Register-based cumulative prevalence of Autism Spectrum Disorders during childhood and adolescence in Central Italy

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ABSTRACT

Background: Studies have evaluated the prevalence of Autism Spectrum Disorders (ASD), focusing on different ages during childhood and adolescence. How cumulative prevalence increases before adulthood remains unclear.
Methods: We used data from the Autism Register of the Regional Reference Centre for Autism in L'Aquila, Central Italy, to retrieve information on individuals born in 2001–2012 with any of the inclusion diagnoses of ASD (DSM criteria) for the period 2001 to 2018. Cumulative prevalence on L'Aquila district population data was calculated as percentages for three-year age strata.
Results: All prevalence data were estimated at December 31st, 2018. The overall crude prevalence was 0.95% (352 cases over 36938 population). Cumulative prevalence was 1.19% among those born in 2001-2003 (15 to 17 years of follow up), 1.15% among those born in 2004-2006 (12 to 14 years of follow up), 1.04% among those born in 2007-2009 (9 to 11 years of follow up), 0.80% among those born in 2010-2012 (6 to 8 years of follow up), and 0.57% among those born in 2013-2015 (3 to 5 years of follow up). The proportion of ASD diagnoses until the age of 5 years, compared to the group diagnosed 6 to 8 years of age, showed a significant increasing trend over calendar time (53.6% for those born in 2001-2003, to 77.0% for those born in 2010-2012).
Conclusions: Cumulative prevalence by time period provides a better understanding of ASD occurrence than a point prevalence. We did not find any difference in frequency of diagnosis comparing age strata and year of birth, suggesting that frequencies of ASD diagnosis remained roughly constant from 2001 to 2015. Results show that cumulative prevalence of autism diagnosis does not substantially change over time; instead, diagnosis of ASD is more likely at earliest ages over time, although new cases of ASD are also detected at later ages.

Keywords: Autism Spectrum Disorder, Cumulative Prevalence, Epidemiologic Register, Childhood, Adolescence

INTRODUCTION

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by a range of deficits in two domains: (a) social communication and social interaction, and (b) restricted, repetitive patterns of behaviours, interests, or activities [1, 2].

ASD are reaching an increasing epidemiological interest according to their rising awareness in western countries documented in terms of both clinical research and public health attention [3].

Signs of ASD emerge from atypical or delayed development of social-communication behaviours, which start between 6 and 12 months [4], and screening at 18 and 24 months are recommended [5]. It is important to notice that 32% of individuals diagnosed with ASD have shown the loss of previously acquired skills on the average age of about 2 years [6]. However, high-functioning individuals with ASD are likely to be diagnosed later [7].

ASD affect the quality of life of individuals and their caregivers, rising the necessity of both interventions based on timely diagnosis, evidence-based and cost-effective strategies bringing behavioural benefits to autistic people and their families, and adequate management of transition from adolescence to adulthood with regard to general health, education, and social care [3].

Individuals with autism put a heavy demand on educational, social, and medical services, and accurate prevalence estimates are needed to planning services. During lifespan ASD determine substantial health loss, and an accurate epidemiological description could inform public health policy to plan support services [8]. A study conducted in Ireland underlined that most of the costs are related to special needs assistants for individuals with ASD and that ASD severity is associated with higher out of pocket expenditures [9]. This is in line with evidence concerning the costs of nervous central system disorders overall: it has been pointed out that in Europe 37% of the total cost of such disorders are healthcare costs, while 40% of costs are associated with patient's production losses [10].

Until the 1990s, the figure of 4 to 5 cases of autism per 10000 people was widely accepted, although as many as 20 per 10000 children showed the diagnostic triad of impairments in social reciprocity, language impairment, and reduced imagination and restricted activities [11]. ASD affect approximately four males every one female [12], and females are diagnosed later than males [13].

Studies have shown increased prevalence estimates for ASD: in addition to a true increase in prevalence, the literature proposes alternative explanations, including changing diagnostic criteria, different methods of ascertainment, inhomogeneous protocols of diagnosis, research protocols, environmental components, cultural factors or awareness in recent years [14].

