Articles

Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study

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Summary

Background Down's syndrome is the most frequently identified cause of mental retardation, but information about mortality and comorbidity in people with Down's syndrome is limited.

Methods We used data from US death certificates from 1983 to 1997 to calculate median age at death and standardised mortality odds ratios (SMORs) for common medical disorders in people with Down's syndrome.

Findings Of 17 897 people reported to have Down's syndrome, median age at death increased from 25 years in 1983 to 49 years in 1997, an average increase of 1·7 years per year studied (p<0·0001). Median age at death was significantly

lower in black people and people of other races than in white people with Down's syndrome. As expected, death certificates with a diagnosis of Down's syndrome were more likely to list congenital heart defects (SMOR 29·1, 95% CI 27·8-30·4), dementia (21·2, 19·6-22·7), hypothyroidism (20·3, 18·5-22·3), or leukaemia (1·6, 1·4-1·8) than were those that did not report Down's syndrome. By contrast, malignant neoplasms other than leukaemia were listed on death certificates of people with Down's syndrome less than one-tenth as often as expected (0·07, 0·06-0·08). A strikingly low SMOR for malignancy was associated with Down's syndrome at all ages, in both sexes, and for all common tumour types except leukaemia and testicular cancer.

Interpretation Identification of factors responsible for the racial differences recorded could facilitate further improvement in survival of people with Down's syndrome. Reduced exposure to environmental factors that contribute to cancer risk, tumour-suppressor genes on chromosome 21, or a slower rate of replication or higher likelihood of apoptosis in Down's syndrome cells, could be possible reasons for paucity of cancer in people with Down's syndrome.

Lancet 2002; **359:** 1019-25

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Introduction

Down's syndrome, the most frequently identified cause of mental retardation, has a prevalence of about 1 in 800 livebirths and stillbirths.[1] Survival is lower in people with Down's syndrome than in those without this disorder.[2-4] The most frequent causes of death in people with Down's syndrome are congenital heart defects and respiratory infections.[4-8] In the past 50 years, survival beyond the first year of life has improved strikingly for people with Down's syndrome, from below 50%[9] to more than 90%.[4] Most studies of death in people with this disorder have focused on survival in the first year of life, and almost all people included in these studies were white.

Satge and colleagues[10] reviewed studies of cancers in people with Down's syndrome published before 1997 and concluded that malignant solid tumours seem to be under-represented compared with the general population. These investigators noted that cancer studies in Down's syndrome had limited numbers of participants and thus limited power to make general inferences. Hasle and colleagues[11] did a cohort study of 2814 people with Down's syndrome and reported a high risk of leukaemia in affected children but a low risk of solid tumours in all age-groups.

We studied patterns of mortality and morbidity in over 17 800 people with Down's syndrome who died during a 15-year period. We assessed changes in age at death by racial group, most frequent diseases associated with death, and occurrence of major categories of malignant neoplasms.

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Methods

Study protocol

We obtained data from multiple-cause mortality files (MCMFs) compiled by the US Centers for Disease Control and Prevention National Center for Health Statistics for 1983-97. MCMFs include: demographic information, International Classification of Disease ninth edition (ICD9) codes for underlying cause of death, and up to 20 disorders that are listed on death certificates.[12] Death certificates record information only for livebirths; stillbirths are not included.[13] MCMFs have used ICD9 codes since 1979, but collection of death certificates was incomplete for 1981 and 1982.[12] We selected all records that contained code 758·0 (Down's syndrome) but excluded records that also contained code 779·6 (pregnancy termination) and age 0 years.

Statistical analysis

We calculated median age at death over time for people with Down's syndrome by sex and racial group (categorised as white, black, or other). We used linear regression to test the trend of median age at death by year and used the non-parametric median scores method to test differences of median age at death by racial group.[14] To investigate the relation between deaths associated with Down's syndrome and other medical disorders, we calculated standardised mortality odds ratios (SMORs).[15] To calculate SMORs, a mortality study can be thought of as a variant of a case-control study, in which cases are deaths from a specific cause and controls are deaths from other causes. The odds of exposure (in our study, the odds of having Down's syndrome) are ascertained in both cases and controls. This odds ratio can be standardised for covariates such as age and sex in the usual manner (panel, A).

