

ORIGINAL ARTICLE

Secular Trend of Sex Ratio and Symptom Patterns Among Children With Autism Spectrum Disorders

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ABSTRACT

An information technology invention embodied in a website serving the interests of the autism community was designed to “let the data talk.” By its use, the authors have detected a downward temporal trend in 2013 in the sex ratio of 2431 members of Autism360.org from a yearly average between 2010 and 2012 of 4.24 to 3.01 in 2013. As of the first two months of 2014, the average sex ratio is 2.69. We report contemporaneous changes in previously reported male vs female symptom patterns. Such changes suggest a convergence in which distinctive severity of certain grouped central nervous, emotional, and immune profile items in females have diminished toward that of males. The data also show correlations among these profile items that add further credence to the sex ratio findings. A wider dispersion of the female data as compared with the male data was found in the year preceding the downward trend in the mean sex ratio. The authors suggest that such a trend toward an increase in the variance of the data points to instability in the biological system—the autism spectrum. We conclude that public policy would be better served by monitoring changes in the standard deviation as compared with the mean in large data sets to better anticipate changes. The findings we report raise questions based on known sex differences in detoxification chemistry. One such question would be whether maternal, fetal, or individual exposure to a novel environmental factor may have breached the taller fence of female protection from toxins.

INTRODUCTION

The male:female ratio of autistic children has been reported and widely accepted as approximately 4 males to every 1 female. A report by Whiteley et al based on data in The United Kingdom and The Republic of Ireland from the first decade of 2000 revealed in 1963 children with pervasive developmental delay (PDD) diagnoses an overall sex ratio of 4.68; 6.54 for autism diagnosis and 6.84 for autism spectrum disorder.¹ A scatter plot of their data showed a linear fit of sex ratios per year of birth with a rise from about 4.2:1 in 1996 to nearly 10:1 in 2006. The authors cite other studies indicating wide differences in PDD sex ratios reported from Asian and other geographical areas. The 2012 Centers for Disease Control and Prevention (CDC) surveillance monitoring system, current as of 2008 reports sex ratios in a range from 7.2:1 (Alabama) to 2.7:1 (Utah).² There was an overall ratio of 4.6:1 in 3820 children with autism spectrum disorder diagnosis of a total of 337,093 from the 14 reporting sites in the United States. CDC's 2014 report bringing the statistics up through 2010 reported a similar variance in both average age and sex ratio while citing the most current (2010) prevalence data for CDC reporting centers 1 in 68 children, with wide geographical ranges in prevalence. These reports alert us to the possibility of both geographical and temporal variability of male:female prevalence in autism spectrum disorders that is worth of further study.

Here we report an analysis of data entered by members of Autism360.org, a website serving the interests of the global autism community in a free exchange between individual and collective data. The data set on

which this report is based comprises 1912 males and 519 females. The data spans a 50-month enrollment period from January 2010 to February 2014. For this period, the average monthly sex ratio of new memberships is 3.86 (SD 1.594).

STATISTICAL ANALYSIS

A one-way analysis of variance (ANOVA) was performed in an effort to detect a statistical difference in the mean sex ratio by year. The summary statistics are shown in Table 1. The ANOVA procedure did not detect a statistically significant difference in the average sex-ratio across the years of 2010 to 2013 ($P=.136$). However, a statistical difference was observed in the variance between the years ($P=.001$). Given this non-homogeneity in the variance, the authors decided to look into whether or not a temporal change during 2013 was a random chance event.

Table 1 Sex Ratio Summary Statistics by Year

| Year | No. of Months | Mean | StDev |
|------|----------------|-------|-------|
| 2010 | 12 | 4.105 | 0.884 |
| 2011 | 12 | 4.467 | 2.092 |
| 2012 | 9 ^a | 4.121 | 2.153 |
| 2013 | 12 | 3.012 | 0.731 |
| 2014 | 2 | 2.692 | 0.153 |

^a Three months excluded where n=0 females enrolled.

SEARCHING FOR TEMPORAL EVENT

In an effort to identify a temporal event, we employed the following model as a means to examine

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Citation
Global Adv Health Med. 2014;3(3):92-101. DOI: 10.7453/gahmj.2014.028

Disclosure
The author completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and had no conflicts to disclose.

Key Words
Autism spectrum disorders, sex ratio, information technology

whether or not the assumption that the sex ratio is constant within limits of random variation:

$$y_i = \mu + \epsilon_i$$

In this expression, y_i is a random variable that denotes the sex ratio. It is equal to the true mean sex ratio, μ , plus, ϵ_i , a random error term. In this model, the mean, μ , is estimated by $\hat{\mu} = \bar{y}$, the overall average sex ratio for the period under investigation. The random error term, ϵ_i , represents the monthly deviations of the sex ratio from the mean μ estimated by \bar{y} . These deviations should be independent and identically distributed about μ having a mean of zero and variance σ_i^2 . This simply means the data should be free of temporal trends that would unduly influence our variance assumptions for ϵ_i . Going forward, the detection of sustained trends invites a search for an antecedent and continuing cause. Such a forerunner—in the context of a phenomenon as complex as sex ratio—suggests a special cause event that is a real phenomenon or some other confounding event. The longer such a special cause event is prolonged supports the notion it is a real phenomenon.

Figure 1 shows a time series chart of the sex ratios for 50 months. Shown is the overall average for the years 2010 through 2012 (4.24) along with an upper limit (7.68) corresponding to two standard deviations.



Figure 1 The sex ratio of monthly enrolment in Autism360 is shown plotted against the overall 50 month average (4.24) and the 2 standard deviation line at 7.68. The attention-getting drop after month 35 raised the question of whether it represented a shift or a trend and whether that trend could be explained as a random event. The probability of it being random is well below $P=.000$.

Two months, 18 and 25, saw the monthly sex ratio exceed two standard deviations. However, months 37 through 50 show a sustained trend below the monthly average of 4.24. This period corresponds to 14 consecutive months. Assuming a random model, the probability the sex ratio would be either below or above 4.24 would be equally split for any particular month. Given that 14 consecutive sex ratio values fell below 4.24, the probability this would occur by random chance alone is well below $P=.000$. Since the probability that such a

sustained event is considered rare we ask the following question: *Is this trend inherent in the autistic population of females and does it suggest the susceptibility of more females, or is it some other confounding event?*

Given the trend observed in Figure 1, the next two figures show the data partitioned into two sets. In Figures 2 and 3, the monthly sex ratio data between months 1 through 36 and 37 through 50 are shown.

