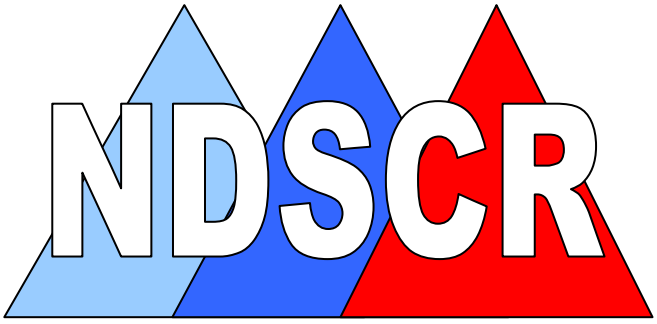

The National Down Syndrome Cytogenetic Register for England and Wales: 2009 Annual Report

Joan K Morris

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National Down Syndrome Cytogenetic Register
Queen Mary University of London
Barts and The London School of Medicine and Dentistry
Wolfson Institute of Preventive Medicine
Charterhouse Square
London
EC1M 6BQ

Phone: +44 (0) 20 7882 6274 / 6220
Fax: +44 (0) 20 7882 6221
Email: ndscr@qmul.ac.uk
Website: www.wolfson.qmul.ac.uk/ndscr

Foreword

This 2009 annual report contains information about the NDSCR as well as detailed data on all reported cytogenetically diagnosed cases of Down syndrome (trisomy 21) from 1989 to 2009, and Edwards syndrome (trisomy 18) and Patau syndrome (trisomy 13) from 2004 to 2009.

We would like to thank all the individuals who contribute to the NDSCR to make it such a valuable resource. We hope that we can continue to count on their collaboration.

Joan Morris (Director)
Eva Alberman
David Mutton
Haiyan Wu
Lynda Risley
Beth De Souza

Executive Summary

- All tables in this report are based on **calendar** years – last year's report was based on **financial** years.
- In 2009 there were 1887 diagnoses of Down syndrome, 62% of which were made prenatally.
- In 2009 there were an estimated 765 Down syndrome live births, a live birth rate of 1.1 per 1000.
- In 2009 there were 163 diagnoses of Patau and 506 diagnoses of Edwards syndrome, of which an estimated 20 and 41 respectively were live births.
- The percentage of prenatal diagnoses with missing outcomes is 5% over all years, with only 2009 above 10%.
- The type of screening that a woman received in 2009 was associated with her age. Older women were more likely to have received a prenatal diagnosis due to a first trimester screening test, were more likely to have a CVS compared to an amniocentesis and consequently received their diagnosis at younger gestational ages.
- Amongst women receiving prenatal diagnoses a greater proprtion had 1st trimester screening rather than 2nd trimester screening in 2009 compared to 2008.
- There were regional differences in the type of screening that women received in 2009.
- The NDSCR is approved to use Section 251 of the NHS Act 2006 and has ethics approval from Trent MREC.
- Data collection for the NDSCR is funded by HQIP until March 2011

Suggested citation of this report:

Morris JK. The National Down Syndrome Cytogenetic Register for England and Wales 2009 Annual Report. Queen Mary University of London, Barts and The London School of Medicine and Dentistry 2010.

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Introduction

The NDSCR is based at the Centre for Environmental and Preventive Medicine, Barts and The London School of Medicine and Dentistry, Queen Mary University of London. HQIP (Healthcare Quality Improvement Partnership) is funding the NDSCR until March 2011. Further funding has not yet been identified. This report refers to Down syndrome (named after Dr Langdon Down), Patau syndrome (named after Dr Klaus Patau) and Edwards syndrome (named after Dr John Edwards).

Aims of the NDSCR

The NDSCR was started in 1989 and we aim to collect all cytogenetic or DNA reports of trisomies 21, 18 and 13 and their cytogenetic variants occurring in England and Wales. These data can then be used to:

- monitor the Down syndrome prenatal screening and diagnostic services, and the impact they have on the diagnosis of trisomies 18 (Edwards syndrome) and 13 (Patau syndrome);
- provide data on annual numbers of affected births to help those planning for their health, education and social care;
- provide information for research into Down, Edwards and Patau syndromes.

How the NDSCR works

All cytogenetic laboratories in England and Wales collaborate with the NDSCR and provide, on standard forms, a notification of all prenatal and postnatal diagnoses of Down, Edwards and Patau syndromes. (A copy of the form used in 2009 is shown in Appendix B). The form is self-copying and has 4 pages. The top (white) copy is sent to the NDSCR by the laboratory, the 2nd (blue) and 3rd (green) are sent to the referring clinician and the 4th (pink) sheet is retained by the laboratory. The clinicians are asked to complete the blue form and send it to the NDSCR and to forward the 3rd (green) copy to the local screening co-ordinator, who is usually based within the Antenatal Unit at the referring hospital. **No direct contact is ever made with the women by the NDSCR.**

What data are collected

The notification form (see Appendix B) contains details of the chromosome analysis and some information on the mother and child, including postcode of residence, mother's age, length of pregnancy, the reason for referral for diagnosis and prenatal screening information. To preserve anonymity, the data do not include full names or addresses, but do include enough information to enable us to identify duplicate registrations and link to other congenital anomaly registers.

Data completion and processing

Postnatal diagnoses

Postnatal diagnoses include all diagnoses made after the birth of the child (both live and still) and following a miscarriage occurring after 20 weeks gestation. Diagnoses following a miscarriage occurring before 20 weeks are not included, because not all early miscarriages are karyotyped. This is consistent with the practice of other congenital anomaly registers.

Follow-up of prenatal diagnoses

For all prenatal diagnoses we request the referring physicians to inform us of the date and gestational age at the outcome of the pregnancy (birth, termination or miscarriage). The data on outcome show that after the prenatal diagnosis of Down syndrome 92% of affected pregnancies are terminated and 8% are continued. Some of the continued pregnancies miscarry naturally, some end as still births, and approximately 6% of prenatal diagnoses are live births. There is often a time lapse before we are informed of these outcomes (see below).

Validation of data

In order to ensure high levels of ascertainment, the data are matched with those held by the National Statistics Congenital Anomaly System and some of the Regional Congenital Anomaly Registers. In previous years this has shown the NDSCR data to be over 94% complete. Annual lists are sent to the laboratories for them to check that all cases have been registered.

