Journal of Autism and Developmental Disorders, Vol. 33, No. 2, April 2003 (© 2003)

Commentary: Blaxill, Baskin, and Spitzer on Croen *et al.* (2002), The Changing Prevalence of Autism in California

Mark F. Blaxill,[1] David S. Baskin,[2] and Walter O. Spitzer[3,4]

INTRODUCTION

Lisa Croen and colleagues (Croen, Grether, Hoogstrate, & Selvin, 2002) suggest that the real incidence of autism has not increased. They propose instead that a pattern of "diagnostic substitution" has moved Californian patients who would previously have been diagnosed as mentally retarded (Croen, Grether, & Selvin, 2001) into the autism category. Their calculations purport to demonstrate that over 100% of the increase in autism from 1987–1994 is an artifact of changes in diagnostic practices. In your editorial commentary, Eric Fombonne praises the study, and claims "Croen *et al.* carefully analyzed the California dataset."

We disagree. Croen *et al.* rest their diagnostic substitution argument on conclusions that are calculated from four solitary pieces of data:

> "During the study period, [autism] prevalence increased from 5.8 [in 1987] to 14.9 per 10,000 [in 1994], for an absolute change of 9.1 per 10,000 . . . [d]uring the same period, the prevalence of mental retardation without autism decreased from 28.8 to 19.5 per 10,000, for an absolute change of 9.3 per 10,000."

Their argument is very sensitive to these four observations, which are mechanically calculated and interpreted by the authors. Closer examination of the data and methods shows that Croen *et al.* made analytic errors in several areas.

- They did not consider the trend information within their own dataset
- They did not consider obvious ascertainment biases within their youngest autism cohorts
- They did not consider similar ascertainment biases in the mental retardation (MR) category
- They did not analyze the implications of their own records review
- They did not define a key element of their principal disease frequency measure: prevalence

Correcting the first four of these errors is sufficient to controvert the authors' argument. The use of incidence rates would have improved the analysis of trends. Collectively, the impact overwhelms their argument in favor of diagnostic substitution.

TREND INFORMATION WITHIN THE STUDY'S OWN DATASET

The authors make a strong claim: that they can observe a clear substitution of one diagnosis (autism) for another (MR of unknown cause) by comparing prevalence trends in both categories. They focus on the endpoints of the period, the years 1987 and 1994, to demonstrate their claim of diagnostic substitution. If their data were as strong as the claim, then they should be able to find the same substitution effect within any shorter period in their data sample. They cannot. In fact, the interim years make a clear argument against diagnostic substitution, as the largest increases in autism prevalence come in periods of no change in MR prevalence and the largest decline in MR comes in a period when the autism rate also fell. Specifically, one can break their study period into three parts.

- Between 1987 and 1989, MR prevalence fell from 28.8 to 24.0 per 10,000. This decline of 4.8 per 10,000 made up over half of the total

[1] Board of Directors: SafeMinds, Cambridge, Massachusetts.
[2] Professor of Neurosurgery and Anesthesiology, Baylor College of Medicine, and Scientific Review Council Co-Chair, Cure Autism Now Foundation Houston, Texas.
[3] Emeritus Professor of Epidemiology, McGill University, Montreal Canada.
[4] Correspondence should be addressed to Walter O. Spitzer, 4920 Bath Road, Bath by Kingston, Ontario K0H1G0, Canada; e-mail: spitzerw@attglobal.net

0162-3257/03/0400-0223/0 © 2003 Plenum Publishing Corporation

decline in MR. But the corresponding change in autism rates was considerably less: an increase of just 1.8 per 10,000.

- Between 1989 and 1992, autism rates rose from 7.58 to 15.21 per 10,000. This increase of 7.63 per 10,000 in just 3 years represents over 80% of the increase in autism during the study period. Meanwhile, the rate of MR in the same period actually *increased* by 3%, from 23.96 to 24.71 per 10,000.
- Between 1992 and 1994, MR rates went down again, from 24.7 to 19.5 per 10,000, with this decline of 5.2 per 10,000 once more making up more than half the total decline. But during this later period, the measured rate of autism *also* went down by 2%.

