

Is Down Syndrome a Disappearing Birth Defect?

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Objective To assess trends in the prevalence of Down syndrome (DS) from 1986 to 2004 in Victoria, Australia (population ~5 million).

Study design The Victorian Birth Defects Register and the Prenatal Diagnosis Database were linked to ascertain all cases of DS. Total and birth prevalence estimates were calculated per year and presented as 3-year moving averages.

Results The total number of cases of DS increased from 113 in 1986 to 188 in 2004. The number of births declined over the first decade of the study, particularly in younger women, but total numbers have fluctuated between 45 and 60 births since 1996. In women under age 35 years, total prevalence was 10/10,000 until 1997 and then increased to 12.5/10,000. In older women, total prevalence increased from 70/10,000 to 90/10,000 in this time frame. Birth prevalence declined at first but remained relatively stable in the later years of the study. The proportion of cases diagnosed prenatally increased from 3% to 60% in younger women.

Conclusions Our findings demonstrate the continuing need to devote resources to support individuals with DS and their families. (*J Pediatr* 2008;152:20-4)

The major factors expected to influence the epidemiology of Down syndrome (DS) are changes in the maternal age distribution in the population and the availability and use of prenatal testing. Over the past 20 years or so, the State of Victoria and Australia as a whole have seen a shift in the age distribution of women giving birth, with the proportion of women over age 35 years increasing quite markedly.¹ There has also been a significant increase in the availability and use of prenatal diagnostic and screening services for the identification of DS. Since the late 1970s, prenatal diagnostic tests—chorionic villus sampling and amniocentesis—have been available free of charge to pregnant women of advanced maternal age, classified in Victoria as 37 years and older. With the introduction of second trimester maternal serum screening in 1996 and first trimester combined screening in 2000, many younger women now receive prenatal diagnosis on the basis of screening risk results.²

Similar changes in maternal age distribution and prenatal testing have been occurring in many countries to a greater or lesser extent, with resulting effects on the prevalence of DS.³⁻¹⁵ Some studies have reported no changes^{6,8,9,11-13} or only minor decreases^{3,5,9,10,14,15} in the live birth prevalence of DS. These populations exhibit variations in maternal age distribution and in the availability and use of prenatal testing, making direct comparison difficult. Moreover, most studies report data only up to the late 1990s or early 2000s, so that more recent trends have not been widely reported.

We have used 2 high-quality statewide data collections on prenatal diagnosis and birth defects to study the epidemiology of DS in a geographically defined population, specifically to examine the net effect of increasing maternal age and uptake of prenatal testing from 1986 to 2004. This comprehensive analysis over a 19-year period will contribute to the global understanding of the epidemiology of DS, particularly that pertinent to other developed countries. It will also provide relevant information for those providing funding for support services as well as clinicians involved in the care of individuals with DS and their families.

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| BDR | Births Defects Register | PDCU | Perinatal Data Collection Unit |
| DS | Down syndrome | | |

METHODS

Databases

Two statewide data collections were used to ascertain all cases of DS in Victoria for the years 1986 to 2004. Access to these data was formally granted by the Consultative Council on Obstetric and Paediatric Mortality and Morbidity of Victoria.

The Births Defects Register (BDR) is a statewide population-based surveillance system administered by the Perinatal Data Collection Unit (PDCU) of the Victoria Department of Human Services. Notifications to the BDR come from multiple sources on all birth defects for live births, stillbirths, and neonatal deaths (20 weeks gestation and later), as well as terminations of pregnancy for birth defects occurring at all gestational ages.¹⁶ Validation studies have shown that a high proportion of pregnancies and births diagnosed with birth defects are reported to the BDR, particularly those due to chromosomal abnormalities.¹⁷

All cases with a code indicating DS were extracted from the BDR, including translocation DS and trisomy 21 but not mosaic trisomy 21. The variables extracted for analysis included age of mother, outcome of pregnancy (live birth, stillbirth, neonatal death, termination of pregnancy, or miscarriage), and gestation at birth or termination.