Data quality

The Table in Appendix A gives the percentage of data on forms that is complete for the years up to 2006 combined, and separately for 2007, 2008 and 2009. This is always lowest in the most recent data where not all the clinicians have been contacted. Requests for missing data are sent out regularly. The major problem is ascertaining the outcome of prenatally diagnosed pregnancies, particularly where the referral was from a centre other than that at which the mother was booked. This occurs for private referrals, which have risen sharply over the years. Missing data for variables other than outcome are rare, with the exception of the numbers of previous pregnancies, a question that may not be seen as relevant by the clinicians although it is important in terms of risk of recurrence. There have been many changes in health authority definitions since the start of the register and regular recoding is carried out to keep these up-to-date.

Speed of reporting

Most laboratories provide data within six months of the diagnosis. The outcomes of prenatal diagnoses cannot be confirmed until a minimum of six months has elapsed to allow for any births to have occured.

Data security, confidentiality and informed consent

Personal information held on a computer system is safeguarded by the Data Protection Act 1998 and the NDSCR is registered under this Act. Paper forms are kept in locked filing cabinets and electronic data are entered onto password-protected computers kept in locked offices. The full data are accessible only to the

research team. The Government has made it clear that informed consent is a fundamental principle governing the use of patient identifiable information. However it also recognises that situations arise where informed consent cannot practicably be obtained. Section 251 of the NHS Act 2006 (originally enacted under Section 60 of the Health and Social Care Act 2001) provides a power to ensure that patient identifiable information needed to support essential NHS activity can be used without the consent of patients. The Act requires that the National Information Governance Board for Health and Social Care (NIGB) consider applications to use patient identifiable information without full informed consent. Since 2003, the NDSCR as a part of the British Isles Network of Congenital Anomaly Registers (BINOCAR) has been given permission to operate without informed consent. In 2006 the application of the NDSCR for ethics approval from the Trent multi-centre research ethics committee (MREC), as part of BINOCAR, was also approved. In 2010 this approval was renewed.

How the data are used

Audit of Down Syndrome Screening

- The NDSCR is the only national source of the numbers of pre- and postnatal diagnoses of Down, Patau and Edwards syndrome cases in England and Wales. The National Congenital Anomaly Service (NCAS) which previously also estimated these numbers no longer collects this data.

- Annual reports are produced describing numbers of prenatal and postnatal diagnoses, and the methods of prenatal screening which led to prenatal diagnoses.

- More detailed information is regularly published in medical journals (see appendix C).

- All local screening co-ordinators should receive the green copy of the NDSCR form to assist them in their audit requirements.

Feedback

- NDSCR leaflets giving information on the trends in Down syndrome diagnosis are produced annually and distributed to cytogenetic laboratories, local screening co-ordinators and clinicians.

- The NDSCR website (www.wolfson.qmul.ac.uk/ndscr) is regularly updated.

- Information is provided on request to medical professionals, researchers, journalists, charities and other interested parties.

- NDSCR leaflets are provided to the Down Syndrome Association and to SOFT (Support Organisation for trisomy 13/18 and related disorders).

Recent special studies

In-house studies

- Are twin pregnancies more likely to be affected with Down syndrome?
- Are mosaic trisomies less likely to be detected by prenatal screening?
- What are the prevalences of cytogenetic variants of Down, Patau and Edwards syndromes (for example translocations)?

Collaborative studies

- Children with Down's Syndrome Study (St James' University Hospital in Leeds and the Epidemiology & Genetics Unit at the University of York).
- We are investigating whether the births in the Down syndrome register can be identified on the National Audiological Database to ascertain if they were automatically recalled for hearing tests at nine months, as is the current recommendation.
- Data on all amniocentesis and chorionic villus sampling procedures on all women in England and Wales for 2008 have been obtained from the majority of cytogenetic laboratories in England and Wales in order to investigate how many women are having these invasive diagnostic tests and the reasons why.

Publications

A list of selected publications based on or using NDSCR data is provided in Appendix C.

The Data in the NDSCR

Down syndrome cases diagnosed in 2009

Outcomes of Down syndrome cases

1887 Down syndrome diagnoses were made in 2009, 1171 (62%) prenatally and 716 (38%) postnatally (Table 1). The outcome of 195 of the prenatal diagnoses is unknown. Assuming that the proportion terminated remains as before 2009, the likely number of Down syndrome live births in England and Wales in 2009 would have been 765 (63 + 690+ 6% of 195), a prevalence of 1.1 per 1000 live births occurring in England and Wales in 2009.

Table 1: Down syndrome cases diagnosed in England and Wales in 2009* according to time of diagnosis and outcome

		Number	%
Prenatal	Termination of pregnancy	876	47
	Live Birth	63	3
	Still Birth / Miscarriage	37	2
	Unknown outcome†	195	10
		1171	62
Postnatal	Live Birth	690	37
	Still Birth / Fetal death	26	1
		716	38
Total		1887	100

* 2009 data are provisional. † About 6% of those with unknown outcomes are likely to result in a live birth.

Acceptance of Screening

Table 2: Acceptance of prenatal screening tests among women with a Down syndrome diagnosis in 2009*

	Stage at diagnosis			
	Prenatal		Postnatal	
	Number	%	Number	%
Screened	1034	88	235	33
Declined screening	55	5	176	24
No information	82	7	305	43
Total	1171	100	716	100

* 2009 data are provisional.

Table 2 shows the percentage of women who declined prenatal screening, where 'prenatal screening' includes 1st trimester and 2nd trimester tests. Women who decided to proceed directly to a diagnostic test due to age were classified as declining screening. Women classified as "no information" include those women with a late ultrasound for whom we do not know if they had had an earlier screening test, and women with postnatal diagnoses for whom we have no screening information. 24% of women with a postnatal diagnosis had declined to be screened. The true percentage is likely to be higher as we have no information on 43% of women with a postnatal diagnosis.

Indication for prenatal diagnosis according to maternal age

Table 3 shows the indication for prenatal diagnosis separately for younger and older women. The integrated test, (serum and NT measured in first trimester, and serum measured in the second trimester) is classified as a '2nd trimester' screening test because the final serum measurement is made in the 2nd trimester. If there was no indication as to the type of screening (for example if only a risk was given) then the gestation at which the sample for diagnosis (eg CVS or amniotic fluid) was obtained was used to classify it as 1st trimester or 2nd trimester screening.

A 1st trimester test was the most likely indication in all women. A greater percentage of younger than older women gave an ultrasound examination (usually the anomaly scan) as the indication. 14% of prenatal diagnoses in younger women occurred at 21 weeks gestation or later, compared to only 4% of prenatal diagnoses in older women (data not shown).

Table 3: Indication for prenatal diagnosis of Down Syndrome in 2009* according to maternal age

Indication for prenatal diagnosis	Maternal Age			
	< 35 years		≥ 35 years	
	Number	%	Number	%
1st Trimester screening	164	47	510	63
2nd Trimester screening	132	38	242	30
Ultrasound	47	14	35	4
Age	-	-	21	2
Other reasons / No information	4	1	7	1
Total	347	100	815	100

* 2009 data are provisional; 9 cases had no maternal age.