A worldwide review commissioned by the World Health Organisation showed a prevalence of autism of 0.62%, discussing the potentially strong impact of ethnical, cultural or socioeconomic factors, and the critical need of research in low- and middle-income countries [15]. Moreover, a recent review estimated a prevalence of 1.5% in developed countries, with an increase of cases without comorbid intellectual disabilities [16].

A study among 8-year old children with autism and developmental disabilities based on a surveillance system network of eleven States in the USA [17] estimated an overall prevalence of ASD of 1.45%: an overall prevalence was found of 2.37% in males and of 0.53% in females. An update from the surveillance system [18] estimated an overall ASD prevalence of 1.68% (2.66% males, and 0.66% females, with M:F ratio of 4:1). Among the eleven sites prevalence ranged from 1.31% to 2.93%.

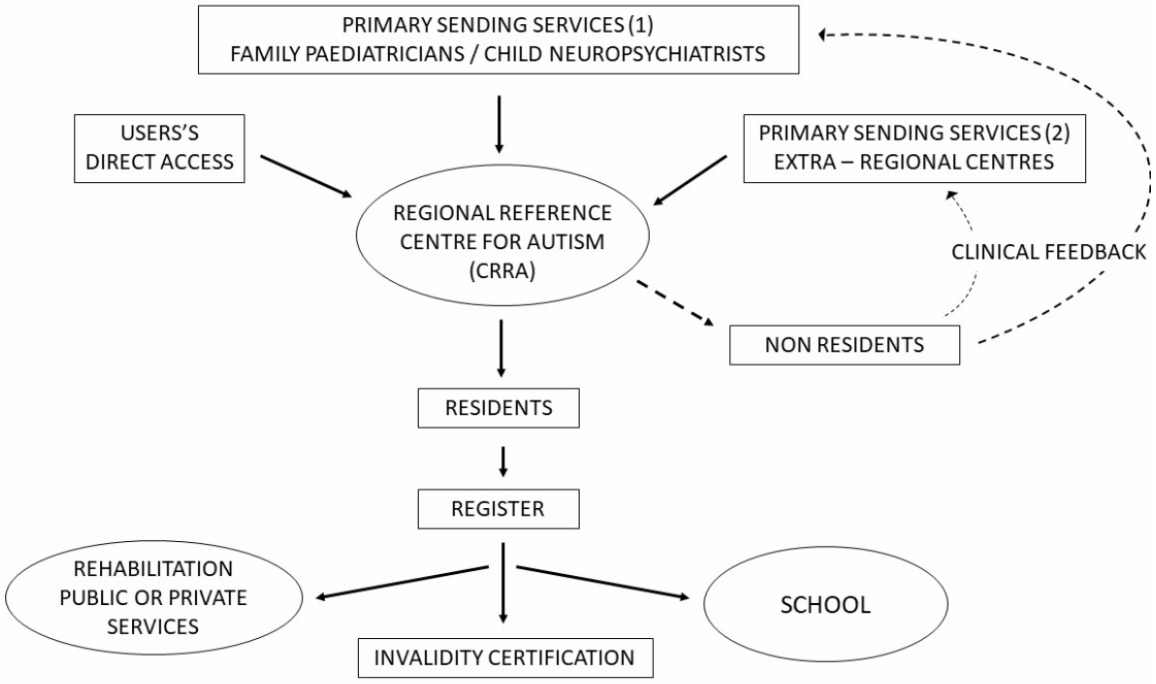
The average prevalence of European countries is reported as 1%, exceeding in Iceland the value of 2.6% [19]. A survey among children aged 5-9 years old attending school revealed a prevalence of 0.99% and suggested that prevalence would reach 1.57% considering undiagnosed cases [20]. A study conducted in Denmark [21] over 13 years found a prevalence of ASD of 0.82% in a cohort born in 1994-1995, and reported a shift in age at diagnosis especially in younger ages. A register-based prevalence study conducted in Sweden, which involved individuals aged from 0 to 17 years in the period 2001-2007, found a prevalence of 1.15% [22].