In two of these three specific time periods, the prevailing trend is the *opposite* of diagnostic substitution, while in the third any effect is barely detectable. The authors' contention thus rests entirely on an artifact of accumulation, through which they aggregate data from three periods with little or no substitution effect, thereby creating an impression of symmetry that they then use to assert an overall effect of substitution that did not occur.

ASCERTAINMENT BIAS WITHIN THE YOUNGEST AUTISM COHORTS

Trend evidence aside, Croen *et al*. underestimate the critical increase in autism prevalence through 1994 for a simple reason: the children born in 1994 were too young—only 4 and 5 years old at the data collection date—to provide an accurate estimate of prevalence. The authors point this out themselves. They concede, "The identification of autism among the youngest children in the study was most likely incomplete" (Croen *et al.*, 2002). This is a critical admission, because the autism rate in the 1994 cohort provides one of the four essential pieces of data they use to build the case for diagnostic substitution. Despite acknowledging their bias, they offer no explicit correction for the error it introduces in their calculations.

Correcting for ascertainment bias is a straightforward exercise of assuming a distribution of age at the time of diagnosis (or of entry into an administrative dataset) and adjusting the reported cases for expected future cases. Reported distributions of age at diagnosis can vary by location and through time, so any *prospective* correction can provide only a rough estimate of the impact of ascertainment bias. But any such revision will be approximately accurate, as opposed to the authors' calculations, which are incorrect.

To obtain an analytical result that is approximately correct, we relied on a recent age distribution reported by Kaye, del Melero-Montes, and Jick (2001) to correct the ascertainment bias in the authors' analysis. (In a similar administrative prevalence dataset from the UK, Kaye *et al*. found that the median age at the autism diagnosis was 4.6 years of age. Because their 1994 birth cohort was only slightly older—ranging from 4.6–5.6 years of age on July 7, 1999, we estimate that the 1994 prevalence number reposted by Croen *et al*. understates the actual prevalence by 30–50%. We also presumed a similar, though smaller, understatement for the 1987 birth cohort of 5–15%—a conservative estimate, since the UK data suggest $<5\%$ of new diagnoses are made after 10 years of age). Based on our corrected prevalence ranges of 6.1–6.8 per 10,000 in 1987 and 21.3–29.8 per 10,000 in 1994, we estimate that the true *change* in autism prevalence was an increase in the range of 14–24 per 10,000, not the 9.1 per 10,000 reported by the authors. This conclusion is supported by other reported age distributions for autism diagnoses. A similar, though not strictly comparable, analysis in California (California Department of Developmental Services, 1999) showed potentially higher rates of ascertainment bias, with nearly two thirds of autistic Californian children born in 1987 diagnosed at 5 years of age or later. By 1998, although the median age of diagnosis had fallen somewhat, nearly half of autistic children were diagnosed at 5 years of age or later. Other studies demonstrate an even larger potential ascertainment bias, reporting mean age ranges at first diagnosis in the United States of 5–8 years (Treffert, 1970) and in France of 5.5–6.9 years (Fombonne & du Mazaubrun, 1992).

The result is clear: The authors' methods failed to correct for ascertainment bias, that is, the incomplete autism diagnoses in their 1994 birth cohort. If past age distributions are a guide, future updates of the California dataset will demonstrate that the rate of autism in the 1994 birth cohort will have risen significantly faster than the rate for the 1987 birth cohort, yielding an eventual increase in autism roughly double the increase reported by the authors.