Tissue used for prenatal diagnosis and gestational age at termination following prenatal diagnosis

The tissue used for prenatal diagnosis reflects the type of screening that led to the prenatal diagnosis, with a greater percentage of older women (61%) having a CVS than younger women (50%), and a smaller percentage of older women having an amniocentesis (37%) than younger women (48%). The tissue was either unspecified or not from an amniocentesis or CVS in 6% of women in both age groups.

For all women, the median time from CVS or amniocentesis to termination of pregnancy was 8 days. 88% of all terminations following CVS and 82% following amniocentesis were within 14 days of the procedure.
The gestation at termination following a prenatal diagnosis also reflects the indication for prenatal diagnosis, and differs by maternal age, as shown in Table 4. 50% of terminations in older mothers took place before 15 weeks gestation, compared to only 37% in younger mothers. 6% of terminations in older mothers took place after 20 weeks gestation, compared to 17% in younger mothers.

Table 4: Gestation at termination following prenatal diagnosis of Down Syndrome in 2009* according to maternal age

Gestation at termination (following prenatal diagnosis)	Maternal Age			
	< 35 years		≥ 35 years	
	Number	%	Number	%
<15 weeks	90	37	311	50
15 to 20 weeks	112	46	275	44
≥21 weeks	42	17	41	6
Total	244	100	627	100

* 2009 data are provisional. Outcomes were assumed to occur one week after diagnostic sample if gestation was missing. 2 cases had no maternal age.

Maternal age at observed or expected date of delivery

The mean age of the mother at observed or expected date of delivery was 36.0 (95% CI: 35.7 - 36.3) years. The mean age for women with a prenatal diagnosis was 36.7 (95% CI: 36.4 - 37.1) compared to 34.6 (95% CI: 34.0 - 35.1) for those with a postnatal diagnosis. Overall 65% (1123/1737) of the women of known age were 35 or older (Table 5).

Table 5: Down syndrome cases diagnosed in 2009* according to maternal age at observed or expected date of delivery

Maternal age (years)	Number	%
< 20	28	1
20-24	99	5
25-29	163	9
30-34	324	17
35-39	635	34
40-44	444	24
≥ 45	44	2
missing	150	8
Total	1887	100

*2009 data are provisional.

Patau and Edwards syndrome cases diagnosed in 2009

Outcomes of Patau and Edwards syndrome cases

87% of Patau and 91% of Edwards syndrome diagnoses were made prenatally. A large proportion of births were still births, due to the severity of the syndromes. The outcome of 25 Patau and 82 Edwards syndrome prenatal diagnoses is unknown. Approximately 4% of Patau and 3% of Edwards syndrome with unknown outcomes are likely to result in a live birth (rather than a termination or fetal loss), therefore the total number of live births is estimated to be 20 and 41 respectively.

Table 6a presents outcomes for Patau syndrome cases. The numbers were too small to present outcomes according to time at diagnosis. Table 6b presents outcomes for Edwards syndrome cases according to time at diagnosis.

Table 6a: Patau syndrome cases in 2009* according to outcome

	Number	%
Termination of pregnancy	107	66
Live Birth	19	12
Still Birth / Miscarriage/ Fetal death	12	7
Unknown outcome†	25	15
Total	163	100

Table 6b: Edwards syndrome cases in 2009* according to time of diagnosis and outcome

		Number	%
Prenatal	Termination of pregnancy	340	67
	Live Birth	9	2
	Still Birth / Miscarriage	29	6
	Unknown outcome†	82	16
Postnatal	Live Birth	30	6
	Still Birth / Fetal death	16	3
	Total	506	100

* 2009 data are provisional; † Approximately 4% of Patau and 3% of Edwards syndrome with unknown outcomes are likely to result in a live birth.

Indication for prenatal diagnosis

The two main indications for a prenatal diagnosis of Patau and Edwards syndromes were 1st trimester tests (for Down syndrome) and late ultrasounds (Table 7). Approximately 25% of prenatal diagnoses of Patau syndrome in younger women were made at 21 weeks gestation or later, compared to 16% in older women. Approximately 24% of prenatal diagnoses of Edwards syndrome in younger women were made at 21 weeks gestation or later, compared to 13% in older women.

Table 7: Indication for prenatal diagnosis of Patau and Edwards syndrome cases in 2009*

Indication for prenatal diagnosis	Patau syndrome		Edwards syndrome	
	Number	%	Number	%
1st Trimester screening	76	54	259	56
2nd Trimester screening	19	13	85	19
Ultrasound	39	27	91	20
Age and other reasons	4	3	5	1
No information	4	3	20	4
Total	142	100	460	100

* 2009 data are provisional.

Maternal age at observed or expected date of delivery

The mean age of the mother at expected or observed date of delivery was 34.5 years for Patau syndrome and 36.1 years for Edwards syndrome, compared to 36.0 years for Down syndrome. For Patau syndrome 59% of women with known maternal age were aged 35 or over, and for Edwards syndrome 69% of women with known maternal age were aged 35 or over (Table 8).

Table 8: Patau and Edwards syndrome cases diagnosed in 2009* according to maternal age at observed or expected date of delivery

	Patau syndrome		Edwards syndrome	
Maternal age (years)	Number	%	Number	%
< 25	14	8	36	7
25-29	27	16	50	10
30-34	32	20	95	19
35-38	50	31	145	29
≥ 40	37	23	162	32
missing	3	2	18	3
Total	163	100	506	100

* 2009 data are provisional.

Regional differences in cases diagnosed in 2009

Down syndrome diagnoses and maternal age according to maternal region of residence

Table 9 shows the numbers of diagnoses of Down syndrome across England and Wales, according to the maternal region of residence. Areas with a lower proportion of mothers 35 years of age or over tend to have lower proportions of prenatal diagnoses. The highest proportions of prenatal diagnoses occur in London and the South East of England.

Table 9: All births and all Down syndrome diagnoses according to region of maternal residence in 2009

Government Office Region (GOR)	All Births †		Down syndrome diagnoses	
	Number (1000)	Percentage of mothers ≥35 (%)	Number	Percentage prenatally diagnosed (%)
North East	30	15	72	47
North West	88	17	186	52
Yorkshire & Humberside	66	16	163	51
East Midlands	54	18	121	62
West Midlands	72	17	154	55
East England	72	21	183	69
London	128	25	444	67
South East	104	24	300	70
South West	59	22	169	64
Wales	36	17	89	57
Total	709	20	1881	62

* 2009 data are provisional. 6 cases have unknown GOR † National data are for calendar year 2008

Indication for prenatal diagnosis according to maternal region of residence

Table 10 shows the indication for a prenatal diagnosis according to region of residence. London and the South East had the highest proportions of women having a diagnostic test due to a 1st trimester screening test result, whereas the North West had the highest proportion of women having a diagnostic test due to an ultrasound. Care must be taken in interpreting Table 10 as the "other/missing" category is large for some regions.