Figure 2 shows the monthly sex ratio. The best-fit

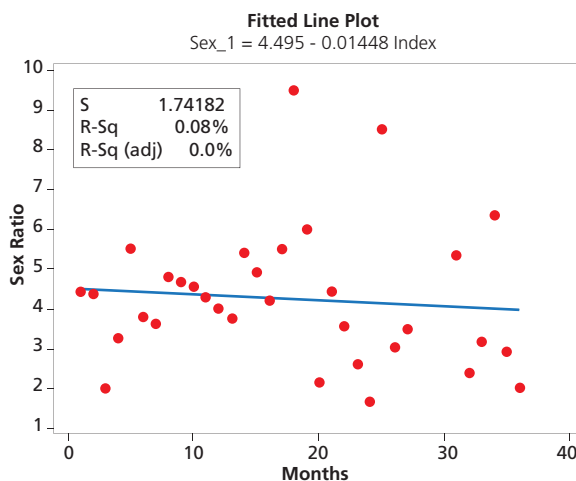


Figure 2 The sex ratio of monthly enrollment in Autism360 during the first 3 years (2010 through 2012). The nearly horizontal best-fit line indicates a statistically insignificant change in the monthly sex ratio during this period.

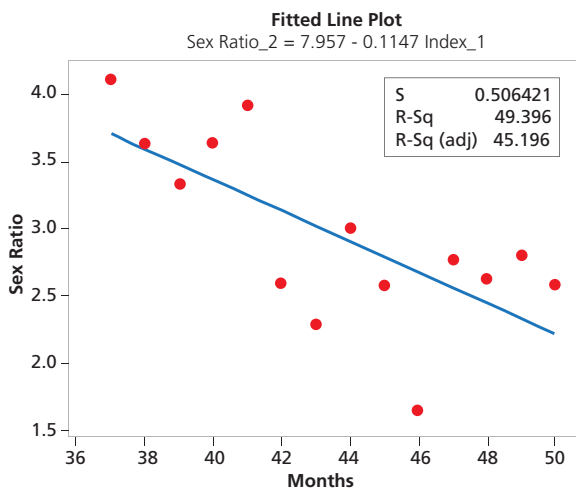


Figure 3 The monthly sex ratio of Autism360 enrollees during the period following the 36th week. The best-fit line indicates a trend, statistically significant at $P=.005$.

line that describes the data is a constant, estimated at 4.459 and statistically significant at $P=.000$. However, the change across the months was statistically insignificant at $P=.625$. As mentioned previously, the months 18 and 25 display sex ratios that were deemed unusual by the fitted model in Figure 2.

Figure 3 shows the sex ratio between months 37 and 50. The nature of the change is consistent with a

downward continuous linear trend.

As shown in Table 2, the negative regression coefficient for months is statistically significant as evidenced by a *P* value of .005. This downward linear trend in the sex ratio explains about 50% of the change in this ratio for this period.

Table 2 Sex Ratio Coefficients 41 Through 51

| Predictor | Coefficient | SE Coefficient | t-value | P value |
|-----------|-------------|----------------|---------|---------|
| Constant | 7.957 | 1.467 | 4.35 | 0.000* |
| Months | -0.11471 | 0.03358 | -3.29 | 0.005* |

*Denotes statistically significant

Analyzing Enrollments by Sex

Do the data show an increase in the relative number of females entering the autism spectrum? To address this question, we begin by examining the total number of children enrolled into Autism360 across all periods. The 1st month, October 2009, saw more than 300 enrollments. The following months saw smaller spikes in monthly enrollments until a consistent level was observed by the 14th month.

As illustrated in Figure 4, the first 11 months showed an increase in participants compared to the post 11 month periods. During the first 11 months, the sex ratio was 4.11 (SD 0.927)

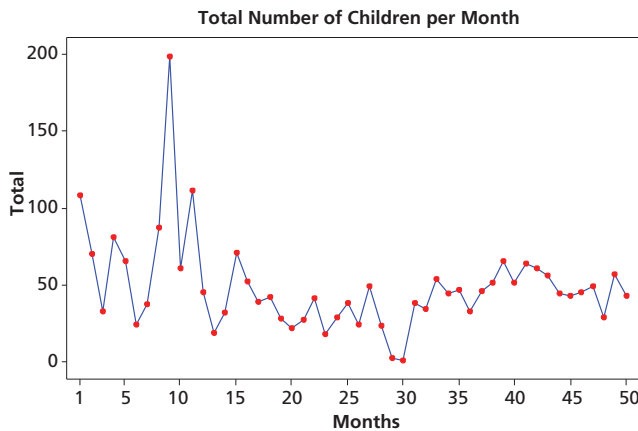


Figure 4 The total monthly enrollment from January 2010 through February 2014. Illustrated here is a continuation of the spikes that occurred in the first 3 months following launch (not shown) followed by an evening out of monthly enrollment.

To analyze the enrollment into Autism360, using a common scale, the average and standard deviation by gender was computed by month. The z-transform is shown below.

$$z_i = \frac{y_i - \bar{y}}{s}$$

The transformed data, z_i , has a mean and standard deviation of 0 and 1 respectively. Computing z_i values by gender yields a common scale to comparatively observe month by month enrollment rates by sex.

As shown in Figure 5, the black and red lines represent the standardized enrollments for both females and

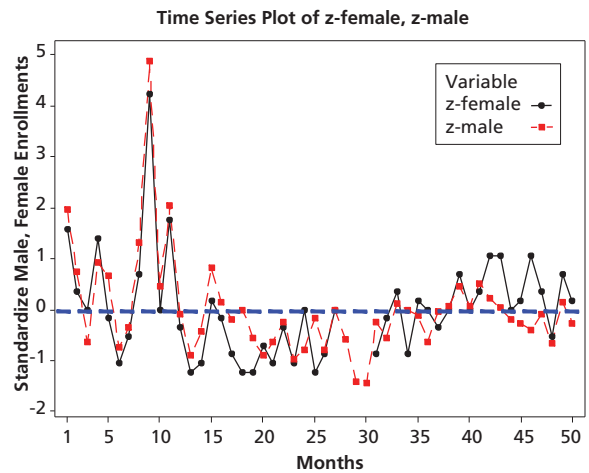


Figure 5 The standardized enrollments for both male and female participates reported as z-scores to illustrate the basis for a skewing effect of the early spikes in membership compared to a standardized monthly average of zero. Note the separation of rising female data after month 35 while the male data stayed close to the mean.

males respectively. Notice that the lines follow each other: When the red line (males) goes up, so does the black line (females) and vice versa. This suggests that the monthly enrollments for males and females are correlated.