Formulae to calculate SMORs

A

$$\text{SMOR} = \frac{(\text{sum})_i\, d_{ik}}{(\text{sum})_i\, d_{ij}\,(R_{ik}/R_{ij})}$$

B

$$R_{ik}=D_{ik}/N_{i1}$$

$$R_{ij}=D_{ij}/N_{i0}$$

$$\text{SMOR} = \frac{(\text{sum})_i\, d_{ik}}{(\text{sum})_i\, d_{ij}\,[(D_{ik}/N_{i1})/(D_{ij}/N_{i0})]}$$

C

$$\text{SMOR}' = \frac{(\text{sum})_i\, d_{ik}}{(\text{sum})_i\, d_{ij}\,(D_{ik}/D_{ij})}$$

d_{ik}=number of deaths from Down's syndrome among deaths from cause *k* in stratum *i*; d_{ij}=number of deaths from Down's syndrome among deaths from other causes *j* in stratum *i*; R_{ik} and R_{ij} are the stratum-specific mortality rates for the case and control causes of death, respectively, in the standard population; D_{ik}=number of non-Down's-syndrome deaths from cause *k* in stratum *i*; D_{ij}=number of non-Down's-syndrome deaths from other causes *j* in stratum *i*; N_{i1} and N_{i0} are the

number of person-years in stratum *i* for case and control causes of non-Down's syndrome deaths, respectively.

Results of studies have shown that SMORs can be estimated with a national representative sample of mortality data for exposed and unexposed individuals without reliance on standard mortality rates.[16] We have extended exposed and unexposed to include individuals affected or unaffected by Down's syndrome (panel, B).

The number of person-years in a specified year that generate the non-Down's syndrome deaths in each stratum is about the same for those who die from a particular cause and those who die from all other causes,[16] so SMOR can be approximated by the equation in the panel (C).

We randomly selected 25% of deaths in the USA from 1983 to 1997 to calculate SMORs. We used SAS logistic regression to estimate SMORs adjusted for age in groups of 5 years (0-4, 5-9, &c, to >70 years), sex, race (white, black, and others), and year of death (1983-87, 1988-92, 1993-97).[6] When the observed number of Down's syndrome deaths for a particular disease was equal to zero, we calculated the expected number of deaths for the disease on the basis of stratum-specific mortality rates in people who died without Down's syndrome, and estimated a 95% CI by assuming that number of deaths in people with Down's syndrome and the other medical disorder is distributed as a Poisson variable.[17]

The disorders listed in table 1 were analysed because they are frequent causes of death in the general population or have been recorded more often than expected in studies of morbidity or mortality in Down's syndrome.[6-8,18,19] Because of the strikingly low occurrence of cancers in people with Down's syndrome, we analysed malignant neoplasms in more detail. We stratified participants into seven age-groups (<10, 10-19, 20-29, 30-39, 40-49, 50-59, and ≥60 years) for study of associations of Down's syndrome with selected medical disorders and into four age-groups (<20, 20-39, 40-59, ≥60 years) for the cancer analysis.

	ICD9 codes	Observed number of deaths	SMOR (95% CI)
Disorder			
Aspiration, pneumonia or influenza	480·0-487·9, 507·0	5199	7·61 (7·36-7·87)
Congenital heart defects	745·0-747·9	5066	29·10 (27·8-30·4)
Seizure disorder	345·0-345·9, 780·3	1619	7·80 (7·39-8·23)
Infectious and parasitic diseases	001·0-139·9	1349	1·14 (1·08-1·20)
Ischaemic heart disease	410·0-414·9, 429·2	1258	0·42 (0·40-0·45)
Diseases of pulmonary circulation	415·0-417·9	1154	3·83 (3·60-4·07)
Dementia	290·0-290·9, 294·0-294·9, 331·0, 331·9	1001	21·10 (19·6-22·7)
Other congenital anomalies	740·0-744·9, 748·0-757·9, 759·0-759·9	596	0·92 (0·85-1·01)
Hypothyroidism	243·0-244·9	504	20·20 (18·5-