Data on all prenatal diagnostic tests (chorionic villus sampling and amniocentesis) performed in Victoria since the late 1970s have been collected by a joint arrangement between the Murdoch Childrens Research Institute and the Department of Human Services in Victoria. All 4 cytogenetic laboratories (2 public, 2 private) in Victoria that process prenatal diagnostic tests contribute to the database.

Data Linkage

The BDR and the prenatal diagnosis database were linked using the mother's name and date of birth, and linked records were checked for accuracy using the date of the test, gestation at the test and birth, and date of birth. Each record in the resulting merged database included details of whether or not there had been a prenatal test, the type of prenatal test, gestational age at the time of the test, and birth outcome information. Identifying information was removed from the database for analysis. A small number of cases in the prenatal diagnosis database had no outcome of pregnancy recorded on the BDR. These cases were assumed to be terminations of pregnancy before 20 weeks' gestation that had not been reported to the BDR.

Data Analysis

"Total cases" refers to all pregnancy outcomes, including termination of pregnancy (both pre- and post-20 weeks' gestation), miscarriages, stillbirths, neonatal deaths, and live births. "Births" refers to outcomes at 20 weeks' gestation or later, including stillbirths, neonatal deaths, and live births but not terminations. All analyses of maternal age exclude DS due

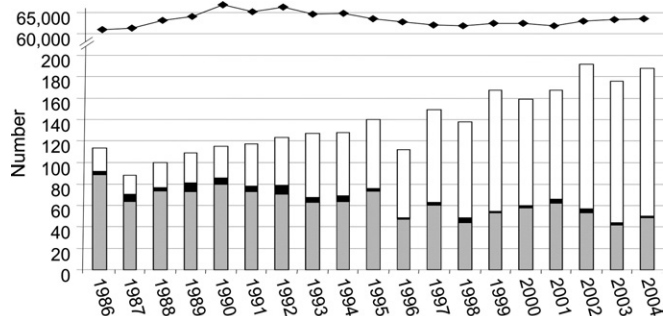


Figure 1. Total numbers of cases of DS according to pregnancy outcome. Termination, number of terminations of pregnancy □; SB & NND, number of stillbirths and neonatal deaths ■; live birth, number of live births ▒; VIC births, total number of births in Victoria -◆-.

to chromosomal translocation, because this is not associated with maternal age.¹⁸

Data are presented according to year of birth or termination of pregnancy. Prevalence estimates were calculated using the numbers of births in Victoria for each year as the denominator and are presented as number of cases of DS per 10,000 births. Three-year moving averages were calculated for prevalence estimates to smooth the fluctuations in prevalence from year to year, and 95% Poisson confidence limits were calculated for prevalence estimates.

Maternal age-stratified analyses are presented as under 35 years and 35 years and over to allow comparison with other studies and populations. Figures showing the proportion of cases diagnosed prenatally are presented in 3 age groups (under 35 years, 35 to 36 years, and 37 years and over) to account for the prenatal diagnosis policies in Victoria (where testing is available free of charge to women 37 years and older). The 35- to 36-year age group represents an important minority group that is likely to differ from the other 2 age groups with respect to use of prenatal diagnosis.

Age-standardized prevalence of trisomy 21 was calculated by the direct method using 5-year maternal age groups of births in Victoria in 1995 as the standard population. Evidence of trends in proportions over time was assessed using χ^2 tests for linear trend with the Mantel extension.¹⁹

RESULTS

Figure 1 shows that against a relatively stable birth rate in Victoria, particularly since 1996, the total number of cases of DS increased from 113 in 1986 to a peak of 192 in 2002. Since 1996, the number of live births has generally been lower and the numbers of pregnancy termination pregnancy higher than in the earlier period.

Among the total cases of DS, the vast majority (97%) were trisomy 21. Over the 19-year study period, there were 72 cases of translocation DS, 85% of which occurred in women under age 35 years (data not shown). The following analyses related to maternal age include only cases of trisomy 21.