The horizontal dashed blue line represents the average number of enrollments for both males and females respectively. Notice that the months between 16 and 32 saw the number of enrollments for both males and females decrease to below average. This is to be expected given that the enrollments were in the months following Autism360’s launch. The monthly enrollments for both males and females increase after the 33rd month. However, at month 43 and beyond, the number of enrollments for females is above average while the enrollment of males is about average: the black line (females) and the red line (males) exceed and cluster about the blue dashed line at zero. Is the decrease in the sex ratio after month 33 an illusion created by data skewing from an average established including data from the first 11—anomalous—months? The enrollment data are more consistent when the enrollment period for the first 11 months is removed. Removing this section leaves the values for the months corresponding to periods 12 through 50 (Figure 6). Under this scenario, the enrollments for both males and females at period 37 (January 2013) and beyond is above average.

In Figure 7, the standardized z-value for males is subtracted from the female. As such, the number of females enrolled with respect to the number of males is larger, and this increase is maintained for several months at month 42.

Lastly, Table 3 shows the bi-yearly average enrollments, by gender, for the years 2011 through 2013. As shown, the average enrollment for females shows a steady increase beginning in the first half of 2012. The trend then continues to increase until the last half of 2013. Comparing 2012 to 2013, there has been an 87.9% increase in the average enrollments for females.

Table 3 Bi-yearly Average Enrollments, by Gender, for the Years 2011 Through 2013

| Period | Females | Males |
|-----------------|---------|-------|
| 2011: Jan - Jun | 6.83 | 35.67 |
| 2011: Jul - Dec | 6.83 | 20.67 |
| 2012: Jan - Jun | 7.00 | 19.33 |
| 2012: Jul - Dec | 9.67 | 32.00 |
| 2013: Jan - Jun | 12.67 | 43.67 |
| 2013: Jul - Dec | 13.00 | 31.33 |

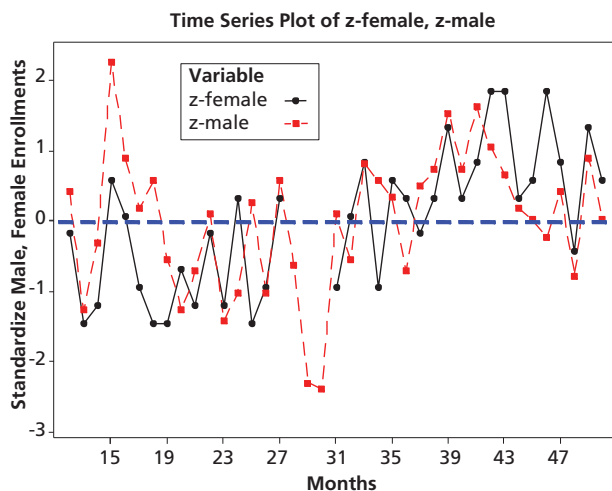


Figure 6 Discontinuing the initial enrollment period, the standardized male and female z scores shows a consistently higher number of female enrollees after week 42.

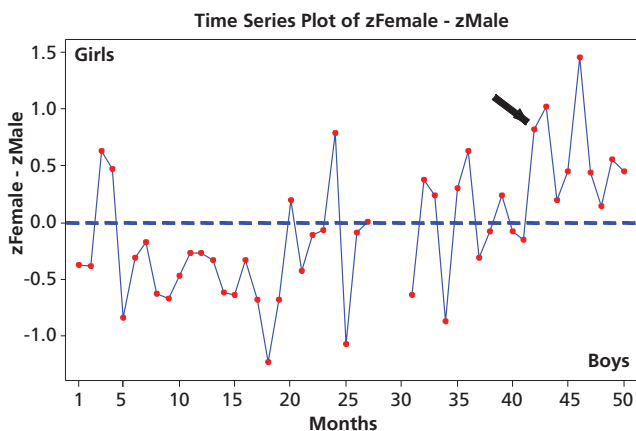


Figure 7 Subtracting the monthly standardized z scores for males from females shows the consistently higher numbers of female enrollees after week 42.

CLINICAL CORRELATION

A series of papers describing the principles, technology, semantics and research findings from Autism360 provides a context for reporting correlations in symptom descriptions of Autism360’s members during the period covered by this report.³⁻⁶ Those correlations provide, in turn, a background for presenting a convergence in symptom descriptions that sup-

port the surprising convergence we have discovered in the sex ratio of Autism360 members.

Autism360’s database consists of more than 120,000 profile items (symptoms, life events, exposures, strengths, etc) of members who recorded a minimum of 15 items including at least one strength at the time of enrollment. Autism360’s database lacks biochemical, immunological, and toxicological measurements. Nor does Autism360 have access to the metrics of formal developmental, behavioral, and psychological evaluation. Autism360’s members volunteer descriptors aimed at capturing their (child’s) individuality by using an interface that presents choices organized around a lexicon developed and coded during three decades of clinical practice. In exchange for providing anonymous data, members receive an organized on-line and downloadable report. The report provides feedback to the user for verification. It further gives users and their clinicians an overview of the member’s narrative. By means of an “others like me” feature, the user is presented with a report of treatment option ratings based on the reported experience of others whose data closely matches him or her by means of dot product proximity analysis of profile item data in the system’s multidimensional coding structure. In other words, Autism360’s users are provided with tangible motives to provide accurate, detailed data the anonymity and structure of which delivers collective value to match its usefulness to individual patients, parents, and practitioners.