Hypothyroidism	243·0-244·9	504	20·30 (18·5-22·3)
Diabetes	250·0-250·9	500	0·63 (0·58-0·69)
Leukaemia	204·0-208·9	345	1·57 (1·41-1·75)
Other malignancy	140·0-203·9	344	0·07 (0·06-0·08)
Obesity	278·0	211	1·87 (1·63-2·15)
Protein/calorie malnutrition	260·0-263·9	156	1·41 (1·20-1·65)
Viral hepatitis	070·0-070·9	151	3·30 (2·81-3·89)
Intestinal obstruction	560·0-560·9	95	1·29 (1·06-1·58)
Sudden infant death syndrome.	798·0	51	0·08 (0·06-0·11)

Table 1: **Standardised mortality odds ratios (SMORs) of selected medical disorders in people with Down's syndrome**

To ascertain whether regional differences in SMORs exist, we also analysed our data by four regions: Northeast (Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, and Pennsylvania); Midwest (Ohio, Indiana, Illinois, Michigan, Wisconsin, Minnesota, Iowa, Missouri, North Dakota, South Dakota, Nebraska, and Kansas); South (Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida, Kentucky, Tennessee, Alabama, Mississippi, Arkansas, Louisiana, Oklahoma, and Texas); and West (Montana, Idaho, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada, Washington, Oregon, California, Alaska, and Hawaii).

Role of the funding source

The US federal government, the sole funding source for this study, employs the study authors, who had sole responsibility for study design and analysis and interpretation of data. The report received approval for publication from other employees of the US government.

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Results

MCMFs for 1983-97 contain records for over 32 million deaths, 17 958 of which list Down's syndrome as a diagnosis. Of these, 61 records also listed the code for pregnancy termination and age 0 years, and these were excluded from the analysis. The remaining 17 897 records represented 5·6 deaths in people with Down's syndrome per 10 000 total deaths in the USA for the study period. Racial distribution in people with Down's syndrome was 87% white, 11% black, and 2% others. Of all US deaths during the study, the racial distribution was 87% white, 12% black, and 1% others.

Of the 17 897 people with Down's syndrome, median age at death increased from 25 years in 1983 to 49 years in 1997, an average increase of 1·7 years per year studied ($p<0·0001$). By comparison, median age at death in the general population increased by only 3·0 years (from 73 years to 76 years, $p<0·0001$) during this period. The largest increase in age at death of people with Down's syndrome was in the early 1990s, as shown by the striking increase in the 25th percentile of age at death and the substantial decrease in proportion of deaths associated with Down's syndrome that

percentile of age at death and the substantial decrease in proportion of deaths associated with Down's syndrome that occurred before age 5 years (figure 1). Patterns of median age at death were closely similar in men and women (figure 2). Differences in median age at death between white people, black people, and people of other races with Down's syndrome were highly significant in the three death-cohorts studied (1983-87, 1987-91, and 1992-97, p=0·0034; figure 2).

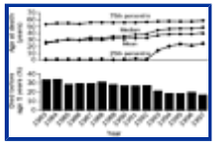

Figure 1: **Age at death (upper) and observed proportion of deaths (lower) before age 5 years of people with Down's syndrome**

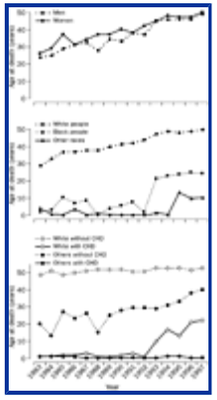

Figure 2: **Median age at death of people with Down's syndrome by sex (upper), racial group (middle), and with or without congenital heart defects (CHD) by racial group (lower)**

In figure 2, we combined the number of black people and other racial groups with Down's syndrome who had or did not have congenital heart defects because the patterns of median age at death were closely similar and because too few cases were available for separate analysis. Median age at death increased steadily in both white people and people in other racial groups without congenital heart defects during the study period, although the difference between these groups persisted. Of those who had congenital heart defects, median age at death remained low and unchanged in other racial groups but increased substantially in white people after 1992.