Gestational age at termination after prenatal diagnosis according to maternal region of residence

The gestational age at termination following prenatal diagnosis reflects the reason given for the diagnosis. Table 11 gives a more accurate reflection of regional variation than Table 10 does as there is no "other" category. (2 cases with missing gestation at termination have been excluded.) However, the number of terminations in some regions is small. Women in London and the South East are the most likely to have a termination before 15 weeks gestation, and women in the North West and East Midlands are the least likely.

Table 10: Indication for prenatal diagnosis of Down syndrome according to region of maternal residence in 2009*

Government Office Region	Number of prenatal diagnoses	Indication for prenatal diagnosis (%)					
		1st trimester screen	2nd trimester screen	Ultrasound	Maternal Age	Other/ Missing	Total
North East	34	38	47	12	3	0	100
North West	97	20	57	21	3	0	100
Yorkshire & Humberside	83	46	42	10	0	2	100
East Midlands	75	47	39	5	7	3	100
West Midlands	84	38	46	10	4	2	100
East England	127	61	32	5	2	0	100
London	298	74	20	4	1	1	100
South East	210	76	20	5	0	0	100
South West	109	64	26	8	1	1	100
Wales	51	25	67	4	4	0	100
Total	1,168	58	32	7	2	1	100

* 2009 data are provisional. 6 cases have unknown GOR.

Table 11: Gestation at termination after prenatal diagnosis of Down syndrome according to region of maternal residence in 2009*

Government Office Region	Number of terminations	Gestation at termination (%)			
		<15 weeks	15 to 20 weeks	21+ weeks	Total
North East	29	38	48	14	100
North West	73	19	61	19	100
Yorkshire & Humberside	66	42	52	6	100
East Midlands	59	34	56	10	100
West Midlands	64	31	53	16	100
East England	93	43	49	8	100
London	195	63	29	8	100
South East	162	57	38	5	100
South West	91	49	42	9	100
Wales	44	25	59	16	100
Total	876	46	44	10	100

* 2009 data are provisional. 4 cases had no gestation at outcome.

Patau and Edwards syndrome diagnoses according to maternal region of residence

Table 12: Proportion of Patau and Edwards syndrome that are prenatally diagnosed according to region of maternal residence in 2009*

Government Office Region	Patau Syndrome (%)	Edwards Syndrome (%)
	Prenatal	Prenatal
North East	86	89
North West	71	83
Yorkshire & Humberside	82	97
East Midlands	100	100
West Midlands	90	81
East England	89	95
London	90	92
South East	100	90
South West	74	89
Wales	67	93
Total	87	91

*2009 data are provisional. 1 case of Patau syndrome and 1 of Edwards syndrome do not have GOR data.

Summary of regional differences

There are clear regional differences in screening for Down syndrome in England and Wales in 2009. However, some of these differences may arise due to the different maternal age distributions (Table 9). Many screening tests (for fixed risk cut-offs) have higher detection rates for older women and these women may also be more likely to present in time to have first trimester screening than younger women. More detailed analyses are required to investigate these apparent regional differences. The numbers of Patau and Edwards syndrome diagnoses are smaller, so regional variations are harder to assess.

Trends over time in Down syndrome diagnoses

Outcomes of Down syndrome cases from 1989-2009

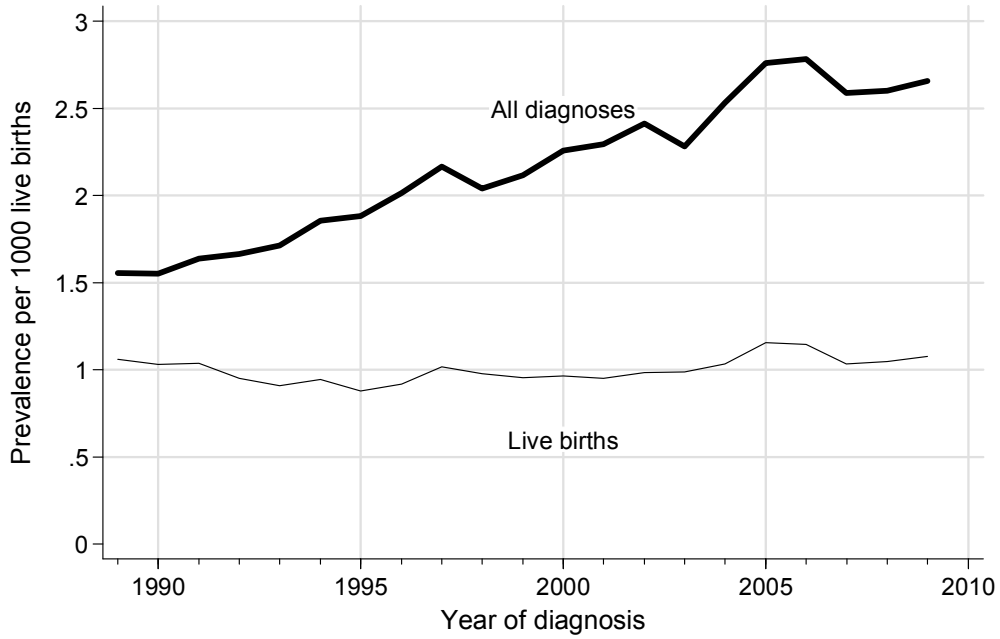
Since the register started collecting data on 1st January 1989 the annual number and prevalence of Down syndrome diagnoses has increased (Table 13 and Figure 1), firstly due to the considerable increases in maternal age, the major known risk factor, and secondly due to the increase in the numbers of Down syndrome pregnancies diagnosed prenatally, many of which were non-viable and would have miscarried and therefore remained undiagnosed in the absence of prenatal screening. The number and prevalence of Down syndrome live births has not changed significantly, this reflects the fact that an increasing proportion of Down syndrome diagnoses are occurring prenatally and that around 92% of women who receive a prenatal diagnosis decide to terminate the pregnancy (Table 13).

