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Theory and Clinical Practice in Pediatrics

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EDITORIAL

Preface for *Theory and Clinical Practice in Pediatrics*

Editor-in-Chief: Giullio Filippo Tarro

Preface

Pediatrics is the branch of medical science that deals with growing development, mental health and disease prevention from fetus to adolescents. With severe global environmental problem, virus mutation, growing cases of children cancer, the emerging advanced methods of examination, diagnosis and therapy (genetic test, new vaccine, precision medicine, metabonomics, molecular imaging, genetic therapy, minimally invasive therapy and interventional therapy, etc.), new theories and methods have sprung up in the field of pediatrics clinical research. The emerging diseases and the significant importance of research aimed at discovering new methods for improving diagnosis and therapy keep the topic of microbe involvement and vaccines among the most interesting and urgent problems of medical science today. It is, therefore, an honor for me and a great privilege to lead a new journal Theory and Clinical Practice in Pediatrics.

The publisher strongly believes in making research readily available to everyone and at the same time wants to provide always ethical services to the readers. Our journal would like to provide a platform for pediatrics researchers and related researchers to share new theories and methods.

Theory and Clinical Practice in Pediatrics is a broad ranging, international peer reviewed journal to pediatrics, publishing theoretical, clinical, and professional practice issues relevant to pediatrics, as broadly defined.

The scope of the journal includes, but not limited to, allergy and immunology, cardiology, critical care, emergency medicine, endocrinology, gastroenterology, hematology, infectious disease, nephrology, neuropsychology, oncology, pulmonology, genetics, neonatology, developmental-behavioral medicine. The journal has the potential to flourish and progress following the international publication and academic guidelines.

The papers to be selected shall cover a wide range and encompass the most up-to-date information on the multifactorial events which lead to potential pathologies in the world.

I would like to express my sincere thanks to the members of SyncSci Publishing Pte Ltd and to all who contribute to their participation, help and interest in the success of the journal. The knowledge that we yield today concerning the involvement in pediatric diseases represents one of the most important advancements of human health.

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COMMENTARY

Exegesis of Sabin poliovaccine in terms of medical science

Giullio Filippo Tarro

Short Story of the Battle Against Poliomyelitis

There are three types of poliovirus. The type 2 Lansing and type 3 Leon have been virtually eradicated everywhere thanks to vaccines developed by Salk first in 1955 and then by Sabin in 1961. The use of the Sabin vaccine has prevailed for the new idea to use an attenuated virus and the convenience of administration (oral and not intramuscular) and because it is cheaper. Two billions and a half am01ong children and adults were vaccined in 200 countries, freeing up 80% of the world of this scourge and bringing down the figure of 35,000 children suffering from polio in 1988 to 279 in 2014, of which 236 cases appeared in Pakistan. The poliovirus type 1 Brunhilde, however, has not been eradicated completely and appeared recently in Pakistan, Somalia, Ethiopia, Guinea, Kenya and Afghanistan. Each recurrence may be the beginning of new infections, so the war can never be said to be completely won.

Meanwhile, for the period 2013C2018, the World Health Organization and the Rotary Foundation allocated US$1 million each a year, for a total of US$5 billion, to the Global Polio Eradication Initiative.

Poliomyelitis (Polio)

Polio is a very serious disease caused by a virus of the Picornaviridae family, genus Enterovirus. Many children and adults who developed severe forms of polio were paralyzed, that is, losing the use of their legs or arms; some, unfortunately, even have died as a result of the disease.

The poliovirus infects the body through the digestive tract (mouth, throat, intestines); from here it can reach the nervous system and cause serious forms of the disease. The most severe cases of polio first cause strong muscle pain and subsequent paralysis, sometimes the immobility of one or both legs, or one or both arms, or worse, of the rib cage with the consequent impossibility to breathe without the help of a machine.

There are no medications, or other treatments that can cure people affected by polio. There is no specific antiviral drug.