As far as Italy is concerned, limited information about prevalence rates of ASD is available from registers or cross-sectional studies. Prevalence of ASD cases ranges from values of 0.05% in the city of Catania in Southern Italy [23] to 0.44% in the age between 6 and 10 years in the region Emilia-Romagna [24] and 0.48% in the region of Piedmont [25] both in Northern Italy. The first population-based ASD prevalence study in Italy so far according to the Autism Spectrum Disorders in the European Union program [19] was recently conducted in the catchment area of Pisa in Central Italy [26] and indicates a prevalence of ASD in children aged 7–9 years of 1.15%, i.e. about one in 87.

Register-based studies have played an important role in mental health research [11, 27]. Nonetheless, most prevalence studies focusing on childhood/adolescence, especially in ASD, are designed as cross-sectional investigations, reporting on populations with specific age ranges and presenting the average prevalence in those age ranges. Indeed, we could find no study that provided the prevalence of ASD by yearly categories throughout developmental ages.

The aim of this study was to estimate the cumulative prevalence of ASD throughout childhood and adolescence, based on data from a register for autism established in a provincial Local Health Authority (LHA) area of Central Italy.

FIGURE 1. L'Aquila register for Autism: data source and pathways



METHODS

Register

An epidemiological register was established in 1997 in L'Aquila (the capital of the Abruzzo Region in Central Italy) with the former denomination of Epidemiological Register for Psychological, Neurological and Sensory Handicaps [28], including also diagnoses of autism. The register was successively denominated Register of Autism in 2007, following the regional health-planning law that established the Regional Reference Centre for Autism (Centro di Riferimento Regionale Autismo, CRRA) in L'Aquila: it is a public, multisource information, prospective registry of ASD users resident in the L'Aquila Local Health Authority area (Azienda Sanitaria Locale n. 1). Its goal is to collect ASD epidemiological data structured according to administrative, diagnostic, clinical and outcome-related items (like the follow up and the evaluation over time of rehabilitative interventions [29, 30]).

Data management and quality assessment is carried on by the CRRA, which operates as a unit of the National Health System (NHS) with multidisciplinary expertise including child and adolescent neuropsychiatrists, adult psychiatrists, clinical psychologists, and epidemiologists. Users accessing directly the service for first-time diagnosis undergo a standardized diagnostic process including clinical observation and a validated test battery. As the Italian NHS does not limit access to services on the basis of regional boundaries, users resident in L'Aquila province may also access the CRRA for second level diagnostic ascertainment, after a diagnosis has been proposed or suspected in other settings, typically paediatric or child-neuropsychiatry settings of any other regional district, as well as in other reference centres in Italy. The take-in-charge of persons with ASD by the public rehabilitation programs within the user's residence area in the Abruzzo Region, as well as the assignment of a state disability pension to the person with ASD, requires a mandatory registration and prescription by the Multidisciplinary Evaluation Unit of the NHS Local Health Authority. The Unit is functionally linked with the CRRA, for evaluation of ASD cases, so that no cases of ASD treated within the NHS or with NHS financial support in accredited private settings may leak from the registry. Moreover, educational support at school for children and adolescents with ASD (implying the definition of an educational plan tailored on student's skills) requires a mandatory public medical certification and the inclusion in the register. In fact, both the inclusion in rehabilitation programs and the school programs – which represent the main take-in-charge for ASD children and adolescents – as well as the administrative data used to assign invalidity, operate as the secondary source of the register, and virtually minimize the risk of missing users taken in charge. Figure 1 describes the register's data source chart.

We conducted a study based on the Register of

Autism of the CRRA, where we report all the cases of ASD found from the 1st of January 2001 until the 31st of December 2018.Figure 1

Case identification and measures of prevalence

Diagnoses of autism from 2001 to 2013 were done and registered according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV [31]). From 2014 to date, diagnoses of ASD were done and registered according to the criteria of the DSM-5 [1], and using as a support the age-pertinent modules of the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) [32]. The ADOS-2 includes five modules, each requiring between 40-60 minutes to administer. The individual being evaluated is given only one module, selected on the basis of his or her expressive language level and chronological age: Toddler Module-for children between 12 and 30 months of age who do not consistently use phrase speech; Module 1-for children 31 months and older who do not consistently use phrase speech; Module 2-for children of any age who use phrase speech but are not verbally fluent; Module 3-for verbally fluent children and young adolescents; Module 4-for verbally fluent older adolescents and adults. Each Module offers standard activities designed to elicit behaviours that are directly relevant to the diagnosis of Autism Spectrum Disorder (ASD), at different developmental levels and ages.