SMORs were analysed for 17 medical disorders in people with Down's syndrome (table 1). Death certificates of people with Down's syndrome were significantly more likely to list congenital heart defects, dementia, hypothyroidism, seizure disorder, aspiration, pneumonia, influenza, viral hepatitis, or leukaemia than were those of people without Down's syndrome. The association of Down's syndrome with these other medical disorders varied by age (table 2). The association with congenital heart defects peaked at age 20-29 years. The SMOR for congenital anomalies other than congenital heart defects was significantly lower than expected in people with Down's syndrome who died early in childhood, but higher than expected in those who died after age 20. People with Down's syndrome had a very high probability of dementia at age 40-49 years, but the SMOR for dementia was much lower in younger (<40 years) and older (

probability of dementia at age 40-49 years, but the SMOR for dementia was much lower in younger (<40 years) and older (≥60 years) age-groups (table 2). The association of Down's syndrome with aspiration, pneumonia, or influenza increased with age (table 2). Ischaemic heart disease was reported less often than expected in people with Down's syndrome.

	Age <10		Age 10-19		Age 20-29		Age 30-39		Age 40-49		Age 50-59		Age ≥60	
	n	SMOR (95% CI)	n	SMOR (95% CI)	n	SMOR (95% CI)	n	SMOR (95% CI)	n	SMOR (95% CI)	n	SMOR (95% CI)	n	SMOR (95% CI)
Disorder*														
Aspiration, pneumonia or influenza	620	3·00 (2·75-3·28)	109	4·15 (3·36-5·11)	260	5·80 (5·05-6·66)	315	4·65 (4·11-5·27)	647	8·03 (7·31-8·82)	1632	14·3 (13·4-15·3)	1616	11·3 (10·5-12·1)
Congenital heart defects	2980	14·3 (13·4-15·1)	423	68·4 (58·5-79·9)	627	85·5 (75·9-96·4)	493	73·8 (65·4-83·2)	315	43·7 (38·3-50·0)	159	25·4 (21·4-30·2)	69	19·3 (15·0-24·6)
Other congenital anomalies	480	0·77 (0·70-0·85)	13	1·13 (0·65-1·97)	20	2·13 (1·36-3·34)	19	3·14 (1·98-4·96)	23	3·84 (2·53-5·82)	25	3·60 (2·42-5·37)	16	3·38 (2·06-5·54)
Ischaemic heart disease	17	1·14 (0·70-1·85)	14	4·55 (2·64-7·85)	44	2·22 (1·64-3·02)	80	0·84 (0·67-1·06)	166	0·42 (0·36-0·50)	407	0·38 (0·34-0·42)	530	0·40 (0·37-0·44)
Dementia	5	0·84 (0·34-2·04)	0	0·00† (0·00-6·15)	0	0·00† (0·00-6·15)	8	8·79 (4·29-18·0)	156	116·0 (93·6-143·8)	430	66·9 (59·5-75·3)	402	10·9 (9·79-12·2)
Leukaemia	164	3·31 (2·79-3·93)	55	2·26 (1·70-2·99)	49	2·11 (1·58-2·81)	33	1·47 (1·04-2·08)	14	0·52 (0·30-0·87)	15	0·35 (0·21-0·58)	15	0·39 (0·24-0·65)
Other malignancy	10	0·09 (0·05-0·18)	11	0·23 (0·13-0·42)	19	0·17 (0·11-0·26)	47	0·14 (0·11-0·19)	85	0·09 (0·07-0·11)	93	0·04 (0·03-0·05)	79	0·044 (0·04-0·06)

*See table 1 for ICD9 codes; †When there were no deaths from Down's syndrome, we calculated expected number of cases on the basis of stratum-specific mortality rates in non-Down's syndrome deaths and used Poisson distribution to estimate 95% CI.