Each patient has a different possibility: some will heal, others will carry some disability to an arm or leg for the rest of their lives, others will remain with severe disabilities, others are likely to die.

In the early 1960s polio was still a widespread disease in Italy and it was rightly feared; just in 1961, the beginning of mass vaccination campaigns about 3,500 cases of paralytic polio were reported. Thanks to vaccination, made compulsory in 1967, polio suffered a sharp decline, and in 1968 only 90 cases were reported throughout Italy.

Over the past 15 years it has been reported only one case, coming, however, from abroad. Polio, in fact, it is still present in some areas of the world, creating a potential risk for travellers who are not vaccinated, as well as the Italian population as a result of the importation of cases affected by poliovirus.

Precisely to prevent an imported case that might cause the onset of an epidemic, it is appropriate to maintain the highest possible number of individuals vaccinated, making the circulation of the virus dificult and thus protecting the few individuals who could not have been vaccinated.

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Correspondence to: Giullio Filippo Tarro, Committee on Biotechnologies and VirusSphere World Academy Biomedical Technologies, UNESCO, Italy; Email:giuliotarro@gmail.com

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Risks of Polio Vaccines

There are two types of polio vaccine. The oral vaccine called Sabin (OPV) consists of live attenuated virus; this means that the virus used for the vaccine, although still alive, is not able to cause disease. The administration of this preparation is carried out thr-ought the mouth in drops. The other type of vaccine uses killed poliovirus (vaccine with phormaline tre01ated virus); It is called Salk (IPV) and is administered by intramuscular injection. At least 90% of those vaccinated with three or more doses of both vaccines are protected against polio.

Sabin Vaccine

In rare cases the vaccine was causing paralysis in people who got it. The overall risk is approximately 1 case of paralytic disease for 2.4 million doses administered. The risk resulting from the first dose, compared to the next one is 1 in 760,000 doses, including vaccines and contacts. In vaccinated people, the risk is about 1 in 1.5 million for the subsequent doses; for contacts exposed to a person who has received the first dose of vaccine the risk is 1 to 2.2 million doses. For subsequent doses, the risk is substantially lower for those vaccinated and their contacts.

In Italy, since 1990, 10 cases of paralytic disease associated with the vaccine have been reported to the Ministry of Health for a rate of one in every 550,000 newborns and for 2,200,000 doses administered.

For people with immuodeficiency the risk is 3200C 6800 times higher than that for people who are immunologically normal vaccinated. For this reason to vaccinate a child or adult living with an immunocompromised patient, the Salk vaccine must be used.

Parenteral Vaccine (Salk)

The vaccination administered intramuscularly can cause slight pain and redness at the injection site. The Salk vaccine should not be administered to people who have severe allergy to antibiotics such as streptomycin, neomycin and polymyxin B; they must get in touch with the doctor before vaccination.

No serious event was associated with the use of the Salk vaccine.

Vaccine Currently Used

The Italian Decree of April 7, 1999 stated that for the first two doses of vaccine against polio, the Salk type should be used, while for subsequent doses (third and fourth), if there were no specific contraindications, one should continue using the Sabin vaccine.

The Decree of the Ministry of Health of June 18, 2002 abolished altogether antipoliomyelitic vaccination with Sabin vaccine and on August 12, 2002 it stated to use only the Salk vaccine for all doses. The transition from the Salk to Sabin vaccine was made possible by the new epidemiological situation of the poliomyelitis disease that, thanks to vaccination performed in the past with the Sabin vaccine, has led to the disappearance of polio in Europe. Therefore the use of only the Salk vaccine aims to eliminate even those rare cases of post-vaccination paralysis that may occur, under the above conditions, with the Sabin vaccine, making this vaccination even safer.

