/10,000 births for the period 1993–2004 in (A) Europe, (B) Australia, and (C) North America.

REFERENCES

Besser LM, Shin M, Kucik JE, et al. 2007. Prevalence of Down syndrome among children and adolescents in Metropolitan Atlanta. Birth Defects A Res 79:765–774.

Bittles AH, Bower C, Hussain R, et al. 2006. The four ages of Down syndrome. Eur J Public Health 17:221–225.

Botto LD, Robert-Gnansia E, Siffel C, et al. 2006. Fostering international collaboration in birth defects research and prevention: a perspective from the International Clearinghouse for Birth Defects Surveillance and Research. Am J Public Health 96:774–780.

Boyd PA, Armstrong B, Dolk H, et al. 2005. Congenital anomaly surveillance in England-ascertainment deficiencies in the national system. Br Med J 330:27–32.

Bray IC, Wright DE. 1998. Estimating the spontaneous loss of Down syndrome foetuses between the times of chorionic villus sampling, amniocentesis and livebirth. Prenat Diagn 18:1045–1054.

Carothers AD, Hecht CA, Hook EB, et al. 1999. International variation in reported livebirth prevalence rates of Down syndrome, adjusted for maternal age. J Med Genet 36:386–393.

Collins VR, Muggli EE, Riley M, et al. 2008. Is Down syndrome a disappearing birth defect? J Pediatr 152:20–24.

De Vigan C, Khoshnood B, Lhomme A, et al. 2005. Prevalence and prenatal diagnosis of congenital malformations in the Parisian population: twenty years of surveillance by the Paris Registry of Congenital Malformations. J Gynecol Obstet Biol Reprod 34:8–16.

Dolk H, Loane M, De Walle H, et al. 2005. Trends and geographic inequalities in the prevalence of Down syndrome in Europe, 1980–1999. Rev Epidemiol Sante Publique 53:87–95.

Goujard J. 2004. Are there any changes in Down syndrome prevalence in France following the implementation of the measurement of nuchal translucency and maternal screening? Gynecol Obstet Fertil 32:496–501.

Hecht CA, Hook EB. 1996. Rates of Down syndrome at livebirth by one-year maternal age intervals in studies with apparent close to complete ascertainment in populations of European origin: a proposed revised rate schedule in genetic and prenatal screening. Am J Med Genet 24:376–385.

ICBDSR (International Clearinghouse for Birth Defects Surveillance and Research) Annual Report 2008. Available at: www.icbdsr.org.

Khoshnood B, De Vigan C, Blondel B, et al. 2008. Long-term trends for socioeconomic differences in prenatal diagnosis of Down syndrome: Diffusion of services of persistence of disparities? Epidemiology 115:1087–1095.

Khoshnood B, De Vigan C, Vodovar V, et al. 2004. A population based evaluation of the impact of antenatal screening for Down's syndrome in France 1981–2000. Br J Obstet Gyneccol 111:485–490.

Kjaersgaard S, Hahnemann JM, Jensen LN, et al. 2008. Prenatal diagnosis of chromosome aberrations after implementation of screening for Down's syndrome. Ugeskr Laeger 170:1152–1156.

Lindsten J, Marsk L, Berglund K, et al. 1981. Incidence of Down's syndrome in Sweden during the years 1968–1977. Hum Genet Suppl 2:195–210.

Olsen CL, Cross PK, Gensburg LJ, et al. 2006. The effect of prenatal diagnosis, ageing, and changing fertility rates on the live birth prevalence of Down syndrome in New York State, 1983–1992. Prenat Diagn 16:991–1002.

Siffel C, Correa A, Cragan JA, et al. 2004. Prenatal diagnosis, pregnancy terminations and prevalence of Down syndrome in Atlanta. Birth Defects Res A Clin Mol Teratol 70:565–571.

Soergel P, Pruggmayer M, Schwerdtfeger R, et al. 2006. Screening for DS with maternal age, fetal nuchal translucency and maternal serum biochemistry at 11–14 weeks: a regional experiency from Germany. Fetal Diagn Ther 21:264–268.