Table 13: Down syndrome diagnoses and outcomes in England and Wales from 1989 to 2009*

	Numbers of Diagnoses					Outcome of prenatal diagnoses ‡ (%)		
Calendar year of diagnosis	All	Prenatal (%)	Live births†		Unknown outcomes	Termi-nation	Miscarriage /still birth	Live births
			Reported	Estimated				
1989	1,069	321 (30)	730	730	8	93.6	2.9	3.5
1990	1,095	374 (34)	726	727	12	90.6	3.3	6.1
1991	1,146	430 (38)	725	726	9	87.7	5.2	7.1
1992	1,148	499 (43)	655	656	18	91.7	2.9	5.4
1993	1,155	558 (48)	612	612	8	92.2	2.5	5.3
1994	1,234	613 (50)	625	627	25	92.2	2.9	4.9
1995	1,220	660 (54)	568	570	25	91.0	3.3	5.7
1996	1,308	721 (55)	595	596	13	92.4	2.4	5.2
1997	1,392	739 (53)	653	654	19	92.2	2.8	5.0
1998	1,298	704 (54)	620	622	26	91.2	2.2	6.6
1999	1,316	728 (55)	591	593	29	92.7	2.0	5.3
2000	1,364	806 (59)	578	582	63	92.1	0.9	7.0
2001	1,364	815 (60)	561	566	83	92.4	2.2	5.5
2002	1,439	885 (62)	581	587	104	90.8	3.1	6.2
2003	1,418	835 (59)	609	613	73	90.9	2.5	6.6
2004	1,620	989 (61)	657	662	84	89.9	3.3	6.7
2005	1,766	1,055 (60)	732	740	141	90.8	3.5	5.7
2006	1,846	1,118 (61)	751	760	143	90.9	3.7	5.4
2007	1,787	1,110 (62)	705	712	123	91.6	2.7	5.7
2008	1,845	1,139 (62)	734	741	110	90.2	2.8	7.0
2009*	1,887	1,171 (62)	753	765	195	89.8	3.8	6.5
Total	29,717	1,6270 (55)	13,761	13841	1,311	91.2	2.9	5.9

* 2009 data are provisional. † Estimated live births includes 6% of unknown outcomes. ‡ Calculated as a percentage of all known outcomes.

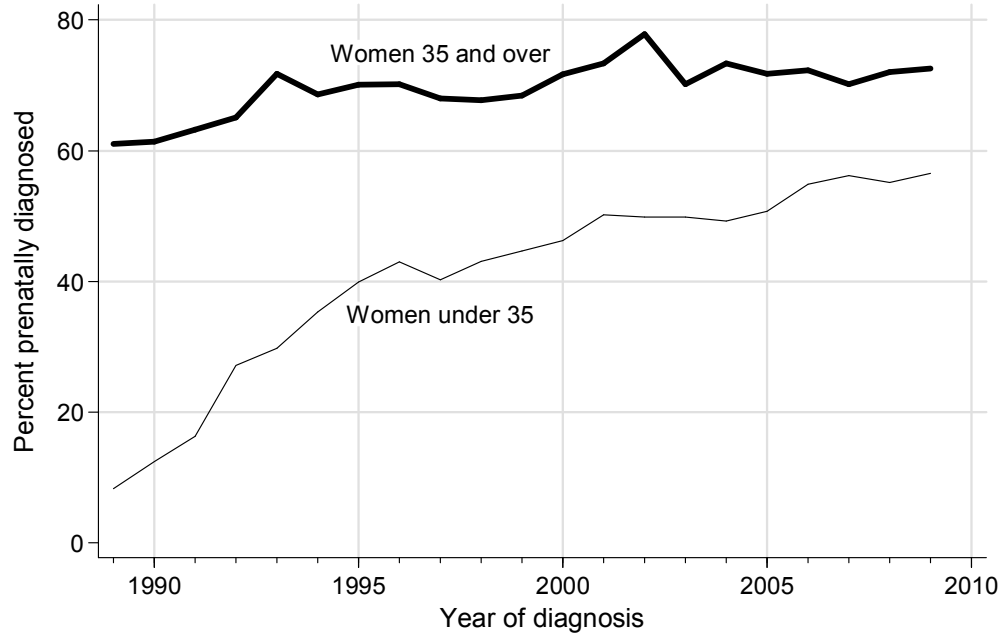
Figure 1: Prevalence of Down syndrome diagnoses and live births per thousand livebirths in England and Wales according to year of diagnosis*



* 2009 data are provisional.

Table 13 shows that the percentages of prenatal diagnoses have increased over time, however, Figure 2 shows that the increases have been greatest amongst women under 35 years of age.

Figure 2: Percentage of Down syndrome cases which were prenatally diagnosed according to maternal age and year of diagnosis*