Vaccine Rating

The social importance of vaccination has justified imposing mandatory extent in many legislations, in view that the non-acceptance of the vaccination offer may endanger the health of the community. In fact, for people to be vaccinated in most cases means not merely to protect themselves, but also constitute a barrier to the spread of pathogens to other individuals of the population. For these same reasons, the legislature included those subjected to compulsory vaccination, that have suffered damage due to the practice of immunization, among those who are entitled to compensation under specific law. The evaluation of these preliminary elements, specific of vaccination and different from therapeutic treatments, is not a simple introductory premise, but also assumes importance as part of understanding the behavior of the public health authorities regarding the management of adverse events by vaccination. In fact, by having preventive and not therapeutic purposes, due to the fact that the vaccinations are targeted to very wide bands of the healthy population (mostly children), special attention was always paid to monitoring the risk/benefit of the vaccine, in order to highlight, in a timely manner, the existence of potential safety problems of the vaccine preparation before its use.

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RESEARCH ARTICLE

Gender differences in height, weight and BMI on self-esteem among rural school-aged children in China

Dafang Wang[1*] Shuqing Ding[1] Jianbing Wang[2] YanHong Gong[3] Xiaoxing Xu[3]

Abstract: 3,344 Children aged between 10 to 16 years from grade 4 to 10 were recruited to explore potential explanatory variables of low self-esteem among rural school-aged children in China. The results showed that the RSE scores were slightly higher for girls than for boys and higher academic achievement didn't contribute higher RSE scores in rural China. A lower height Z-scores resulted in a lower self-esteem in girls, and low SE was associated with height Z-score less than -1 versus scores more than -1 (OR=1.69, 95% CI 1.19-2.38, P=0.003). The findings indicated that it was height and BMI rather than weight to girls and weight to boys that were significantly associated with low self-esteem in rural China under the premise of very low rate of obesity.

Keywords: Gender Differences, Self-esteem, BMI

Self-esteem, also called self-worth, is a major predictor of satisfaction with life. A number of studies have investigated the factors that affect self-esteem on children, and current research focus such as the impacts of gender,[1] socio-economic status,[2] academic achievement,[3] age,[4] weight[5,6] and BMI[7] on self-esteem often reached conflicting conclusions in different areas or in different population. A theory of social comparisons explains how individuals evaluate their own opinions and abilities by comparing themselves to others who are similar to the self or who are upward (superior to the self) or downward (inferior to the self) on some attributes or dimensions, children or early adolescents assess whether they did better or worse than classmates in different but important areas.[8–10] These comparisons play an important role in shaping the childs self-esteem and influence the positive or negative feelings they have about themselves.[9–11]

As part of the attempt to understand self-esteem, gender differences often have been examined.[12–15] Results are mixed, researchers have found higher scores for male participants, higher scores for female participants, and no gender difference in self-esteem. For example, most early studies demonstrated no gender difference for children under 12 years, for adolescents, and for adults, but a reanalysis and update of these same studies showed that men were higher than women in self-esteem.[12,16–19] However, in a prior meta-analysis of the literature, Sahlstein and Allen found that women scored higher than men on comprehensive measures and on the cognitive aspect of self-esteem, but men scored higher than women on social and physical aspects and most differences were small in size.[20]

During the school years, academic achievement is considered as an important contributor to self-esteem development. A student consistently achieving success or consistently failing strongly affects their individual self-esteem.[21–24] Despite popular beliefs that high self-esteem facilitates academic achievement, only a modest correlation was discovered between general self-esteem and school performance.[25] A prior meta-analysis estimated that the effect of the favorable influence of positive self-beliefs on academic achievement is modest and the overall estimated relation is about 0.08.[26]

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*Correspondence to: Dafang Wang, Department of Pediatrics, Tsinghua University YuQuan Hospital, Beijing 100040, China; Email: wangdafang73@163.com

[1] Department of Pediatrics, Tsinghua University YuQuan Hospital, Beijing 100040, China

[2] Department of Infectious Diseases,Tsinghua University YuQuan Hospital, Beijing 100040, China

[3] School of Social Development and Public Policy, Beijing Normal University, Beijing 100875, China