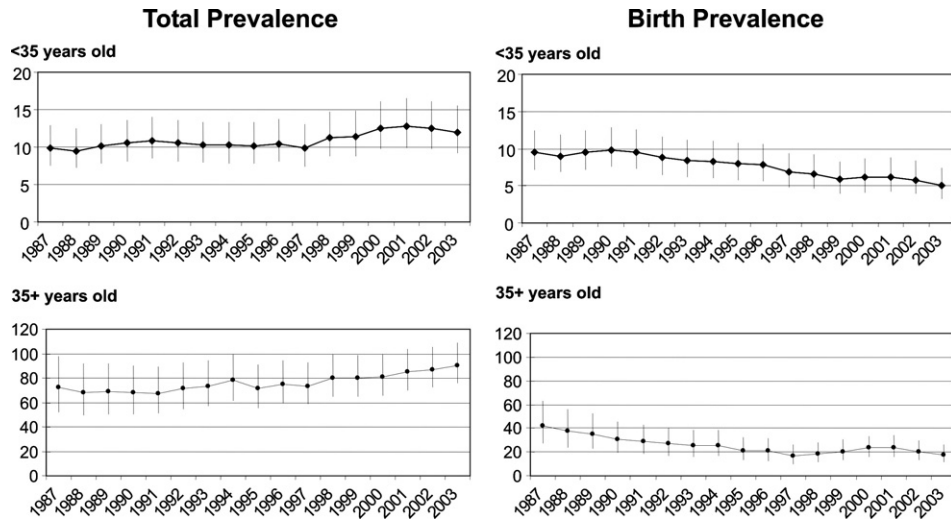


Figure 3. Total and birth prevalence of trisomy 21 per 10,000 births according to maternal age groups, presented as 3-year moving averages.

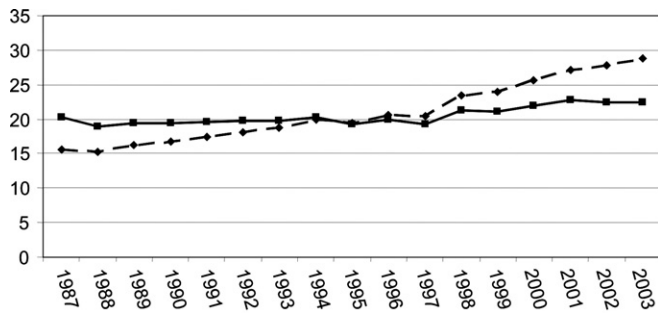


Figure 4. Crude and age-standardized* prevalence of total trisomy 21 per 10,000 births, presented as 3-year moving averages. *Standardized to 1995 maternal age distribution of births in Victoria. -◆-, crude; -■-, age-stand.

When considering births (20+ weeks' gestation) only, in younger women, there has been a steady decline over time, with 22 in 2004 compared with more than 60 in 1986 (Figure 2; available at www.jpeds.com). However, in older women, the numbers have not changed greatly, with 25 in 1986 and 26 in 2004. The more dramatic decrease over time in the number of births to women under age 35 years has resulted in a declining proportion of births with trisomy 21 in women in this age group. In 1986, 72% of births with trisomy 21 were to women under age 35, compared with 46% in 2004 (data not shown).

The total prevalence of trisomy 21 in women under 35 years stayed relatively stable, with 3-year averages of around 10/10,000 from 1987 to 1997, but increased to around 12.5/10,000 from 1998 onward (Fig 3). In older women, there was a gradual increase in total prevalence from about 70/10,000 to 90/10,000 in this same time frame. Conversely, birth prevalence has decreased in both age groups, with prevalence in the final 3-year period about half that in the first 3-year period.