Table 2: **Standardised mortality odds ratios (SMORs) and observed number of deaths from selected medical disorders among people with Down's syndrome**

For most medical disorders and malignancies, we did not note appreciable differences when SMORs were stratified by region (data not shown). The SMOR for dementia in the Northeast (30·8, 95% CI 26·8-35·4) was higher than that for Midwest (18·7, 16·3-21·4), South (17·0, 14·6-19·6), and West (21·0, 17·5-25·2). SMORs for seizure disorder in the Northeast (10·1, 9·1-11·3) and Midwest (8·4, 7·7-9·3) were higher than those in the South (6·8, 6·2-7·6) and West (5·4, 4·7-6·2). SMORs for viral hepatitis in the Northeast (4·7, 3·4-6·5) and Midwest (5·2, 3·8-7·0) were higher than those in the South (2·6, 1·9-3·6) and West (2·2, 1·5-3·3).

Children with Down's syndrome younger than 10 years of age were over three times more likely to have leukaemia mentioned on their death certificate than were those without Down's syndrome (table 2). The association with leukaemia decreased with age and was not apparent after age 40 years. By contrast, malignant neoplasms other than leukaemia were listed less often than expected on death certificates of people with Down's syndrome (0 ·07, 0·06-0·08). This was true for all ages (table 2), both sexes, and all three racial groups (data not shown).

The SMORs for malignant neoplasms at almost all sites other than leukaemia were significantly lower than expected for all ages in people with Down's syndrome (table 3). The only exception was for neoplasms of the testis in those who were younger than 60 years of age.

	ICD9 codes	Age <20		Age 20-39		Age 40-59		Age ≥60		All ages	
		n	SMOR (95% CI)	n	SMOR (95% CI)	n	SMOR (95% CI)	n	SMOR (95% CI)	n	SMOR (95% CI)
Cancer type											
Lip, oral cavity, and pharynx	140·0-149·9	1	0·87 (0·12-6·34)	0		0·0 (0·00-0·76)*		2	0·05 (0·01-0·19)	1	0·04 (0·01-0·30)	4	0·05 (0·02-0·14)
Stomach	151·0-151·9	0	0·0 (0·00-18·4)*	1		0·12 (0·02-0·85)		6	0·14 (0·06-0·30)	3	0·11 (0·04-0·35)	10	0·13 (0·07-0·24)
Colon, rectum, rectosigmoid junction, and anus	153·0-154·9	0	0·0 (0·00-3·88)*	3		0·14 (0·04-0·42)		12	0·07 (0·04-0·12)	11	0·09 (0·05-0·16)	26	0·08 (0·06-0·12)
Liver and intrahepatic bile ducts	155·0-155·9	2	0·41 (0·05-1·49)	11		1·77 (0·88-3·16)		13	0·37 (0·20-0·64)	1	0·05 (0·00-0·27)	27	0·41 (0·28-0·59)
Pancreas	157·0-157·9	0	0·0 (0·00-13·2)*	1		0·18 (0·03-1·29)		14	0·16 (0·09-0·27)	5	0·09 (0·04-0·21)	20	0·14 (0·09-0·21)
Trachea, bronchus, and lung	162·0-162·9	1	0·77 (0·11-5·59)	1		0·04 (0·00-0·26)		10	0·02 (0·01-0·03)	5	0·01 (0·00-0·03)	17	0·02 (0·01-0·02)
Malignant melanoma of skin	172·0-173·9	0	0·0 (0·00-4·50)*	1		0·04 (0·00-0·25)		4	0·08 (0·02-0·21)	0	0·0 (0·00-0·27)*	5	0·06 (0·02-0·14)
Female breast	174·0-174·9	0	0·0 (0·00-12·3)*	3		0·04 (0·01-0·12)		12	0·03 (0·02-0·05)	10	0·07 (0·04-0·13)	25	0·04 (0·03-0·06)
Cervix uteri	180·0-180·9	0	0·0 (0·00-26·3)*	0		0·00 (0·00-0·13)*		0	0·0 (0·00-0·08)*	0	0·0 (0·00-0·38)*	0	0·0 (0·00-0·04)*