Pending collaboration with laboratories and clinicians, Autism360’s capacity for clinical correlation is limited to profile item data. Those data are encoded by a means fully described and illustrated in the above cited references. The code represents the meaning of each medical description as an intersection between defining dimensions (vectors or rows and columns) with the provision that the conceptual space in which data analysis can take place has a core of at least four dimensions. The names of the four dimensions that encode the meaning of each profile item are System, Function, Where, and Severity. Thus, for example, an itch of moderate severity on a hand lies at the intersection between Skin, Itch, Hand, and Moderate. Further specificities may, if desired, add time descriptors (onset, periodicity, duration of episodes, duration, date recorded, etc) and descriptions of precipitating, aggravating, and alleviating factors. Grasping the illustrations and other data presentation in this report requires the reader to understand the scope of the System and Function dimensions, which may be envisioned as headers on columns and rows of a table. “System” embraces the conventional medical systems: gastrointestinal, respiratory, central nervous, etc, along with others based on the logic of language presented during the invention of this technology. Behavior naturally figures prominently in descriptions of symptoms (profile items) of the autism spectrum. Like any other bodily process, it is subject to modification in the form of abnormal, increase, decrease, etc. These modifiers

Table 4 A Fraction of the Autism360's Multidimensional Database Shown in Spreadsheet Form

| Vernacular name | System | Function | Where |
|---|----------|----------|---------------|
| Does not try to communicate with words and gestures | Behavior | Decrease | Communication |
| Lack of imaginative play | Behavior | Decrease | Play |
| Easily distracted | Behavior | Decrease | Attention |
| Does not try to communicate with words or gestures | Behavior | Decrease | Communication |
| Problem with eye contact | Behavior | Decrease | Socialization |
| Pay no attention when spoken to | Behavior | Decrease | Socialization |
| Poor social interaction | Behavior | Decrease | Socialization |
| Don't listen - spaced out | Behavior | Decrease | Attention |
| Problem with eye contact | Behavior | Decrease | Socialization |
| Pay no attention when spoken to | Behavior | Decrease | Socialization |
| Run away / no sense of danger | Behavior | Decrease | Attention |
| Lack of appropriate facial expression | Behavior | Decrease | Socialization |
| No or poor imitation of gestures | Behavior | Decrease | Communication |
| Problem with eye contact | Behavior | Decrease | Socialization |
| Hyperactivity (under active) | Behavior | Decrease | Activity |

contribute to the coded capture of the meaning of the vernacular names of various behaviors. Table 4 shows a snippet consisting of 4 (out of 34) columns and 15 (out of 125,397) rows that encode the details of Autism360's current profile item data with Medigenesis' technology. Medigenesis is the donor to Autism360 of a license to its patented system and method for the automated presentation of health data to, and its interaction with, a computer maintained database to generate information regarding possible remedies, therapies, problem solutions, and beneficial practices to improve user health.

Table 4 shows a fraction of the Autism360's multidimensional database rendered in the form of a spreadsheet to illustrate how three of Medigenesis' core dimensions capture the meaning of a section of an individual's record where behaviors described as "decreased" are listed along with their "Where" dimension. Here the reader can see the way Medigenesis' coding system followed linguistic logic to name the dimension embracing the notion of locale. Depending on context, locale may be anatomical or geographical or embrace a multitude of terms used to narrow the coded meaning of the profile item. As described fully in the cited publications the System and Function dimensions are parsimonious, numbering 39 and 42, respectively. The number of "Where"s in the current database runs into the hundreds. The notion of the Where dimension does not figure in the following description of correlations among profile items defined by the Systems, Behavior, Emotion, and Immune modified by the functional descriptor "increase." Increase in this context, like "decrease" in Table 4, captures the meaning of similar nuances as applied to various Systems: various aspects of hyperactivity in the case of Behavior, anxiety in the case of emotion, and symptoms representing an abnormal increase in reactivity in the case of

the immune system, which comes down to allergy in Autism360's data, which lacks explicitly auto-immune profile items. In the following description of correlations, the reference to "increase" as applied to each of the three Systems is not to be confused with the notion of increase in enrollments.

We sought to understand the reduction in sex ratio during the course of 2013 by summarizing the monthly profile item data for females. We concentrated our analysis on Behavior, Emotion, and Immune systems and found statistically significant correlations. This was consistent with a previous contribution,⁴ where the intersections of increase with Immune (mostly allergy) and Emotion (mostly anxiety) stood out as distinguishing features in male and female data. For the current analysis we developed the following model as a means to grasp symptom changes that might have accompanied the increase in female enrollments and the subsequent reduction in sex ratio over the last 14 months starting in January 2013. While the correlations shown in Figure 8 are statistically significant at $P < .05$, we are quick to point out this does not imply causation. Rather, it suggests a framework the authors will study in another contribution. Furthermore, it provides a reference for further scrutiny by the broader research community.

Given the behavioral systems relationship to both immunity and enrollment, we sought to determine if the immune and behavior systems showed a sustained increase in onset severity with time. In Figure 9, we show the standardized onset severity scores and confidence intervals for female subjects across 4 years. As illustrated, standardized immune scores show onset severity has increased every year since 2010. However, the onset severity scores for behavior appear consistent year after year.

In an effort to capture if the onset severity in both

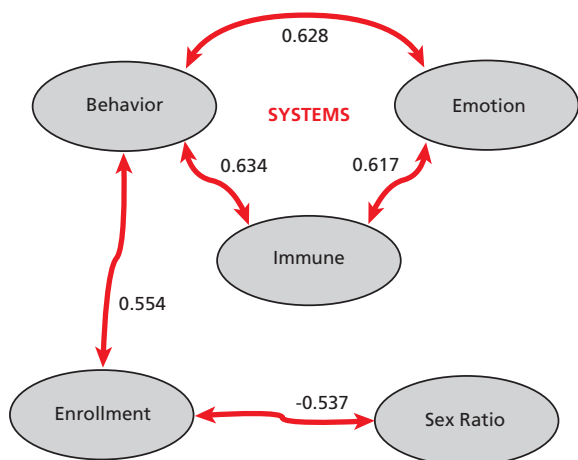


Figure 8 Relationship in female systems, enrollment, and sex ratio. The correlation between Behavior, Emotion and Immune System Profile Items with Increase as the Function intersection: roughly speaking, hyperactivity, anxiety and allergy. With respect to female subjects, the correlation coefficients.