ASCERTAINMENT BIAS WITHIN YOUNGER COHORTS OF CHILDREN WITH MILD MENTAL RETARDATION OF UNKNOWN CAUSE

For similar reasons, the putative *decline* of 9.3 per 10,000 in MR prevalence between 1987 and 1994 is also a statistical artifact. Again, the authors point this

out themselves (although in a previous publication): "children with mild MR, especially those with no other neurologic impairments, may never enter the system or may not do so until puberty. Because the youngest children in our study sample (2) were only 4 years old, it is likely that children with mild MR were underascertained to a significant degree."

Just as there is a documented ascertainment bias in autism, a similar pattern has been found among children with a diagnosis of MR. Age at first diagnosis for MR of unknown cause is typically older than in autism. Peak registration levels for an MR population are usually not reached until puberty (Croen *et al.*, 2001). Indeed, one study in Sweden put the peak registration age at over 14 years (Hagherg, Lewerth, Olsson, & Westerberg, 1987). More recent studies of 10-year-old populations in Atlanta demonstrated the same effect, with a median age at diagnosis in the 6–7 year range and measured prevalence rates that increased through the last year of observation, that is, the tenth year (Yeargin-Allsopp, Drews, Secoufle, & Murphy, 1995).

Based on these patterns, any presumption of a decline in prevalence based on an endpoint in a 4- and 5-year-old MR population must be considered suspect. The most logical interpretation of the authors' MR trend information is that they are simply observing normal service registration patterns for this diagnosis. Based on the Atlanta study (Yeargin-Allsopp *et al.*, 1995), only 21% of the MR population was diagnosed before their sixth birthday. Applying this ratio, the California MR population was far more likely to be *rising* between 1987 and 1994 than declining by 9.3 per 10,000.

There can be no substitution effect if there is no decline in the rate of MR.

VALIDATION OF THE HYPOTHESIS THROUGH RECORDS REVIEW

The authors did not attempt to verify the diagnoses of either MR or autism for their California sample, nor did they directly assess any children to see whether or not the hypothesis of diagnostic substitution had a basis in reality. They did, however, conduct a medical records review, examining records for a small sample of 85 autistic and 155 MR children. There were no criteria reported as operational for verification of any diagnosis and no sample size justification given. Oddly, these records were not chosen from the time period of the study sample. Instead, the authors chose to review records for children born between 1983 and 1985 and compared the rate of misdiagnosis in this group with a similar sample born between 1990 and 1996.

Based on this review, Croen *et al*. reported a modest amount of diagnostic error, a finding they used to support their hypothesis. Among the autistic children, they found no incorrect diagnoses. In the MR group, however, they did find a diagnostic trend. Specifically, they argued that as many as 10% of the older group should have been diagnosed with autism. In the younger group, this rate had dropped to 3.7%.

The authors failed to note, however, that this observation does not support their case for diagnostic substitution. Even if one assumes that this trend should be projected onto their 1987–1994 time series, one still cannot explain the observed decline in MR. The impact of diagnostic substitution can be estimated based on their review sample by removing "false negatives: 10% of the 1987 MR population and 3.7% of the 1994 population. If one then purges the MR population of such "false negative" autism cases, there is little change in the overall trend. Over 75% of the decline in MR prevalence remains.

A more extensive study failed to support this more specific suggestion of missed autism diagnoses. An earlier MR population in Atlanta, born between 1975 and 1977, was surveyed systematically for biomedical conditions. These investigators conducted a medical records review of 509 cases of mild MR with unknown cause. They found a diagnosis of pervasive developmental disorder (PDD) (including autism) in only 3.4% of this group (Yeargin-Allsopp, Murphy, Cordero, Decoufle, & Hollowell, 1997). Although this is only one comparable observation, it goes against both the magnitude of the problem (3.4% is lower than either of their estimates) and the trend (because the 1975 and 1977 cohort preceded their investigations) suggested by the authors.