To adjust for the effect of increasing maternal age, age-standardized prevalence estimates (3-year moving averages)

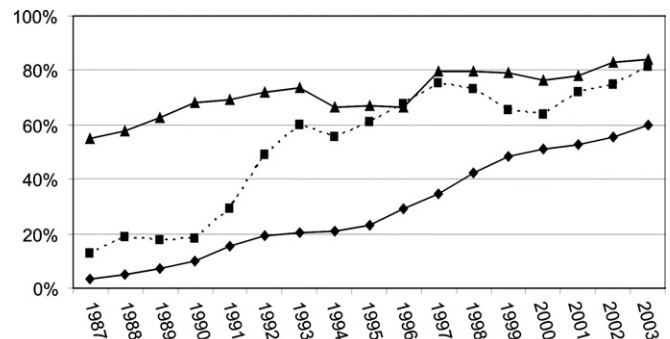


Figure 5. The proportion of cases of DS diagnosed prenatally according to maternal age groups, presented as 3-year moving averages. -◆-, <35; -■-, 35-36; -▲-, 37+.

are presented in Figure 4. The age-standardized prevalence fluctuated around 20/10,000 until 1997, after which it increased gradually, reaching 22.6/10,000 in 2003.

The proportion of DS cases that were diagnosed prenatally has changed dramatically for women under age 35 (Fig 5), increasing from 3% in the earliest 3-year average to 60% in the latest 3-year period ($\chi^2_{\text{trend}} = 150$; $P < .001$). A significant change in this percentage also occurred in women at age 37 and over, increasing from about 50% in the earlier period to around 80% in the latest period ($\chi^2_{\text{trend}} = 17$; $P < .001$). Although the numbers are lower in the 35- to 36-year age group, an upward shift in the proportion of cases diagnosed prenatally from 1992/1993 onward can be seen ($\chi^2_{\text{trend}} = 44$; $P < .001$).

Most cases diagnosed prenatally have resulted in termination of pregnancy. Over the entire study period, 5.3% of pregnancies with a prenatal diagnosis were not terminated. Although some fluctuations in the proportions occurred year by year, there is no evidence of a trend over time (data not shown).

DISCUSSION

This comprehensive analysis of the epidemiology of DS provides essential information for various stakeholders. The data can be used by policy makers and service providers to assess current programs and prioritize resources for the provision of prenatal testing programs. Importantly, the data highlight the ongoing need for support services for people with DS and their families. In addition, accurate current information is vital for consumer and support groups, such as the Down Syndrome Association, whose functions include providing information about DS to many sectors of the community.

The total prevalence of DS has increased in both age groups, which can be largely explained by the overall increase in the age of women giving birth during the study period. In 1986, 8% of women giving birth in Victoria were 35 years or older; by 2004, this percentage had increased to 23%.¹ Comparison of crude and age-standardized total prevalence of trisomy 21 reveals that increasing maternal age over time had a substantial effect on prevalence. This effect also has been seen in other populations in which similar demographic shifts have occurred.³⁻⁹ However, after the effect of age is removed, the most recent 6 years shows an increase in age-standardized prevalence. Since the introduction of nuchal translucency screening and first trimester combined screening, DS is diagnosed earlier in pregnancy. Thus, pregnancies that in the past would have miscarried before diagnosis due to the relatively high rate of early miscarriage of almost 1/3 of fetuses with DS²⁰ are now being detected through screening. The 13% rise in age-standardized prevalence can be attributed to this earlier detection.

Direct comparison of the prevalence of DS across populations is hampered by differing maternal age distributions and prenatal testing availability. Moreover, few studies have reported data as recent as 2004, with most reporting only up to the late 1990s. Nonetheless, a similar rise in total prevalence has been reported in Australian,^{3,4} British,^{6,11} North American,²¹ and Western European,^{5,9} populations, all of which have experienced significant increases in maternal age over time.

Victoria has seen a decline in birth prevalence over the study period, particularly in younger women, in whom <50% of all DS diagnoses resulted in a birth in the most recent period. This finding reflects the increasing access to prenatal screening in the younger age group; only about 50% of the babies born with DS in 2004 were born to women in the younger age group, compared with 75% in earlier years.