immune and behavior is homogeneously dispersed across all female subjects, we plotted the confidence intervals shown in Figure 9. Notice that the dispersion in behavior onset severity appears to be relatively constant across the years 2010 through 2014. However, the dispersion in immune onset severity increases every year since 2010. This suggests the change in onset severity may not

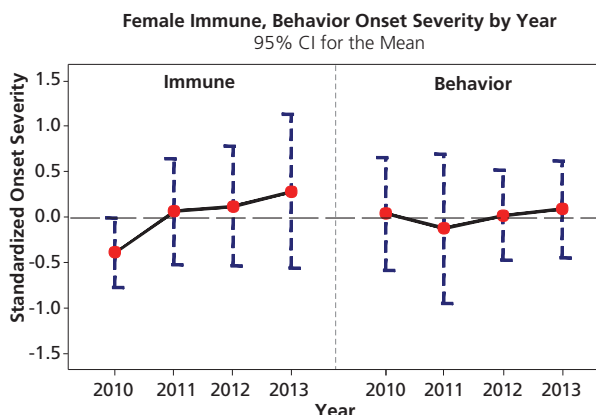


Figure 9 The yearly standardized onset severity is shown for female subjects across four years. Year after year, a sustained increase in mean immune onset severity is observed. However, no such trend is observed in Behavior. This plot also displays confidence intervals about the mean severity scores. These confidence intervals describe the dispersion in data about the mean. It reflects the disposition of individuals unlike the mean that describes the state of a group of individuals. When the confidence interval is small, it suggests the individuals share traits that are common to the group. As the confidence interval increases, it suggests some individuals may be on the verge of expressing traits that are dissimilar from the mean tendency of the group. As such, what is small versus large can only be assessed with time. When confidence intervals for fixed samples sizes are homogeneous across years, it suggests there is a stable expression in the trait of individuals. If, however, the confidence interval increases with time, it raises concerns that such a perturbation may spread throughout the group and unduly influence a change in the mean of that group. With respect to immune, an increase in both the mean and dispersion in onset severity is observed.

be homogeneously dispersed across all female subjects and that a subset of females may be experiencing an increased level of severity compared to others females.

In Figure 9, we see the “scatter” in the female data illustrated by wider confidence intervals for behavior, especially between 2010 and 2013. Given a fixed number of observations, the spread in the confidence interval is a function of the scatter or dispersion in data expressed as a standard deviation. Dispersion in biological data is characteristic of systems in transition. If, for example, one compares squirrels that are long-term inhabitants of the depths of an established forest with another population of squirrels in a transitional zone that is subjected to some type of disturbance, nature will seek variety as part of the solution to an adaptive problem. In other words, in the established ecosystem, the squirrels all look alike. In a transitional ecosystem, the squirrels show a variation in their features that would reveal a higher standard deviation in their statistical characterizations. In the same way, perhaps, females who, metaphorically speaking, are newcomers to the autism spectrum may be found exhibiting greater deviations from the norm. The authors suggest that data showing such a higher standard deviation in data correlated with their increasing enrollment in Autism360 provides support for the notion that the convergence in sex ratio and the correlation of symptoms expressing that convergence are expressions of the same reality.

The authors performed a cursory analysis of specific symptom categories. Within this defined space, we analyzed the proportion of female subjects, their mean symptom counts and severity, and their dispersion in symptom counts and severity. Our cursory analysis suggests there is an increase in female subjects that exceeds males for the same category. It suggests females may be becoming more like males due to a greater expression of specific symptom patterns that are motivating an increase in enrollment. Further analysis will be performed and reported in another contribution.

We further illustrate the notion that females are becoming more like males in Figure 10. Here the annual trend of symptoms captured by the Function “increase” as applied to four Systems is displayed. Shown is a convergence in the data between females and males; that is, with respect to the count of profile items (symptoms) expressed as a difference in the mean for the enrollment group by gender. A trend has developed where females show similar mean counts of reported symptoms closely resembling males in 2013.

Figure 11 illustrates a collective picture of the strengths of individuals in our data. Here, a three-dimensional plot displays time and sex on one axis against two Systems (Behavior and CNS) with the onset severity rate for Strength measured on the vertical axis. That rate is calculated by summing the score reflecting the Strengths of a member’s positive attribute or skills. If, for example, the score given to each of three Strengths in a member’s record were 3, 6, and 6 (mild, moderate,