DEFINITION OF THE PRINCIPAL ELEMENTS OF THE DISEASE FREQUENCY MEASURE: PREVALENCE

Prevalence is a "snapshot" of the rate of affected persons (cases) within a defined population (e.g., by geographic boundaries and/or age and/or gender) in a moment of time divided by that defined population in the same moment of time. *Incidence*, in contrast, is the number of *new* cases arising from a defined population (e.g., a birth cohort) during a specified period. Incidence describes occurrence over time. Prevalence

incorporates all cases pre-existing in the pool of numerators; incidence excludes old cases who entered the pool before the inception date(s) as defined. Therefore, new cases derived or presumed from prevalence estimates are diluted by pre-existing cases in the databank pools. Further, it takes time to ascertain prevalence. Accordingly, *period prevalence* is usually reported and the period chosen is specified. The details of methodology, the reason for choosing prevalence rather than incidence in the analysis of trends, and the justification of the denominator period in the rates, have not been given in Methods by *Croen et al*. The California datasets are one of the few that permit finer evaluations of trends because birth cohorts by year can be defined and new cases can be determined for the same year(s). Only the cruder estimates were employed. Superimposed on the probable systematic error of substitution of prevalence for incidence, is the bias of ascertainment. Different biases or systematic errors are seldom interdependent in population studies but exert their distorting influences separately. That is likely the case in Croen's work.

CONCLUSION

Croen *et al*. support arguments to set aside the growing body of evidence that we have an epidemic of autistic diseases. They have suggested that "diagnostic substitution" accounts for an apparent increase in the incidence of autism in California that is not real. This hypothesized substitution is not supported by proper and detailed analyses of the California data. On the contrary, California continues to provide the strongest evidence for the explosion in the incidence in autism. The authors' superficial analysis is of concern, particularly because such data can and likely will be used by funding agencies to allocate funds for research and treatment. Autism is already seriously underfunded, if one considers funding for other disorders with a much lower incidence in the population. We look forward to the day when all researchers and funding agencies recognize the existence of a clear and alarming increase in the incidence of autism and turn expeditiously to facing, measuring, and coming to terms with this unprecedented crisis.

REFERENCES

California Department of Developmental Services. (1999). Changes in the population of persons with autism and pervasive developmental disorders in California's Developmental Services System: 1987 through 1998. *A Report to the Legislature, Department of Developmental Services,* Sacramento, CA: Author.

Croen, L. A., Grether, J. K., & Selvin, S. (2001). The epidemiology of mental retardation of unknown cause. *Pediatrics, 107,* E86.

Croen, L. A., Grether, J. K., Hoogstrate, J., & Selvin, S. (2002). The changing prevalence of autism in California. *Journal of Autism and Developmental Disorders, 32,* 207–215.

Fombonne, E. & du Mazaubrun (1992). Prevalence of infantile autism in four French regions. *Society of Psychiatry and Psychiatric Epidemiology. 27,* 203–210.

Hagberg, G., Lewerth, A., Olsson, E., & Westerberg, B. (1987). Mild mental retardation in Gothenburg children born between 1966–70: Changes between two points of time. *Upsala Journal of Medical Sciences* (Suppl.)44, 52–57.

Kaye, J. A., del Melero-Montes, M., & Jick, H. (2001). Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: A time trend analysis. *British Medical Journal, 322,* 460–463.

Treffert, D. A. (1970). Epidemiology of infantile autism. *Archives of General Psychiatry, 22,* 431–438.

Yeargin-Allsopp, M., Drews, C. D., Decoufle, P., & Murphy, C. C. (1995). Mild mental retardation in black and white children in metropolitan Atlanta: A case-control study. *American Journal of Public Health, 85,* 324–328.

Yeargin-Allsopp, M., Murphy, C. C., Cordero, J. F., Decoufle, P., & Hollowell, J. G. Reported biomedical causes and associated medical conditions for mental retardation among 10-year-old children, metropolitan Atlanta: 1985 to 1987. *Developmental Medicine and Child Neurology, 39,* 142–149.