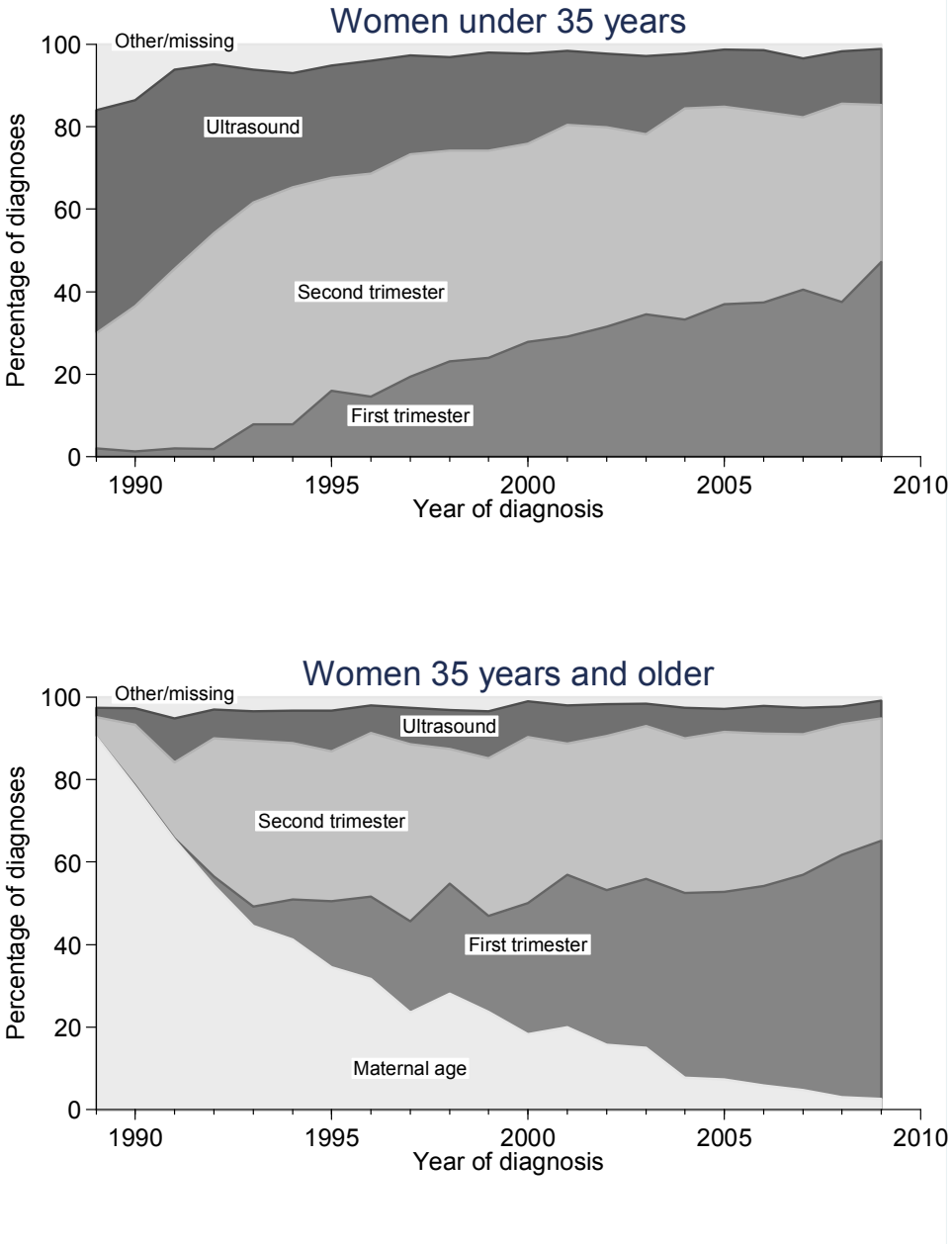


* 2009 data are provisional.

Indication for prenatal diagnosis 1989-2009

Figure 3 and Table 14 show the changes in the indications for a prenatal diagnosis of Down syndrome. For older women there has been a clear shift from having a diagnostic test due to advanced maternal age to having a diagnostic test due to a high risk predicted from screening. For younger women, at the start of the register the majority of prenatal diagnoses were due to anomalies seen during the fetal anomaly scan. A greater proportion is now detected due to screening. In 2009 there was a much greater proportion of younger women having first trimester screening.

Figure 3: Indication for Down syndrome prenatal diagnosis according to year of diagnosis and maternal age*



* 2009 data are provisional

Table 14: Indication for Down syndrome prenatal diagnosis according to maternal age from 1989 to 2009*

Calandar Year of diagnosis	Women under 35 (%)				Women 35+ (%)				
	1st Trimester	2nd Trimester	Ultra-sound	Other/ Missing	Age alone	1st Trimester	2nd Trimester	Ultra-sound	Other/ Missing
1989	2	28	54	16	90	0	5	2	3
1990	1	35	50	14	78	0	15	4	3
1991	2	43	48	6	65	0	18	11	5
1992	2	52	41	5	54	2	34	7	3
1993	8	54	32	6	44	5	40	7	3
1994	8	57	28	7	41	10	38	8	3
1995	16	52	27	5	35	16	36	10	3
1996	15	54	27	4	32	20	40	7	2
1997	19	54	24	3	23	22	43	9	3
1998	23	51	23	3	28	27	33	9	3
1999	24	50	24	2	24	23	38	11	3
2000	28	48	22	2	18	32	40	9	1
2001	29	51	18	2	20	37	32	9	2
2002	32	48	18	2	16	37	37	8	2
2003	35	44	19	3	15	41	37	5	2
2004	33	51	13	2	8	45	38	7	3
2005	37	48	14	1	7	45	39	6	3
2006	37	46	15	1	6	48	37	7	2
2007	40	42	14	3	5	52	34	6	3
2008	37	48	13	2	3	59	32	4	2
2009	47	38	14	1	2	63	30	4	1

* 2009 data are provisional.

Gestational age at termination following prenatal diagnosis

The shift towards earlier screening has increased the percentage of prenatal diagnoses with terminations before 15 weeks gestation, for younger and older women (Table 16). The percentage of terminations taking place at 21 weeks gestation or later has decreased for younger and older women but it remains higher for younger women.

Maternal age at observed or expected date of delivery 1989-2009

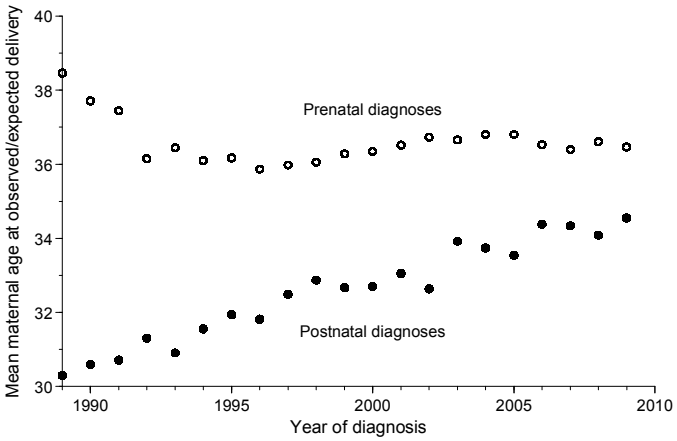
At the start of the register, the main prenatal screening test available was a mother's age and so the majority of prenatal diagnoses occurred in older women. As more screening tests became more available and detection rates for younger women improved, more younger women received prenatal diagnoses. This is reflected in the average maternal age (Figure 4). The average age for prenatal diagnoses is declining, whilst the average age for postnatal diagnosis is increasing. This has important implications for the long term care of these children, by increasingly older parents.

Table 16: Gestation at termination after prenatal diagnosis of Down syndrome according to maternal age from 1989 to 2009*

Calandar year of diagnosis	Women under 35 (%)			Women ≥35 (%)		
	<15 weeks	15 to 20 weeks	≥21 weeks	<15 weeks	15 to 20 weeks	≥21 weeks
1989	2	45	52	17	65	18
1990	8	46	46	13	65	22
1991	1	53	46	14	67	19
1992	2	63	35	9	71	20
1993	12	44	45	14	62	24
1994	8	54	38	18	66	16
1995	18	50	33	21	63	16
1996	14	52	33	25	62	13
1997	19	54	27	28	59	13
1998	24	50	26	29	59	13
1999	23	52	26	29	58	13
2000	27	48	25	35	54	11
2001	28	48	24	42	48	11
2002	32	47	21	42	51	8
2003	31	47	21	44	50	7
2004	31	49	20	45	47	9
2005	34	48	18	45	46	9
2006	34	45	21	43	48	9
2007	40	42	17	51	41	8
2008	33	50	16	55	38	7
2009	37	46	17	50	44	6

* 2009 data are provisional. Gestation at termination was estimated where necessary using the median time between diagnostic sample and termination according to year of diagnosis and tissue used for diagnosis.