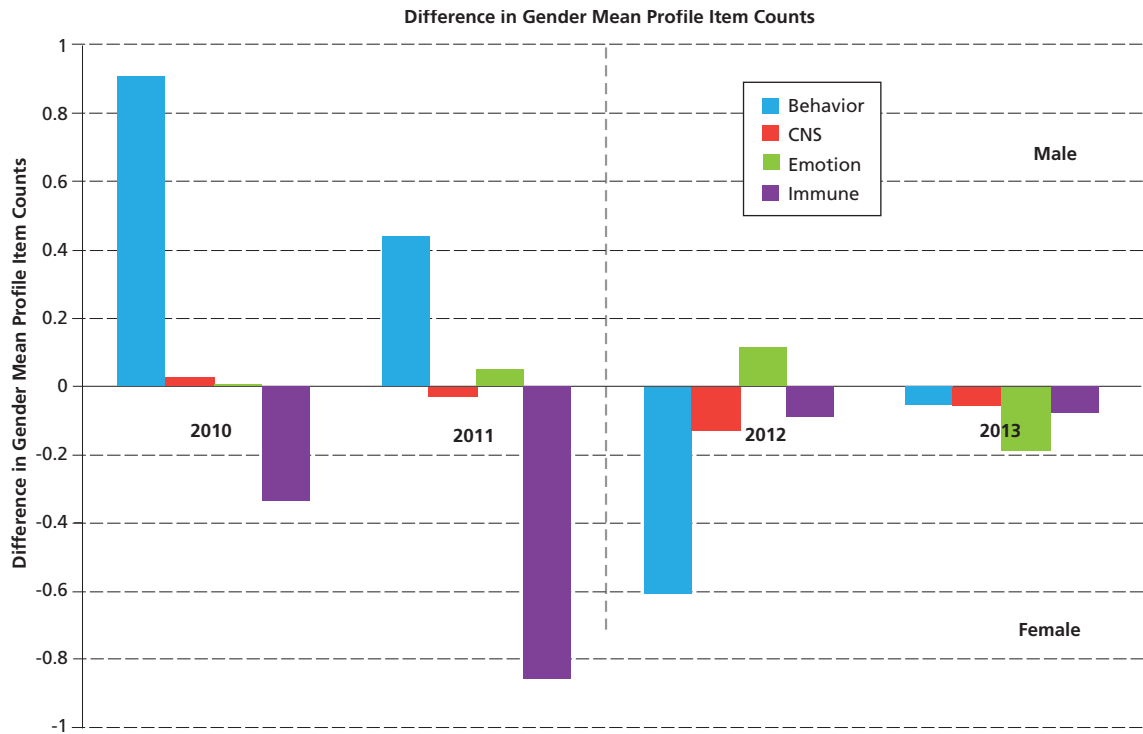


Figure 10 Previous reports of symptom group differences (Reference 3) and a detailed analysis yielding specific symptom sex differences (Reference 5) provide a focus for presenting the data illustrated in figure 1 showing changes in the difference in mean profile symptom across 2010 to 2013.

moderate) for skills related to the CNS, the sum of that individual’s Severity score would be 15. The selection of profile items exemplifying the overall consistency of Autism360’s data are Strengths in Behavior (such as joint attention, knows colors, knows numbers, mechanical assembly [putting things together], mechanical disassembly [taking things apart], memory – melody, memory – music lyrics, memory – names; and Strengths in CNS (such as OK if parents leave, ability to persevere, affectionate, pleasant/easy to care for, wants to be liked, cuddly, sensitive to people’s feelings, reaches out to be held, strong will/desire to do things, accepts new clothes). Any of the intersections in Autism360’s data could illustrate the point of consistency. The authors chose Strengths for two reasons. First they are often overlooked in the literature and office settings of the autism spectrum, and we believe patients, parents, practitioners, and researchers will benefit from their notice. Second, the list provides a motive to list descriptors in the Where dimension of the coding system to give readers insight into the lexicon of Medigenesis, which provides the foundation of Autism360’s technology. As sampling of Where modifiers for Behavior is socialization, generalized, and will; and for CNS, perception, memory, ear, socialization, awareness.

The finding of sex differences between males and females that we highlight in this report is more credible when considered against the background of the overall consistency over time of the comparisons between males and females in the data. That consistency is reassuring with regard to the question of whether

Autism360’s interaction with members in its autism community yields data that are reproducible over time.

DISCUSSION

The following summarizes the features of the data and conclusions of this report.

It is large, detailed, and coded at the moment of entry from its source (the patient/parent) and fed back to the source for verification and to provide value in the form of portraiture and options based on the experience of others who match the user by proximity algorithms.

The data structure has permitted analysis revealing patterns that answer questions, some of which we would not have known to ask, such as the allergy-behavior-emotion correlations and others with surprising answers, such as the dramatic change in sex ratio in Autism360’s population.

The data’s consistency over time is reassuring on the question of anomalies in enrollment, utilisation, and demographics.

Four aligned findings support the credibility of our conclusions.

1. A trend in male:female ratio of Autism360’s population shows convergence from greater than 4:1 in 2010 to 2012 to less than 3:1 in the year 2013.
2. Strong correlations among the three categories (Behavior, CNS, and Immune) of symptoms that have been previously reported as characterizing male-female differences.
3. A descriptive trend and difference in the standard

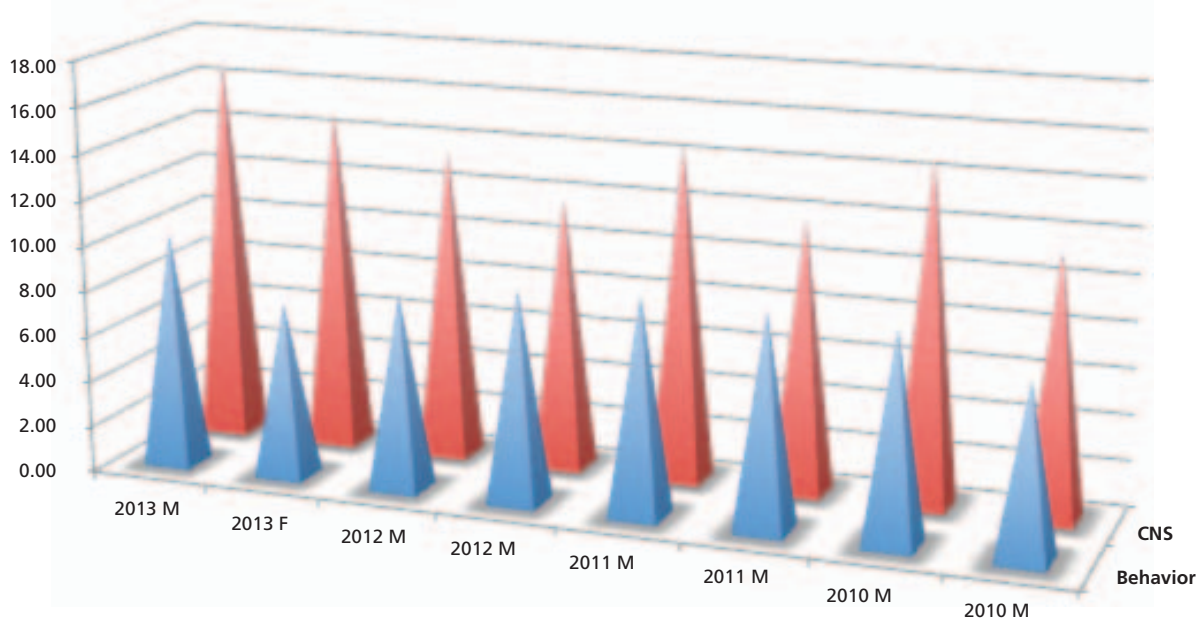


Figure 11 The severity rate for Strengths in Central Nervous (CNS) and Behavior Systems reported for female (F) and male (M) members of Autism360 for the years indicated reflect a general consistency in the data in contrast to the shifts seen in Figures 8-11.

deviation in Immune measures, with time, in female data that will be the subject of further analysis.

