Survival of Persons with Down Syndrome in Italy

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Abstract: Down syndrome (DS) is a major cause of congenital malformation and disability. No updated data are available on life expectancy of persons with DS in Europe. We collected information on age, sex and area of birth of 3,217 persons with DS died from 1997 to 2009 in Italy. Survivals rates and mean survival time was calculated using a life tables calculated from cross sectional data. Some factors influencing the survival were also analysed using a semi-proportional hazard model. Survival rates of 91.4% at one year and 88.3% at ten years were found. Mean survival time at birth was 47.1 years (C.I. 95%: 46.5-47.7). There was 8-year significant difference in survival between north-central regions and southern regions. Male life expectancy was 46.9 years (C.I. 95%: 46.1-47.8), lower than females 47.3 years (C.I. 95%: 46.5-48.2) even though not statistically significant (p=0.23). Almost nine out ten children with DS now survive at least 10 years. Adequate educational and health service provisions needs to be made for them. The disadvantage of Down persons born in the Southern regions in terms of life expectancy is impressive. Quality of medical care provided in the South of Italy in the first months of life is the most likely determinant of the high mortality observed among persons with DS born in that area.

Keywords: Down syndrome, survival, gender, geographical differences, Italy.

INTRODUCTION

Life expectancy (LE) of persons with Down Syndrome (DS) has greatly improved over the past decades and has been amply documented [1]. The better living conditions and overall progress in the prevention and treatment of many diseases have led to a considerable increase in life expectancy of the entire population. Over the past few years the understanding of clinical problems associated with chromosomal alterations in general, and in particular with the DS, has dramatically improved. This has led to the development of medical therapies and pharmacological addressed to the treatment of conditions associated with DS and has had consequences especially with regard to the survival of people with DS. Compared to the past LE in DS is significantly increased. In less than fifty years LE at birth increased from 12 years in the forties to over 60 years in late 90s [2]. This increase is due to an improvement in the quality of life at all levels. Crucial is the fact that compared to the past, at present action is taken to eliminate or reduce congenital heart defects. In adulthood and elderly individuals with DS are predisposed to a particular form of Alzheimer's disease, with the typical features in the brain, often without characteristic symptoms. This affects dramatically the quality of life and survival.

DS is recognized as a leading cause of mental disability (MD) [3]. In Italy, the prevalence of persons with MD is estimated by Italian National Institute of Statistics (ISTAT) in 800 thousand people [4], that of persons with DS is about 38,000 [5]. DS is the most frequent cause of MD among people aged less than 45 years. The estimated number of newborns with DS, based on the five Italian regional registries on congenital anomalies (Lombardia, North-East, Emilia Romagna, Tuscany, Campania), is 522 per year, with a large variability in the prevalence among regions, mainly due to differences in number of terminated cases after prenatal diagnosis [6].

Data on survival of DS have not been published recently in Italy, except one study limited to children up to 8 years [7]. Factors which have been demonstrated as influencing the survival of DS are sex, area of birth and presence of congenital heart defect (CHD) [8].

This study aimed at reviewing the existing literature on LE of DS and estimating the LE at birth of DS in Italy using a “fictious” cohort of persons with DS died from 1997 to 2009, identified through the death reports. Survival was analysed according to sex and area of birth.

SUBJECTS AND METHODS

As first we performed a review of studies on life expectancy of DS, including papers available on Medline or Scopus using the following keywords: Down syndrome, Trisomy 21, life expectancy, survival. Secondly we analysed the death reports available in Italy through the ISTAT [9] in order to obtain an updated estimate of survival of persons with DS. The survey of death reports is a total survey carried out by ISTAT since 1887. Starting from 1997 the underlying cause of death has been registered with co-morbid

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E-ISSN: 2292-2598/14

conditions listed on the death certificate. The files of multiple-cause mortality include demographic information about the decedent and codes of the causes of death. The underlying cause of death and contributing conditions are coded using the Manual of the International Statistical Classification of Diseases, Injuries and Cause of Death, based on recommendations of the Ninth Revisions Conference (ICD-9). All deaths that contained the code for DS (758.0) anywhere in the record were selected. From January 1, 1995 to December 31, 2009 3,217 persons with DS were registered in the multiple-cause mortality files. Data were not available for the years 2004 and 2005. For each record the age at death, sex, and region of birth were collected.