Given the differences between DSM-IV and DSM-5 classifications, we considered participants diagnosed according to the DSM-IV criteria for Autistic disorder, Asperger's Disorder, Childhood Disintegrative Disorder or Pervasive Developmental Disorder-not otherwise specified (PDD-NOS), as ASD individuals according to the DSM-5, which clustered these conditions in the spectrum of autism [1].

The holders of parental rights who access the CRRA undersign a specific informed consent form for data registration, so that an undersigned consent form is then available for each person included into the register. Data are stored and collected according to the national prescriptions about security and privacy of personal sensitive data. Any use of the register's data, including this study, was done according to the Declaration of Helsinki [33]. The study was registered by the Ethical Committee of the LHA of L'Aquila (protocol number 0211551/19).

The study included users from zero up to 18 years of age registered as ASD until December 31st 2018. We calculated the number of people registered with an ASD diagnosis by year of birth and age, cumulating time figures (year-of-birth strata: 2001-03, 2004-06, 2007-09, 2010-12, 2013-15; age strata: 3-5, 6-8, 9-11, 12-14, 15-17 years) to smoothen annual random variations: age strata are constructed on a 3-year basis; the first age stratum ranges from 3 to 5, as in the ages 0-2 diagnosis cannot be definitely confirmed. To calculate cumulative prevalence, we divided the cumulative number of registered cases by the relevant populations at risk, i.e. the L'Aquila LHA population of the same age group. Population frequencies were obtained from the Italian Institute of Statistics website [34]. We did not exclude those who had died from both the index cases and the general population, as the figures were negligible. We calculated 95% confidence intervals (CI) according to Gardner and Altman [35].

The structure of the data retrieved enabled us to compare children whose first diagnosis was assessed until the age of 8 years by a chi-squared test for trend [36] with fist type error set at 5%. We performed statistical analysis using the package Coin [37] running under R statistical software [38].

RESULTS

Table 1 displays new diagnoses of ASD by year of birth and age at diagnosis, and cumulative prevalence at December 31st 2018. The register identified 352 people <18 years diagnosed with ASD: 285 (81%) were males, and 67 (19%) were females, that yields a 4:1 male-female ratio. Considering the population of registered users born between 2001 and 2015 as a whole, the population at risk sums 36938 that yields a crude prevalence proportion of 0.95%.

Those born in 2001-2003 reached a cumulative prevalence of 1.19% at the age of 15-17. Those born in 2004-2006 reached a cumulative prevalence of 1.15% at the age of 12-14. Those born during 2007-2009 reached a cumulative prevalence of 1.04% at the age of 9-11. Those born during 2010-2012 reached a cumulative prevalence of 0.80% at the age of 6-8. Those born during 2013-2015 reached a cumulative prevalence of 0.57% at the age of 3-5.

Reading the data in terms of early diagnosis and considering only registered users diagnosed with ASD from 0 to 8 years of age, it is worth noting that the proportion of ASD diagnoses definitely given until the age of 5 years, compared to the group diagnosed 6 to 8 years of age, shows a significant increasing trend through year of birth, rising from 53.6% (30 out of 56) for those born in 2001-2003, to 61.4% (35 out of 57) for those born in 2004-2006, 62.3% (38 out of 61) for those born in 2007-2009 , and 77.0% (46 out of 60) for those born in 2010-2012 (χ^2_{trend}=6.20, p=0.01) .