4. A convergence in the severity of symptoms in the three above-mentioned categories suggesting females may be becoming more like males by the measures we report.

The original intent of the data system (Medigenesis) on which Autism360 is based was the democratization of medical information and the production of an exchange between individual and collective health data that would let the data talk to individuals and to the research community. The authors wish to emphasize that this report, while based on the largest data set of user-entered detailed clinical profile items, is now what has been dubbed “big data.” It is “smart data” in that its origins are personal, detailed, and verified and valued by its source, the patient/parent. The data “talk” in two ways. First, they reveal patterns in what has aptly become known in vernacular and scientific language by a spatial metaphor: the autism spectrum. Second, the population served by Autism360 has shown the above-mentioned convergences and correlations. Neither mean age, Table 5, nor exposure to any special publicity, nor changes in Autism360’s interface, nor geographic distribution of our member provide any doubt as to the above conclusion. Figures 12 and 13 illustrate Autism360’s membership’s geographic distribution, which has not changed substantially over the time periods in question in this report.

The mean age of Autism360’s enrollees decrease by a year since the the launch of the website (Table 5). The decrease may reflect the entry of older children as a reflection of Autism360’s novelty, in as much as the decline stabilized in 2012 and 2013 while other aspects

of the demographics reported in this article showed significant trends.

The mother of two autistic children reported that she had been motivated to enter her daughter’s data but not her son’s because the former—a brilliant, non-verbal teen—is much more complicated. The senior author’s informal polls at gatherings of parents, practitioners, and researchers found general consent to the notion that female members of the autism spectrum were more complex or “difficult” but without any precision offered to that description. Autism360’s data shows that difficulties and decreases in CNS function and increases in anxiety and allergies did characterize the females. The implication of the mother’s observation, if generalized, would not find support in the fact of the trend in sex ratio nor by the convergence found in the symptom data that appear to show the females looking “more like males” in symptom expression and severity. Another implication of these sorts of observations could be that there are unique characteristics of the population that enrolls with Autism360 and the changes noted here are not reflective of the larger population of patients with autism spectrum disorder. On the other hand, Autism360’s underlying technology has been in use for more than two decades. Neither in its original embodiment (MCares—a system for use by physicians) nor in Medigenesis (the donor of a license to Autism360) has any anomaly of usage or analysis occurred with use in the setting of a medical office or via the Internet.

Autism360’s anonymous data achieves value to collective users by being both timely—in the sense of accessibility in real time—and being representative of medicine’s imperative: “Listen to the patient.” The merit of data initiated by the patient—as opposed to that elicited by questionnaire, interview, diagnostic

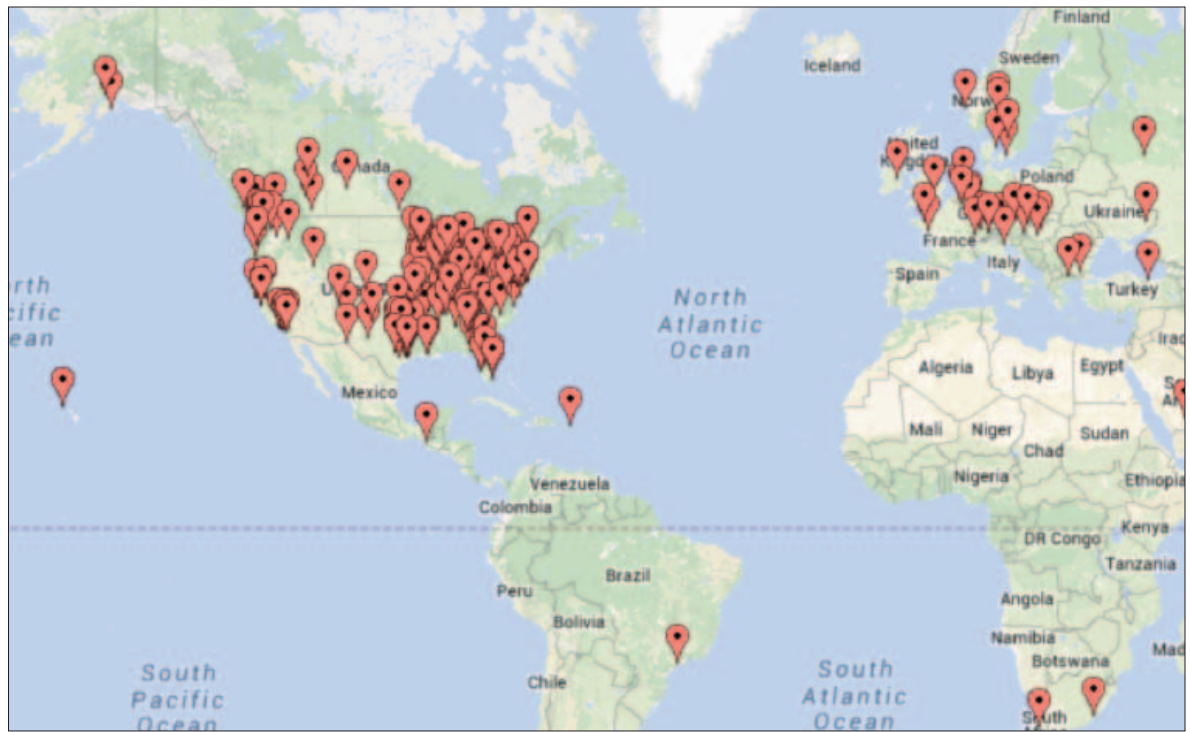


Figure 12 The distribution of subscribers to Autism360 as determined by postal codes is shown in the above map from which the Asian regions—with few members—have been excluded.

testing or examination—is inferior in many ways, including standardization. On the other hand, its spontaneity may surpass the value of data acquired in the medical model of “we know what questions to ask.” Collective research and public policy users benefit from access to fresh granular data. A basic principle of information technology—the capture of data as directly as possible from its source—encounters challenges in the traditional dependence on caregivers for the transcription, summarization, coding, and transfer of medical information in clinical and administrative settings. Autism360’s data makes up in detail, structure, and volume for what it may lack in answering the question “How do you know that your members are ‘really autistic?’” Its immediacy may compensate for its lack of admission criteria beyond the common sense that few people other than the parents of autistic children would be attracted to interacting with a website called Autism360. Timeliness has been lacking in the history of autism’s slow movement against the tide of authoritative opinion that autism was the purely result of faulty mothering or, more recently, genetics. The popularization of the “autism spectrum” as a defining term over the last decade provides support to the notion that autism is not a “disease entity” that may be usefully defined in any one child or any group of children by precise metrics. The word *spectrum* has, on the other hand, brought about our thinking about biological formulations—such as diseases—in ways that depend more on consideration of extremes than a focus on the means in our data.