Body of uterus and of uterus, part unspecified	179·0-179·9, 182·0-182·9	0	0·0 (0·00-61·5)*	1	0·38 (0·05-2·74)	6	0·24 (0·11-0·53)	3	0·16 (0·05-0·51)	10	0·22 (0·12-0·42)
Ovary	183·0	0	0·0 (0·00-2·11)*	1	0·08 (0·01-0·56)	5	0·05 (0·02-0·13)	4	0·10 (0·04-0·26)	10	0·07 (0·04-0·13)
Prostate	185·0-185·9	0	0·0 (0·00-16·8)*	0	0·0 (0·00-17·6)*	2	0·11 (0·03-0·45)	3	0·06 (0·02-0·19)	5	0·08 (0·03-0·18)
Testis	186·0-186·9	2	4·87 (1·17-20·3)	18	3·31 (2·07-5·29)	6	3·06 (1·36-6·86)	0	0·0 (0·00-14·2)*	26	3·23 (2·19-4·78)
Bladder	188·0-188·9	0	0·0 (0·00-12·7)*	1	0·91 (0·13-6·56)	4	0·21 (0·08-0·56)	3	0·14 (0·05-0·45)	8	0·20 (0·10-0·40)
Kidney	189·0-189·9	0	0·0 (0·00-0·60)*	0	0·0 (0·00-0·73)*	6	0·12 (0·05-0·27)	1	0·04 (0·01-0·26)	7	0·08 (0·04-0·17)
Brain	191·0-191·9	4	0·08 (0·03-0·22)	2	0·06 (0·01-0·23)	9	0·12 (0·06-0·22)	2	0·07 (0·02-0·28)	17	0·09 (0·06-0·15)
Lymphatic and haemo-poietic tissue (excludes leukaemia)	200·0-203·9	2	0·14 (0·03-0·54)	11	0·21 (0·11-0·37)	25	0·19 (0·13-0·29)	7	0·10 (0·05-0·20)	45	0·17 (0·13-0·23)

*When no deaths from Down's syndrome were recorded, we calculated expected number of cases on the basis of stratum-specific mortality rates of non-Down's syndrome deaths and used Poisson distribution to estimate 95% CI.

Table 3: **Standardised mortality odds ratios (SMORs) and observed number of deaths for selected cancer types**

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Discussion

Our results show that median age at death of people with Down's syndrome rose strikingly in the USA from 1983 to 1997 but that substantial disparity exists between different racial groups. As expected, congenital heart defects and respiratory infections were the most frequently reported medical disorders on death certificates of people with Down's syndrome. Malignancies, except leukaemia and testicular cancer, were reported much less often than expected in people with Down's syndrome.

We used median age at death to approximate survival of people with Down's syndrome over time. Survival is usually

We used median age at death to approximate survival of people with Down's syndrome over time. Survival is usually measured in a cohort study, but such data were unavailable to us. Median age at death is a very crude measurement, and must be interpreted with caution. Figure 1 provides a more complete picture of distribution of age at death in people with Down's syndrome included in this study, but we cannot calculate age-specific survival rates without information on size of the living population with Down's syndrome. Nevertheless, our findings and those of other studies [2-5] are consistent with a striking improvement in survival of people with Down's syndrome, especially since the early 1990s.

Factors that could have contributed to this improvement in survival include: de-institutionalisation and initial placement of affected infants with their families;[20] better treatments for frequent causes of death; and changes in medical practice, including provision of cardiac surgery for children with Down's syndrome in circumstances in which it would not have been offered previously.[21]

In theory, improved survival of liveborn babies with Down's syndrome might result from a greater likelihood of pregnancy termination after a prenatal diagnosis of Down's syndrome that is more, rather than less, severe. Since prenatal diagnosis and decision about pregnancy termination are usually based on fetal karyotype, this explanation will probably not account for the size of the survival increase that we recorded.

