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Epidemiological controversies in autism

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Summary

Once considered to be rare with a prevalence of 4–5/10,000, autism today has a prevalence in the range of 0.9–1.5%. The increased prevalence reflects mostly a broadening of the diagnosis, and improved awareness and identification among children. The hypothesis that the rise in autism prevalence was due to increased use of childhood vaccines has been refuted in well-controlled and replicated studies. Few environmental causes are well established (advanced paternal age, prenatal exposure to valproate); most other findings require replication.

Keywords: *autism, prevalence, epidemiology, environment, risk factor, vaccine, immunisation, valproate, paternal age*

The first survey of autism was published in 1966 in the UK. In this study, and those that soon followed, surveys were merely head-counting exercises of how many children in a given area had a diagnosed Kanner clinical syndrome. The phenotype was severe, considered to be rare, with a prevalence of 4–5/10,000 (or 0.05%). In the 1980s and 1990s, autism was progressively recognised among subjects without language delays or intellectual deficits. Asperger syndrome and partial forms (pervasive developmental disorder not otherwise specified) were added to both the International Classification of Disease, 10th edition (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). The concept of autism became more dimensional as reflected by new diagnostic tools such as the Autism Diagnostic Interview-Revised [1] and the Autism Diagnostic Observational Schedule [2]. As a result of this enlarged definition, of increased awareness and of improved ascertainment techniques, the prevalence in surveys conducted around year 2000 rose to 0.6–0.7%.

Epidemiological research subsequently accelerated with surveys now conducted in multiple countries, including non-Western and lower-income ones [3, 4]. Yet, there is no standardisation of survey methodology. Each survey has unique design features that reflect the particularities of the local health and educational services, as well as local social policies, awareness and values towards disabilities. Recent reviews show a huge heterogeneity across surveys [5]. Prevalence ranges from 0.01% to 2.6%, the most plausible range being 0.9% to 1.5%. Autism affects four males for every female, and occurs in all social strata. Two adult surveys yielded figures of 1%. The proportion of autistic individuals with associated intellectual disability is in the 30% to 40% range [5].

Increased prevalence over time (fig. 1) fuelled concerns about an epidemic of autism driven by environmental changes. However, strong evidence exists that most of this increase can be attributed to broadening of the autism concept, to corresponding changes in diagnostic algorithms, diagnostic switching (whereby a child previously diagnosed with intellectual disability, or language disorder, are re-diagnosed with autism spectrum disorder [ASD]), and better case ascertainment [5, 6]. For example, the ≈18% decrease in prevalence derived from the same survey whether DSM-IV or DSM-5 is used (everything being equal otherwise) illustrates how prevalence results are influenced by method factors (fig. 2 [6, 7]). However, it remains plausible, but is yet unproven, that a secular change in the incidence also took place, contributing to some of the upward trend [5].

Claims that childhood vaccines fuelled an epidemic of autism were widely publicised in the late 1990s. One “theory” incriminated the measles component of the triple measles-mumps-rubella (MMR) vaccine, the second one implicated thimerosal (ethylmercury) received through other childhood vaccines. However, trends in rates of ASD were shown to be uncorrelated to trends in uptake of MMR or thimerosal-containing vaccines [8]. Controlled observational studies (case-control and cohort studies) equally failed to show increased risk of ASD in individual children exposed to MMR or thimerosal-containing vaccines in various doses [9]. Thimerosal was removed from vaccine production in the early 2000s, with no effect of autism trends. Younger siblings of children with ASD also have no raised risk of ASD after immunisations [10]. Remarkably, no study has ever supported a risk association of autism with vaccines, and as shown in meta-analyses and systematic reviews [9], the convergence of negative findings across investigators, study designs, samples and countries has been impressive. Further claims were made that the risk could be confined to a small, vulnerable, subgroup that epidemiological studies would not be capable to detect. Systematic search for this hypothetical subgroup (defined by regression, onset immediately after MMR shot, co-occurrence of gastrointestinal symptoms and inflammation, and abnormal persistence of measles virus in the gut wall) failed to validate its existence [11–13].