From the age at death of persons with DS has been obtained a life table based on cross sectional data [10]. Arranging the events in a life table by the age of death, the death proportion in each single year is calculated by dividing the number of persons alive at age x and dying before age x+1 by the number of persons at risk as of the middle of that year. The estimate of the survival function is than obtained by calculating the continued product of the death proportions. An estimate of the variance of the survival function is given by Greenwood [11]. The life expectancy can be estimated as the mean of the product-limit of the survival function. A confidence interval for the life expectancy was obtained by using the upper and lower limits of a confidence interval for the hazard rate. Separate life tables by area of birth (North, Centre and South), and sex were also calculated. Finally the survival curve for DS was compared with that of the general population. Survival among different groups was compared through the log-rank test [12]. A multivariate analysis was carried out using Cox's proportional hazard model to determine the effect of the different variables on survival. Data were also analysed separately by cohort of death, considering the cohorts 1995-1998; 1999-2003 and 2006-2009. Data were analysed using Stata version 9 [13].

RESULTS

We collected information from 23 articles published from 1955 to 2012 in 8 countries investigating the survival of people with Down syndrome (Table **1**).

The probability of survival at 1 year increased from 69% (3 out of 10 children died before the completion of the first year) for children born around 1950 to 93% for those born after 1990. The probability of surviving at

Table 1: Survival of Persons with DS by Country, Author, Death Cohort and Sample Size (N). Studies Conducted from 1955 to 2012

Country	Author	Publication year	Death cohort		N	Survival at 1 year	Survival at 5 year	Survival at 10 year	Survival at 50 year
			From	To					
UK	Record	1955	1942	1952	252	0.50			
UK	Carter	1958	1944	1955	725	0.47			
UK	Lunn	1959	1953	1958	117	0.76			
Australia	Collman	1963	1948	1957	729	0.69		0.46	
USA	Fabia	1970	1950	1967	2421	0.76		0.65	
Canada	Gallagher	1975	1952	1971	927	0.89	0.83		
Australia	Mulcahny	1979	1966	1976	231	0.84			
UK	Fryers	1979	1961	1975	48	0.83			
Sweden	Frid	1999	1973	1980	224	0.85		0.76	
Canada	Baird	1987	1952	1981	1341		0.81	0.77	
Australia	Bell	1989	1976	1985	426	0.87			
Italy	Mastroiacovo	1992	1978	1994	905	0.80	0.76		
Ireland	Hayes	1997	1980	1989	389	0.88		0.83	
Australia	Leonard	2000	1980	1985	139	0.89		0.79	
Australia	Leonard	2000	1986	1990	133	0.92		0.85	
Australia	Leonard	2000	1991	1996	165	0.94			
USA	Nembhard	2001	1995	1997	456	0.92			
Italia	Mastroiacovo	2002	1985	1995	2013	0.88			
UK	Dastgiri	2003	1980	1997	6153		0.84		
USA	Day	2005	1988	1999	14781				0.46
USA	Goldman	2011	1990	2006	1305	0.93			
UK	Tennant	2010	1985	2003	1294	0.88		0.84	
Denmark	Zhu	2012	1968	2009	3272	0.89			0.64

Table 2: Life Expcectancy (LE) at Birth by Sex and Area of Birth with 95% Confidence Interval