We noted significant racial disparities in median age at death in people with Down's syndrome, though we cannot ascertain how well this finding indicates differences in survival without cohort data. After 1992, the gap between races seemed to be closing, especially in black people (figure 2). The causes of these large disparities are unknown. Part of the difference might be that manifestations of Down's syndrome differ somewhat between races. SMORs for obesity and congenital anomalies other than congenital heart defects were higher in people of other races than in white people with Down's syndrome (SMOR 1·61, 95% CI 1·38-1·87); and 2·34, 1·71-3·19, respectively). Diseases of pulmonary circulation and congenital heart defects were also reported more frequently on death certificates of people of other races with Down's syndrome than on those of white people with this disorder (1·59, 1·29-1·96; and 1·87, 1·71-2·04, respectively). However, we do not know whether this finding indicates different rates of congenital heart defects in people of different races with Down's syndrome, under-ascertainment or under-reporting of heart defects in white people, a higher likelihood of receiving successful corrective heart surgery and thus better survival in white people, or some other differential factor. No significant difference in prevalence of congenital heart defects in people with Down's syndrome of white and other races is apparent from 1985-94 data from the Metropolitan Atlanta Congenital Defects Programme (unpublished data), suggesting that the rate of congenital heart defects does not differ between racial groups. The possibility that treatment of congenital heart defects varied in people of different races with Down's syndrome is supported by the striking improvement in median age at death for white people--but not for black people and people of other races--with Down's syndrome who had congenital heart defects (figure 2).

Other factors, such as socioeconomic status, parental education, community support, and access to, use of, or quality of preventive health care, might account for the large difference that we saw in median age of death in people with Down's syndrome of different races. A combination of factors seems probable, which seems to be the case for racial disparity in mortality seen in the general population of the USA.[22] Identification of factors responsible for these racial disparities could facilitate further improvement in survival of people with Down's syndrome, especially those who are black or of other races.

We recorded significantly raised SMORs for congenital heart defects, diseases of the pulmonary circulation, infectious and parasitic diseases, hypothyroidism, viral hepatitis, dementia, seizure disorders, leukaemia, malnutrition, obesity, and

intestinal obstruction in people with Down's syndrome. These disorders have all been associated with Down's syndrome in previous studies,[4-8,18,19] and the closely similar associations we report lend support to the validity of our methods. As expected, the association with dementia was noted only in older people with Down's syndrome, especially those in the fourth and fifth decades of life. The association with leukaemia was recorded only in younger people with Down's syndrome. We noted regional differences in SMORs for dementia, seizure disorders, and viral hepatitis in people with Down's syndrome. The causes of these regional variations are unknown.

We saw strikingly low SMORs for almost all malignant neoplasms in people with Down's syndrome of both sexes, all age-groups, and all racial groups studied. The exceptions, leukaemia and testicular cancer, are consistent with previous observations that these particular neoplasms are unusually frequent in people with Down's syndrome.[6,10,11,23]

Without information about number of people with Down's syndrome living in the USA during every year of the study, we cannot be certain that our low SMORs actually show altered disease-related survival in people with Down's syndrome. The SMORs that we noted for cancer in people with Down's syndrome could be falsely reduced if the rate of cancer mortality is unchanged but the death rate for other medical conditions--eg, dementia--is greatly increased.

Despite substantial improvements in recent years, death rates for people with Down's syndrome still greatly exceed those for the general population. We did a sensitivity analysis to test the possibility that excess deaths from other causes in people with Down's syndrome might account for our findings. With data from death certificates and US census data for 1993-97, we estimated the death rate from cancer to be 25·8 per 1000 and the death rate from all other causes to be 44·2 per 1000 in the general population aged 50-59 years. If we assume that the death rate from cancer for people with Down's syndrome is actually the same as that for the general population, the death rate from all other causes for people with Down's syndrome has to be more than 25 times greater than that for the general population to produce the SMOR of 0·04 that we recorded for cancers in this age-group. This number is very large; it exceeds the number of people with Down's syndrome who die of all causes in this age-group.