Figure 4: Mean maternal age according to year of diagnosis and stage at diagnosis*



* 2009 data are provisional

Trends over time in Patau and Edwards syndromes diagnoses

The number of diagnoses of Patau and Edwards syndromes has risen since data started being collected in 2004 (Tables 17 and 18) due to increases in maternal age, the major known risk factor, and due to the increase in the number of pregnancies diagnosed prenatally (due to screening for Down syndrome), many of which were non-viable and would have miscarried and therefore remained undiagnosed in the absence of prenatal screening. The number of diagnoses of Patau syndrome in 2009 is lower than in 2008, the reason for which is unclear.

Table 17: Patau syndrome diagnoses and outcomes in England and Wales from 2004/5 to 2009*

Year of diagnosis	Patau syndrome: Numbers of Diagnoses				
	All	Prenatal (%)	Live births		Unknown outcomes
			Reported	Estimated†	
2004	152	139 (91)	16	16	8
2005	160	138 (86)	26	26	11
2006	193	175 (91)	23	24	16
2007	204	183 (90)	24	24	9
2008	190	171 (90)	24	25	14
2009	163	142 (87)	19	20	25
Total	1062	948 (89)	132	135	83

* 2009 data are provisional. † Estimated live births include 4% of unknown outcomes.

Table 18: Edwards syndrome diagnoses and outcomes in England and Wales from 2004/5 to 2009*

Year of diagnosis	Edwards syndrome: Numbers of Diagnoses				
	All	Prenatal (%)	Live births		Unknown outcomes
			Reported	Estimated†	
2004	369	332 (90)	40	41	47
2005	433	388 (90)	41	43	56
2006	454	393 (87)	63	64	49
2007	483	442 (92)	51	52	42
2008	493	458 (93)	40	41	42
2009	506	460 (91)	39	41	82
Total	2,738	2,473 (90)	274	284	318

* 2009 data are provisional. † Estimated live births include 3% of unknown outcomes.

Appendix A

Data Completeness

The following Table shows the completeness of the different data items for the years 1989 to 2006, 2007, 2008 and 2009. We are still following up the missing data from 2007 onwards. The data from 1989 to 2006 are included for comparison purposes to demonstrate the levels we are aiming to achieve for the more recent data.

Table A1: Completeness of data from 1989 to 2009*

Data Item	Percentage complete			
	1989-2006	2007	2008	2009*
Reason for referral for diagnosis	99	98	98	98
Type of tissue karyotyped	99	96	96	96
Sex of fetus (some DNA based diagnoses such as FISH and q-PCR do not include sex chromosome analysis)	99	97	97	96
Maternal age	96	96	94	93
Gestational age at sample for prenatal diagnosis	100	99	99	99
Outcome of pregnancy	96	93	93	88
Post Codes (some information)	93	96	96	94
Maternal NHS number (requested from 2005)	N/A	70	71	62

* 2009 data are provisional.

Appendix B: Form in 2009

Reference No. 16438 NDSCR |__|__|__|__|__|

NATIONAL DOWN SYNDROME CYTOGENETIC REGISTER

NOW INCLUDING TRISOMIES 13 AND 18 *(In collaboration with the National Screening Committee)*

PLEASE RETURN THIS FORM TO:
Joan Morris, Wolfson Institute of Preventive Medicine, Barts and the London, Charterhouse Square, London, EC1M 6BQ
Telephone: 020 7882 6220 Fax: 020 7882 6221 Website: http://www.wolfson.qmul.ac.uk/ndscr/
AND FORWARD BLUE AND GREEN COPIES TO THE REFERRING CLINICIAN. THANK YOU FOR YOUR HELP.

Laboratory ID |__|__| TRISOMY 21 |__| 13 |__| 18 |__|

Specimen ID |__|__|__|__|__|__|__|__|__|__|

Date of LMP (D D M M Y Y) |__|__|__|__|__|__|

Best estimate of EDD |__|__|__|__|__|__|

Karyotype .....

Karyotyping Full |__| PCR |__| FISH |__|

PCR / FISH result .....

Date sample taken (D D M M Y Y) |__|__|__|__|__|__| gest |__|__| wks

Sample CVS |__| Amnio |__| Postnatal |__| Other .....

Confirmation of previous diagnosis |__|
ID |__|__|__|__|__|__|__|__|__|__|

SCREENING TESTS
(please complete at least one of the following three sections)

|__| **Yes (NHS)** Screen: +ve |__| -ve |__| Risk 1 in .....
1st trimester (Tick all markers tested)
NT |__| .....mm PAPP-A |__| Freeβ-hCG |__| Other .....
2nd trimester (Tick all markers tested)
AFP |__| uE_3 |__| hCG (any) |__| Inhibin-A |__| Other .....

|__| **Yes (Private)** Screen: +ve |__| -ve |__| Risk 1 in .....
1st trimester (Tick all markers tested)
NT |__| .....mm PAPP-A |__| Freeβ-hCG |__| Other .....
2nd trimester (Tick all markers tested)
AFP |__| uE_3 |__| hCG (any) |__| Inhibin-A |__| Other .....

|__| **No screening because:**
Too late |__| Not offered |__| Declined |__|
Other .....

TIMING OF DIAGNOSIS AND INDICATIONS

Prenatal Screen result |__| Mat Age |__| Family history |__|
|__| U/S findings (please specify) |__| .....
Other .....

Postnatal No indication |__| Indication but test declined |__|
|__| Diagnosed after miscarriage |__| Other .....

FOR AUDIT PURPOSES ONLY— please complete

Mother's hospital ID |__|__|__|__|__|__|__|__|__|__|
First 3 letters of mother's surname |__|__|__| Initial |__|
Mother's NHS No. |__|__|__|__|__|__|__|__|__|__|
Infant's hospital ID |__|__|__|__|__|__|__|__|__|__|
Infant's NHS No. |__|__|__|__|__|__|__|__|__|__|

Mother's date of birth (D D M M Y Y) |__|__|__|__|__|__| age |__|__| (age at testing)

Father's date of birth |__|__|__|__|__|__| |__|__| (age at testing)

OUTCOME

Termination |__| Miscarriage |__| Stillbirth |__| Livebirth |__|

Date of outcome/ termination/ birth (D D M M Y Y) |__|__|__|__|__|__|

Gestation at outcome |__|__| wks

Infant's birth weight |__|__|__|__| gms

Name of referring clinician and hospital:
.....

If terminated or delivered elsewhere, name of clinician and hospital:
.....