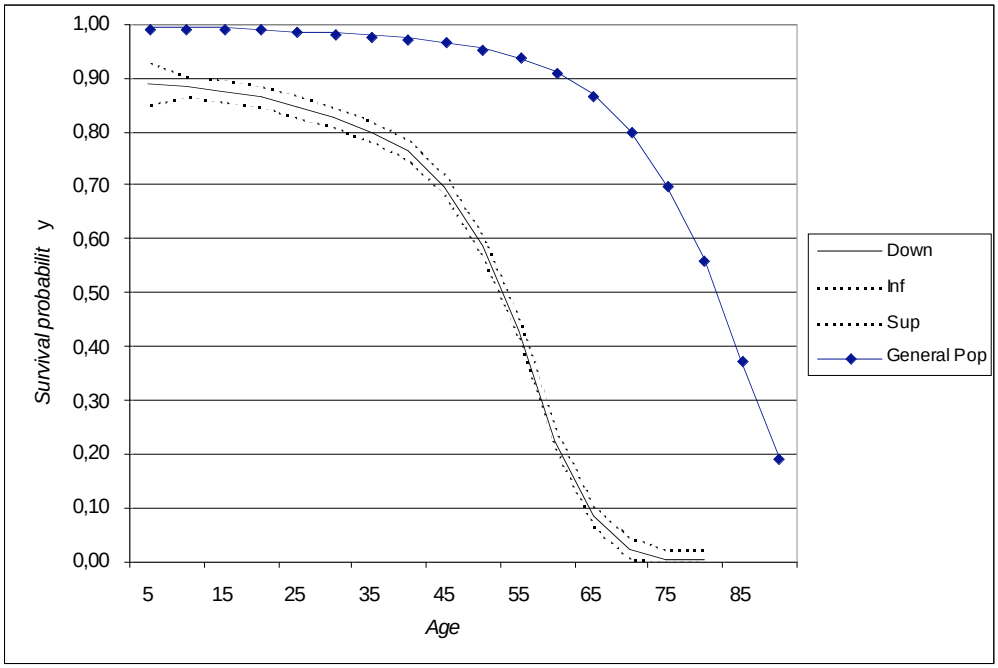
	N.	(%)	LE	Conf Int 95%
Sex				
Males	1,626	50.5	46.9	(46.1-47.8)
Females	1,591	49.5	47.3	(46.5-48.2)
Total	3,217		47.1	(46.5-47.7)
Birth area				
North	1,164	36.2	50.8	(49.9-51.7)
Center	530	16.5	51.1	(49.8-51.4)
South	1,022	31.8	42.6	(41.4-43.9)
Unknown/Abroad	501	15.6		

least 10 years have rose from 46% (less than one in two children) in 1957 to over 85% in the 90s.

The estimated LE at birth was 47.1 years (C.I. 95%: 46.5-47.7). Males showed a LE similar to females: 46.9 years (C.I. 95%: 46.1-47.8) *vs.* 47.3 years (C.I. 95%: 46.5-48.2), not statistically different (p=0.99) Survival in North and Central areas differed significantly from Southern area (p<0.001) (Table **2**).

Overall survival was 91.4% at one year and 89.0% at 5 years but greatly differed between North-Central area and South (94.1% *vs*. 86.5% at one year, 92.4% *vs.* 83.6% at 5 years) (data not shown). The median survival time was 49.3 (C.I. 95%: 48.1-51.5). The influence of sex and geographical area of residence on mortality was also analysed using Cox's proportional model. Living in Southern regions compared to north and central regions together, adjusted for sex, has a hazard ratio of 1.46 (C.I. 95%: 1.26 - 1.77). The survival curve of DS, after the first quinquennium, has a shape similar to that of the general population (Graph **1**) but shifted of about 10 years at 10 year of age, and shifted of 20 years at from 40 year of age and onward.

Finally, considering separately the cohorts of death we estimated a LE at birth of 41.6 years for the cohort 95-98; 45.4 for the 1999-2003 cohort and 50.9 for the cohort 2006-2009.