The paucity of cancer reported on death certificates of people with Down's syndrome in our study is consistent with a recent population-based cohort study of incident cancers in 2814 people with Down's syndrome.[11] The standardised incidence ratio for all solid tumours was 0·50 in this cohort study, and malignancies of most sites were seen less frequently than expected. The exceptions were leukaemia, which was noted more often than expected in people with Down's syndrome younger than 30 years old, and testicular cancer, ovarian cancer, and retinoblastomas, which were seen more often than expected, but not significantly so.

There are several possible reasons why people with Down's syndrome might have a greatly reduced chance of developing most malignancies. Reduced exposure to environmental factors that contribute to cancer risk, such as tobacco, alcohol, and certain occupational exposures, could be implicated. Another possibility is occurrence of important tumour-suppressor genes on chromosome 21. People with Down's syndrome have three copies of all tumour-suppressor genes on chromosome 21, and a cell in an individual with Down's syndrome is less likely to lose all three functional copies than that of an individual without this disorder is to lose two copies. Loss of part or all of chromosome 21 has been seen occasionally in several different kinds of tumours.[24] These studies implicate the presence of tumour-suppressor genes on chromosome 21. However, these genes are unlikely to be important in a large enough proportion of tumours to explain the large reduction in cancer-associated deaths that we observed.

Another possibility is that cells from people with Down's syndrome replicate more slowly than cells from people who do not

Another possibility is that cells from people with Down's syndrome replicate more slowly than cells from people who do not have this disorder, giving less opportunity for replication errors in genes involved in tumorigenesis. Trisomy-21 fibroblasts seem to divide more slowly in culture than normal fibroblasts,[25,26] which is consistent with this hypothesis. Alternatively, trisomy-21 cells might be more prone to apoptosis than non-trisomic cells if they sustain additional mutations.[27,28]

Our study was based on data derived from death certificates and thus is limited by their shortcomings.[29-31] Causes of death on death certificates are frequently incomplete or inaccurate, especially for medical disorders that do not usually result in death or for deaths that occur outside hospital.[29] These limitations will probably apply in a similar manner to death certificates for people with or without Down's syndrome.

We cannot accurately assess whether we completely ascertained people with Down's syndrome without doing a population-based cohort study in this group of people. If we assume that the prevalence of Down's syndrome in liveborn infants is 9·2 per 10 000 (based on 17 US states reporting a total of 7·8 million liveborn infants during 1983-90)[32] in a closed stable population--ie, birth rate equals death rate and there is an absence of migration--we recorded about 61% of expected deaths of people with Down's syndrome. However, survival of people with this disorder has risen substantially and is still rising.[4] This increase would produce fewer deaths than births in people with Down's syndrome until a new equilibrium is reached, and would, therefore, lead to an underestimate of number of cases. In addition, prevalence of Down's syndrome in livebirths has been reduced by prenatal diagnosis and elective pregnancy termination in recent years.[33,34] Results of studies have shown that the proportion of pregnancies that were terminated after prenatal diagnosis of Down's syndrome is high (more than 80%).[33,34] Prenatal diagnosis and elective termination of pregnancy would lead to fewer births and, therefore, fewer individuals who are likely to die, again leading to underestimation of the number of cases.

Deaths from causes other than the one of interest, which might be related to Down's syndrome, should not be considered when calculating SMOR.[15] We were unable to do this elimination because we could not rule out the possibility that any cause of death might be related to Down's syndrome. In view of the fact that overall mortality is greater in people with Down's syndrome than in those without this disorder, the SMORs we calculated are likely to underestimate true cause-specific standardised mortality ratios for most causes of death.

Contributors

All investigators were responsible for design, data analysis, interpretation, and writing and revision of the report.

Conflict of interest statement

None declared.

Acknowledgments

This report was written while J M Friedman was on sabbatical supported in part by a career development award from the Association of Teachers of Preventive Medicine under contract from the Centers for Disease Control and Prevention. We thank Cynthia Moore, W Dana Flanders, Muin J Khoury, Adolfo Correa, Tom Sinks, and J David Erickson for their helpful

thank Cynthia Moore, W Dana Flanders, Muin J Khoury, Adolfo Correa, Tom Sinks, and J David Erickson for their helpful comments on early drafts of the report. This study was funded by the US federal government.

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