It is the opinion of the authors, in other words, that

potential statistics, within the medical community, are often restricted to a view that seeks to identify changes in the mean of a population. This is not to say that such a view is incorrect; rather, that it is important when trying to identify specific traits common to that population. Changes in those traits in the general population is of great importance in consideration of causality and therapeutics. Such indicators, based on changes in means, are lagging indicators in as much as they only confirm a finding of a shift in the population when determined to be beyond random chance. Public policy reaction that awaits such proof risks substantial lags. The authors believe other statistics, describing the dispersion in data, such as the standard deviation, are useful statistics. They capture and describe individuality in ways that appeal, moreover, to the human need to be seen and treated as an individual and the medical maxim that the patient, not the disease, is the proper target of treatment for chronic conditions. Biological (human) systems, like mechanical (machine) systems tend to show signs of strain prior to any observable, statistically significant changes in measures of mean values. Such events cause the system to become unstable in a few individuals before they are generally expressed in the population, while the general population follows the above cited squirrel example. Strain is reflected as a wobble in or dispersion of various metrics. Those metrics may, moreover, not be in the core of features that carry the identity of the population. As such, a view of the data that shows an increase in the dispersion of data, such as the onset severity that is the basis of this contribution, suggests an underlying system may be beginning to show signs of strain that is a precur-

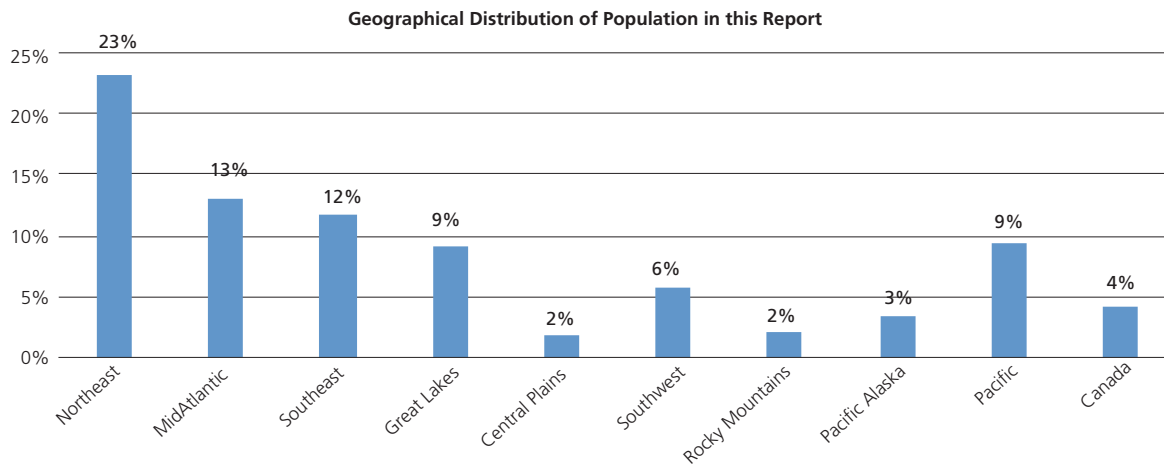


Figure 13 83.46% of Autism360's enrollees reported in this article showed postal codes within the regions and distribution shown here.

sor to a degradation in the mean of a population. Given that the estimates of dispersion for onset severity in Immune across prior years, shown in Figure 9, was increasing, we suggest this may be a precursor to an increase in the enrollment of females in the following year. As such, it provided an earlier warning that some females expressed signs of system strain that began to appear more and more as evidenced in the increase in enrollments in the following year.

The freshness and singularity of the data reported here make little room for interpretation pending confirmation and discussion with representatives of relevant disciplines. The view held by the senior author has for many years been that the reported increase in the overall incidence is real and pertains to environmental factors. Such factors touch on one of the most prevalent problems among children in the spectrum: sensitivity. Taste, touch, smell, vision, hearing, and the corresponding immunologically mediated perceptual and reactive repertoire are frequently heightened, sometimes beneficially but usually to the point of disability. The line our language and the normal distribution curve of toxicology draws between toxins and allergens is blurred in ways that appear clinically to find autistic children getting sick from exposures tolerated by others. These exposures recruit syndromes that we classify as allergic and autoimmune. Another way of putting it is a quote from one of the world's foremost immunologists: "While some would say that 'everything is autoimmune until proven otherwise' reading the chapters in this book written by world leaders in autoimmunity

brings one to the conclusion that everything after all is infectious until proven otherwise (including autoimmune diseases)."⁷ The light that Dr Shoenfeld shines on microbes illuminates the microbiome. It is certainly the major constant source of complex burdens placed on the body's immune and detoxification systems. Sex differences in detoxification are discussed with citations in reference 6. The senior author pictures the relevant landscape of childhood bisected by a metaphorical fence: grassy and clean on one side, muddy at the boundary where the autism spectrum begins. Males seem to have had a four-fold greater tendency to traverse the fence as compared with females. Once there, the females seem to have gotten muddier in the sense of being—before the convergence reported in this paper—more troubled in certain aspects of CNS, Emotion, and Immune function. The data presented here provides only the suggestion that the females who have more easily accessed the muddy side of the fence are more like males. If that similarity is related to detoxification mechanisms, one might look for environmental factors⁸ that erode or overcomes their mitochondrial advantage.

Acknowledgments
This study was supported by The Moody's Foundation of New York and other donors to Autism360 and the gift of a license to its technology by Medigenesis.

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Table 5 The Mean Age of Autism360's Enrollees From 2010 Through 2013

| Year | Mean Age ^a |
|------|-----------------------|
| 2010 | 7.14 |
| 2011 | 6.88 |
| 2012 | 6.20 |
| 2013 | 6.19 |

^a Mean age of all children under the age of 19 years.