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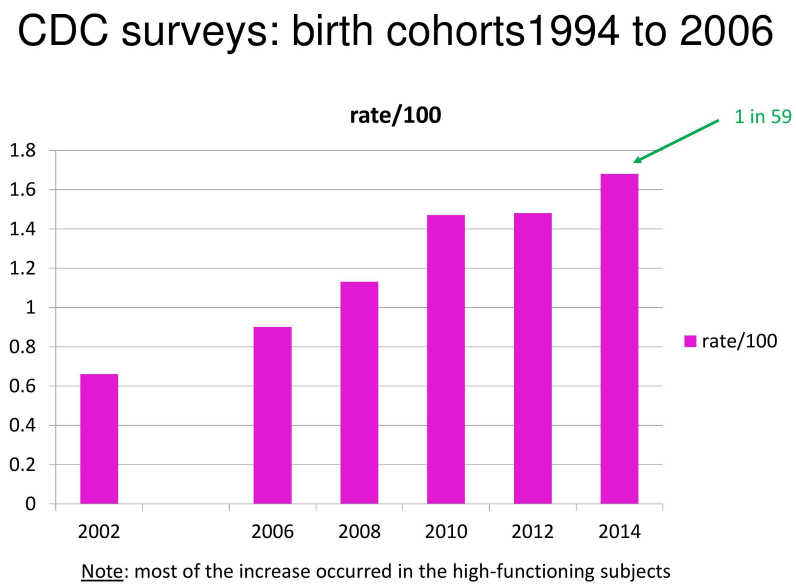
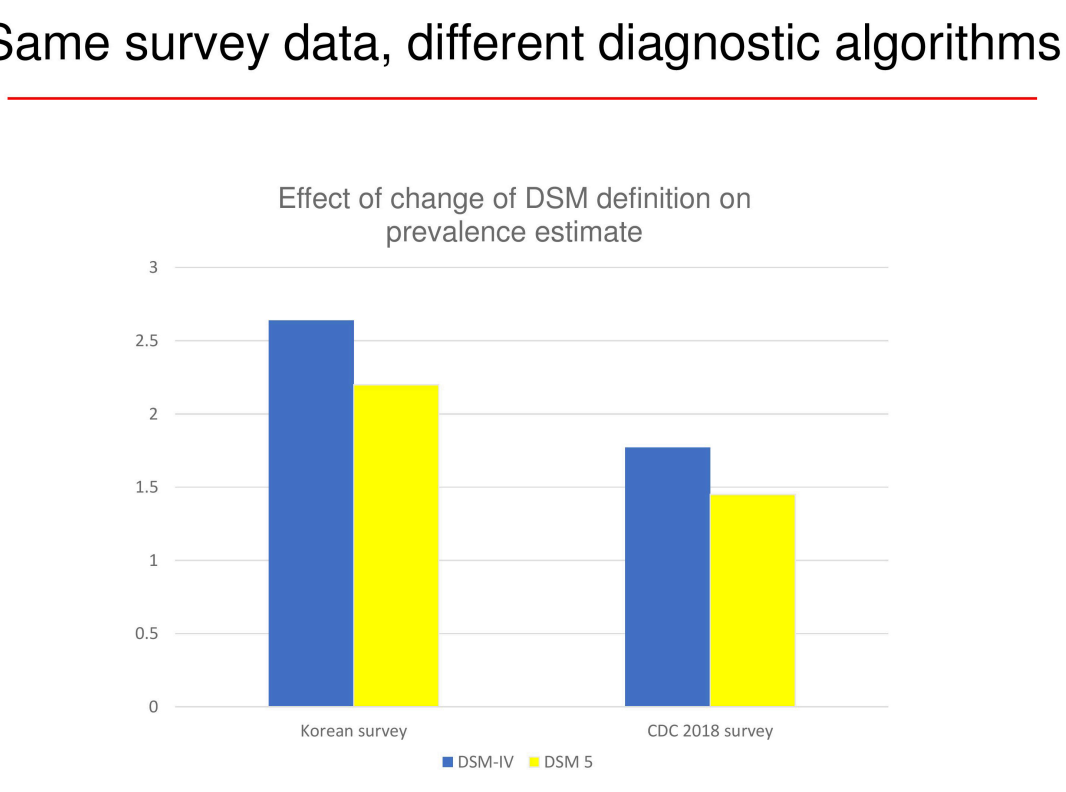
Figure 1: Change in prevalence of autism spectrum disorders over time. CDC = Centers for Disease Control and Prevention



More recent research on other environmental risk is pointing at factors that may operate, alone or in conjunction with susceptibility genes, during prenatal life although most remain to be confirmed and replicated in independent studies. Advanced paternal age [14], and the rare prenatal exposure to valproic acid [15], are two exceptions that are associated with increased risk of ASD in offspring. However, taken together, these two exposures cannot explain more than a small (<5%) fraction of ASD in a given population. Genetic factors play a strong role in ASD [16], and both genetic and phenotypic heterogeneity complicate research on gene-environment interactions and on underlying mechanisms.

Figure 2: The effect of changes in the DSM definition of the prevalence of autism spectrum disorders. Sources: Kim et al. 2014 [7], Fombonne 2018 [6]. CDC = Centers for Disease Control and Prevention; DSM = Diagnostic and Statistical Manual of Mental Disorders



Key messages

- Prevalence of autism spectrum disorders (ASD) has increased and currently lies between 0.9% and 1.5%.
- Most of the increase in prevalence can be attributed to methodological factors such as broadening of the concept and diagnosis of autism, and better ascertainment due to heightened awareness and improved detection and early diagnosis.
- It is plausible, but unproven, that a true increase in the incidence also occurred, contributing partially to raised prevalence figures.
- Childhood immunisations were incriminated 20 years ago as a cause of rising rates of autism, but systematic, well replicated research, has demonstrated that exposure to measles- or mercury-containing vaccines does not raise the risk of autism.
- With the exception of advanced paternal age and prenatal exposure to valproic acid, few environmental risk factors have thus far been robustly confirmed.

Disclosure statement
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