In the latter years, the live birth prevalence of DS has stabilized even in the younger age group. Prenatal diagnosis is a major contributor to this change in the number of births with DS, because most cases diagnosed prenatally result in a termination of pregnancy. In fact, only 5% of the pregnancies diagnosed prenatally resulted in a live birth. A similar termination rate has been reported for the UK,¹⁰ with slightly lower rates seen in Belgium,¹² Hungary,²² and Scotland.¹⁵ Our data show that in the past 7 or 8 years, the proportion of

cases of DS diagnosed prenatally has held relatively stable at around 80% in older women, although in younger women there is an upward trend that may continue for some time. Older women have had access to both prenatal diagnosis and prenatal screening tests in Victoria for many years now; this proportion, which is similar to that seen in the UK in 2003 (75%),¹⁰ may not get much higher. Higher rates in this age group have been reported for France and Switzerland (>80%), and lower rates have been reported in other European countries.^{5,9,23}

Whether or not the prevalence of live births will continue to decrease remains to be seen, but it would require a decrease in the maternal age distribution and/or a further increase in the use of prenatal testing. Earlier ascertainment of DS may become more common as early testing becomes the norm, but this should not affect the prevalence of live births, with most of these pregnancies resulting in termination. Alerting women to the risks of child-bearing at older ages²⁴ may affect the maternal age distribution in the future. Furthermore, barriers that affect access to prenatal testing, such as geographic location^{25,26} or socioeconomic status,²⁷ may be removed by changes to the system, resulting in wider and more equitable use of prenatal testing.

The data reported here relate to a population with broad access to prenatal testing and termination of pregnancy after prenatal diagnosis, with community support for the notion of informed choices about family planning. The trends that we have observed are likely to be relevant for other developed countries with similar conditions, as supported by the studies from the US, UK, and Europe cited earlier. However, data from Europe highlight the variations in the use of screening by younger women and the live birth prevalence of DS among populations.⁹ Countries in which termination of pregnancy for birth defects is limited or prenatal screening has not yet become widely available for all ages will show trends quite different than ours.²⁸ However, over time it is likely that many populations will experience a similar demographic shift in maternal age, with a consequent increase in the availability and acceptability of prenatal testing. The net effect of these 2 factors will affect the changes in prevalence over time.

A strength of this study is the high ascertainment of cases. A high level of reporting of DS to the Victorian BDR has been shown in a validation study¹⁷ while linking BDR records to the prenatal diagnosis register has further increased ascertainment, particularly for pregnancy terminations.

This is one of the few studies that have reported data as recent as 2004. Because collecting this information is time-consuming, reporting it in a timely fashion can be difficult. The relevance to various stakeholder groups, including those making policy decisions, is contingent on having the most recent data.

A limitation of database studies is that we can only surmise (albeit with good background information) about the factors responsible for the observed trends. It is likely that there are system factors as well as individual factors that feed

into the changes in prevalence of DS, and these can only be fully understood by ascertaining the choices that individual women and couples are making.

The data presented in this article, together with the greater life expectancy now experienced by people with DS,²⁹ underline the need for continual monitoring to ensure appropriate provision of services for individuals born with DS and their families.³⁰

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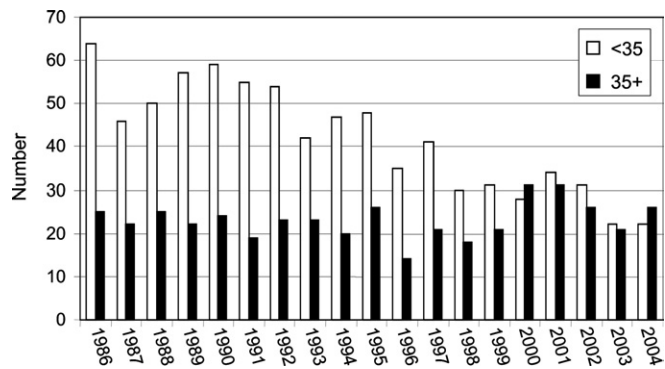


Figure 2. Number of births (20+ weeks' gestation) with trisomy 21 according to maternal age groups (under 35 years; 35 years and over).