Multiple pregnancy? No |__| Twin |__| Triplet |__| Other |__|
If yes, please give sex and outcome of all other fetuses / babies:
.....

Is this the first pregnancy? Yes |__| No |__|
If no, please give number of outcomes of previous pregnancies:

Terminations |__| Miscarriages |__| Stillbirths |__| Livebirths |__|

No. previous pregnancies with trisomies 21 |__| 13 |__| 18 |__|

Other chromosomal anomaly, including parents' if known:
.....

If previous anomaly, please specify outcome .....

Mother's usual town of residence:
.....

Postcode |__|__|__|__| |__|__|__| PCT |__|__|__|

Note: (e.g. condition of infant, previous family history, fertility problems, etc.)
.....
.....
.....

(Please continue overleaf)

FOR OFFICE USE ONLY A
Reference No. 16438 NDSCR |__|__|__|__|__|
Laboratory |__|__| Trisomy 21 13 18 pren/ postn/ misc
Specimen ID |__|__|__|__|__|__|__|__|__|__|

Appendix C: Selected NDSCR Publications

1. Morris JK, Alberman E. Trends in Down's syndrome live births and antenatal diagnoses in England and Wales from 1989 to 2008: analysis of data from the National Down Syndrome Cytogenetic Register. *BMJ* 2009; **339**:b3794.
2. Savva GM, Morris JK. Ascertainment and accuracy of Down syndrome cases reported in congenital anomaly registers in England and Wales. *Arch Dis Child Fetal Neonatal Ed* 2009; **94**:F23-7.
3. Morris JK, Mutton DE, Alberman E. The proportions of Down's syndrome pregnancies detected prenatally in England and Wales from 1989 to 2004. *J Med Screen* 2006; **13:**163-5.
4. Crane B, Morris JK. Changes in maternal age in England and Wales – Implications for Down syndrome. *Down syndrome research and practice* 2006; **10**:41-43.
5. Savva GM, Morris JK, Mutton DE, Alberman E. Maternal age-specific fetal loss rates in Down syndrome pregnancies. *Prenat Diagn*. 2006; **26**:499-504.
6. Morris JK, Mutton DE, Alberman E. Recurrences of free trisomy 21: Analysis of data from the National Down Syndrome Cytogenetic Register. *Prenat Diagn* 2006; **25**:1120-8.
7. Morris JK, de Vigan C, Mutton DE, Alberman E. Risk of a Down syndrome live birth in women of 45 years of age and older. *Prenat Diagn* 2006; **25**:275-8.
8. Kovaleva NV, Mutton DE. Epidemiology of double aneuploidies involving chromosome 21 and the sex chromosomes. *Am J Med Genet* 2006; **134A (1):**24-32.
9. Alberman E, Huttly W, Hennessy E, McIntosh A. The use of record linkage for auditing the uptake and outcome of prenatal serum screening and prenatal diagnostic tests for Down syndrome. *Prenat Diagn* 2003; **23**:801-6.
10. Smith-Bindman R, Chu P, Bacchetti P, Waters JJ, Mutton D, Alberman E. Prenatal screening for Down syndrome in England and Wales and population-based birth outcomes. *Am J Obstet Gynecol* 2003; **189:**980-5.
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12. Morris JK, Mutton DE, Alberman E. Revised estimates of the maternal age specific live birth prevalence of Down's syndrome. *J Med Screen* 2002; **9**:2-6
13. Vrijheid M, Dolk H et al. Chromosomal congenital anomalies and residence near hazardous waste landfill sites. *Lancet* 2002; **359**:320-3.
14. Smith-Bindman R, Waters J, Mutton D, Alberman E. Trends in the effectiveness and efficiency of prenatal Down syndrome (DS) screening in England and Wales, 1989-1999. *J Med Genet* 2001: Supplement 1 SP33.
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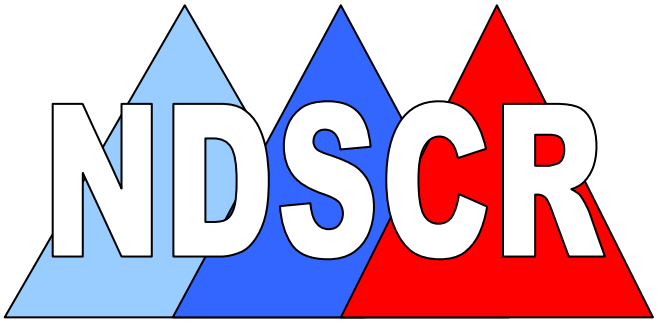
16. Morris JK, Wald NJ, Watt HC. Fetal loss in Down's syndrome pregnancies. *Prenat Diagn* 1999; **19**:142-145.
17. Morris JK, Alberman E, Mutton D. Is there evidence of clustering in Down syndrome? *Int J Epid* 1998; **27**:495-8.

18. Mutton D, Bunch K, Draper G, Alberman E. Children's cancer and Down syndrome. *J Med Genet* 1997; **34**:S65.
19. Huang T, Watts HC et al. Reliability of statistics on DS notifications. *J Med Screen* 1997; **4**:94-97.
20. Hook EB, Mutton DE, Ide R, Alberman ED, Bobrow M. The natural history of Down syndrome conceptuses diagnosed prenatally which are not electively terminated. *Am J Hum Genet* 1995; **57**:875-881.
21. Mutton DE, Alberman ED, Hook EB. Cytogenetic and epidemiological findings in Down syndrome: 1993. *J Med Genet* 1996; **33**:387-394.
22. Williamson P, Harris R, Church S, Fiddler M, Rhind J. Prenatal genetic services for Down's syndrome: access and provision. *Br J Obstet Gynaecol* 1996; **103:**676-83.
23. Alberman E, Mutton D, Ide R, Nicholson A, Bobrow M. Down's syndrome births and pregnancy terminations in 1989 to 1993: preliminary findings. *Br J Obstet Gynaecol* 1995; **102**:445-7.
24. Mutton DE, Ide R, Alberman E, Bobrow M. Analysis of National Register of Down's syndrome in England and Wales: trends in prenatal diagnosis. *BMJ* 1993; **306**:431-2.
25. Mutton DE, Alberman E, Ide R, Bobrow M. Results of first year (1989) of a national register of Down's syndrome in England and Wales. *BMJ* 1991; **303**:1295-7.



Queen Mary University of London
Barts and The London School of Medicine and Dentistry
Wolfson Institute of Preventive Medicine
Charterhouse Square
London
EC1M 6BQ

Web site: www.wolfson.qmul.ac.uk/ndscr
Phone: +44 (0) 20 7882 6274 / 6220
Fax: +44 (0) 20 7882 6221
Email: ndscr@qmul.ac.uk