DISCUSSION

Registers, intended as organized data collection systems for one or more purposes, have much in common with observational studies, and therefore meet very similar requirements. The main advantage of population register-

TABLE 1. Registrations and cumulative prevalence of 1st asd diagnosis by year-of-birth and age at diagnosis

		YEAR OF 1ST ASD DIAGNOSIS				
Year of Birth strata	**Population**	**2004-2006**	**2007-2009**	**2010-2012**	**2013-2015**	**2016-2018**
		3-5 years	**6-8 years**	**9-11 years**	**12-14 years**	**15-17 years**
2001-03	7503	30 30 0.40% [0.26-0.54]%	26 56 0.75% [0.55-0.94]%	16 72 0.96% [0.74-1.18]%	12 84 1.12% [0.88-1.36]%	5 89 1.19% [0.94-1.43]%
			3-5 years	**6-8 years**	**9-11 years**	**12-14 years**
2004-06	7468		35 35 0.47% [0.31-0.62]%	22 57 0.76% [0.57-0.96]%	18 75 1.00% [0.78-1.23]%	11 86 1.15% [0.91-1.39]%
				3-5 years	**6-8 years**	**9-11 years**
2007-09	7311			38 38 0.52% [0.35-0.69]%	23 61 0.83% [0.62-1.04]%	15 76 1.04% [0.81-1.27]%
					3-5 years	**6-8 years**
2010-12	7516				46 46 0.61% [0.44-0.79]%	14 60 0.80% [0.60-1.00]%
						3-5 years
2013-15	7140					41 41 0.57% [0.40-0.75]%

Cell figure legend: age at diagnosis, frequency, cumulative frequency, percent cumulative prevalence, 95% C.I. of percent cumulative prevalence.

based data is the opportunity to get cumulative prevalence on a population scale. Moreover, considering the cumulative frequencies as the variable of interest allows understanding how prevalence increases over calendar time.

Results show us that diagnosis of ASD frequencies reached 1.19%, i.e. one every 84, for those born in 2001-2003 considering the population until 18 years of age. This result is in line with European prevalence studies reported in literature where autism prevalence is roughly 1% of the population.

Our results did not find any difference in frequency of diagnosis comparing age strata and year of birth, suggesting that frequencies of ASD diagnosis remained roughly constant from 2001 to 2018 considering year of birth. In summary our results show that cumulative prevalence of autism diagnosis does not substantially change over time; instead, diagnosis of ASD is likely to be done at earliest ages over time, although new cases of ASD are also detected at later ages, especially concerning higher functioning cases (i.e. level 1 cases as described by the DSM-5).

Although, we must point out that our study is register-based. The functioning of the register is based on a core institutional structure (the CRRA) which takes in charge individuals with ASD in order to enter public rehabilitation programs. The multisource characterization of the register

allows comprehending a territorial monitoring of structures in contact with the target population during early development (i.e. paediatricians and child neuropsychiatrists) and during school age. Individuals can also have a direct access to the CRRA. Moreover, access to public national health system services or to accredited private rehabilitation services requires a second level diagnostic ascertainment and follow up evaluation by the CRRA.

A potential limitation of the study, relying on the register base, is that individuals with ASD diagnosed and followed up in a fully private setting could not be reported to the CRRA, although it must be pointed out that they would not have access to NHS financial support: we could then hypothesize that the number of persons with ASD not accessing the register is very low.

Another important aspect is the change of the diagnostic criteria from DSM-IV to DSM-5: in fact, Matson and colleagues [39] found that DSM-5 tends to diagnose fewer cases than DSM-IV. In this view, the constancy of cumulative prevalence of ASD through the classification change may suggest a real increment of incidence cases.

To our best knowledge, this is the first register-based study grounded on institutional NHS organisation in Italy, investigating cumulative prevalence over a large time period and across all ages until 18 years. Our data confirm that the prevalence of ASD overall is around 1% in childhood and adolescence, thus indicating an important need for specifically dedicated rehabilitation and public health interventions. Italian law has recently enforced the inclusion of ASD treatment in the Essential Levels of Health Care (Livelli Essenziali di Assistenza, LEA), thus implying that any person with ASD has the right to be taken-in-charge by the territorial units of the NHS. To date, a rough and minimalistic estimate of costs of the sole health assistance per person with ASD per year in the L'Aquila Local Health Authority amounts to about 12.000 Euro, with a wide range depending on the disability level of persons with ASD. Additional social costs for families are of the same order of magnitude.

An accurate monitoring of occurrence indicators, especially cumulative prevalence and incidence, allows regional and local health authorities to allocate adequate financial resources to respond to the growing demand of services in a lifetime perspective.

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