Graph I: Survival of persons with DS by quinquennia, with inferior (inf) and superior (sup) limits of 95% confidence interval, compared with general population. Italy 1997-2009.

DISCUSSION

Results from this study are in agreement with findings in the recent literature. Survival at 5 year was 89.0%, much higher than 75% found by Mastroiacovo [7] on a cohort of infants with DS born between 1978 and 1984. This testifies the dramatic improvement of survival of persons with DS in the last 20 years. This was also confirmed by the analysis performed by cohort of birth in the present study showing a steady improvement of LE from 41.6 years for the cohort died in 95-98 to 50.9 for the cohort 2006-2009. The estimated median survival time (49.3 years) matches the findings of the US study for white population [14]. The study showed as - contrary to what happens in the general population - males with DS do not have a lower LE at birth, confirming previous findings of Masaki [15], Mastroiacovo [5] and Strauss [16].

This study allowed for the first time in Italy to have indices of survival of persons with DS throughout their whole lifespan, analysed according to sex and area of birth. We showed that 88.3% of children with DS now survive at ten years. Adequate educational and health service provisions needs to be made for them. The disadvantage of Down persons birth in the South area in terms of life expectancy is impressive (more than 7 years). Such a disadvantage is mainly due to differential survival in the first year of life. These findings are consistent with infant and child mortality in the general population, which is higher in the South compared with the North [17]. However this geographical disadvantage looks to be a catastrophic risk factor for infants with DS. Quality of medical care provided in the South of Italy is the most likely determinant of the high mortality observed among persons with DS born in that area, along with the different level of prenatal care, that is much higher in North-Central regions than in Southern regions [6]. Hence, more cases with severe foetal anomalies are detected (and terminated) in the North-Central regions: such differences may influence the difference in survival rates among regions. Findings of this study are useful both for health policy makers and families who need to plan for the long term care of children born with DS.

Limitations concern the possible underreporting due to poor description of the diagnosis or because Down syndrome was not considered among the factors which lead to death. However, considering that the main objective of the study was to estimate the life expectancy in DS, no occurring bias in reporting age at death of persons with DS could be argued. Having a malformation associated with SD is an important predictor of mortality. In presence of a cardiac malformation the risk of death in DS is three times higher compared with no malformation association, in cases of severe cardiac defects the risk is quintupled [8]. Not to have information on the presence of cardiac defects constitutes an important limitation in the study of survival of DS.

Ascertainment of the cases was upon the responsibility of the certifying physician, who is often the GP of the person. This assures a good reliability of reported cases. Even if no selection bias is argued in terms of age of reported cases, this might happen more likely among younger people. Estimates from this study might therefore underestimate the real mean survival time of persons with DS.

LEs computed in this study from cross-sectional data are not really expectancies in the common sense used in statistics, as they are based on prevalent cases and not on incident ones. Therefore they describe the actual situation, like a census does, but cannot be used to simulate the future "expectations" of a cohort which would, at each age, have the actual prevalence. Prevalent data come from in and out flows and therefore cannot be supposed to remain constant over time even if "nothing changes". It can be the case only if the flow rates are consistent with the stock, ie if the incidence rates are consistent with the prevalence. This is rarely the case if prevalence is itself changing. However such estimates provide a good approximation of the future life expectancy based on real data.

This study has exploited the enormous informative power of the Italian arichives on multiple-cause mortality, from which it is possible to estimate the survival of persons affected by various diseases in Italy, including rare disease (e.g. cystic fibrosis, spina bifida) using the simple methodology presented herein.

ACKNOWLEDGEMENTS

The study was granted by “Fondazione Cariplo” within the project “Oltre la famiglia:strumenti per l’autonomia dei disabili”.

CONFLICT OF INTEREST

There is no conflict of interest.

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Received on 02-06-2014 Accepted on 18-06-2014 Published on 26-09-2014

DOI: http://dx.doi.org/10.6000/2292-2598.2014.02.02.5