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Associations between overweight and psychosocial factors have been inconsistent, with some studies reporting an inverse relationship between BMI and self-esteem, and others showing no association.[27–30] Some of the postulated reasons for the divergent findings include methodological differences in measuring self-esteem, differences in samples surveyed (clinical and nonclinical groups), and in sociodemographic profiles. Previous studies have found that taller adults tend to enjoy better mental health than their counterparts of average and below-average stature. For instance, Osika and Montgomery found that height was associated with a reduced risk of reporting low mood among adults 18 years of age and older.[31] It is possible that the relationship between adult height and psychological well-being is driven by an omitted variable (or variables).[32] A plausible alternative is that height is directly related to mental health.

The great majority of the previously research on self-esteem of children was conducted in Western individualist societies, and some have questioned its relevance to non-Western countries, especially to China.[33] The main goal of this study were to compare the difference of self-esteem between boys and girls in rural China, and to explore the potential explanatory variables, such as economic status, academic achievement, height, weight, body mass index (BMI), that may associated with self-esteem in different learning phrases.

1 Methods

1.1 Study design and participants

A cross-sectional study was conducted between November and December 2008.The protocol and sampling methodology of this survey have been described previously.[34] The analysis sample comprised of 4th- to 10th- grade 3,344 rural Children (1668 boys and 1676 girls) aged between 10 to 16 years. According to the local economic development and the concentration of migrant workers population, the Henan and Shaanxi provinces were chosen as study sites and nine schools were randomly selected from the two areas.

1.2 Instruments and procedure

The individual level of self-esteem was measured using the Rosenberg Self-esteem Scale (RSES). The RSES consists of 10 statements dealing with a persons general beliefs about himself or herself. Each item is answered on a four-point scale, from strongly agree to strongly disagree, with five items being reverse scored so that a higher score indicates higher self-esteem. The score obtained with the scale may vary from 10 to 40, calculated through the sum of the scores obtained from the answers given to the 10 statements. Each statement may receive a score from 1 to 4. A satisfactory self-esteem is defined as higher or equals to 30 at the Rosenbergs Scale, or dissatisfactory with a score lower than 30.[35]

The heights and weights of the participants were consistently measured one by one outside of the classroom by trained interviewers with universal measurement. Height was measured using the portable rigid stadiometer, which measures to the nearest 1mm to a height of 207 cm; weight was measured using digital scales which were regularly calibrated and shown to be accurate within 20 g. Investigation of anthropometric reliability found no evidence of systematic bias for intra-rater or inter-rater comparisons. BMI was calculated (weight (kg)/height (m)2). In addition, height, weight and BMI were transformed to standardized (Z) scores based on gender and exact age, using the LMS method and the Centers for Disease Control and Prevention 2000 Growth Chart data, and were divided into three levels (Z-score: less than -1, -1 to 1 and more than 1).

The data of economic status were collected by question to students of participants and phrased as: how is your family economic status?, and response choices range from very rich to very poor on a five point scale. Considering the sample size distribution (few students chose very rich), we re-divided the options into three levels comprised of top-level (very rich and rich), medium-level and low-level (poor and very poor) during data analysis. Similar to economic status, the data of academic achievement were divided into three levels as above.

1.3 Statistical analysis

Descriptive statistics for all variables were calculated, and comparisons of mean self-esteem scores across age, economic status, academic achievement, weight Z-score, height Z-score and BMI Z-score between boys and girls were made, ANOVA and Scheffes test were used for multiple comparisons among groups with unequal sample sizes, and T-test was used to compare the difference of RSE scores between girls and boys.

Binomial regression with a logit link was then used for the dependent variable self-esteem status (satisfactory/dissatisfactory) to estimate the multivariate odds ratios (OR) of dissatisfactory self-esteem after controlling for other factors. A regression analyses was conducted to compare the impacts on self-esteem among levels of interesting variables by the regression coefficients. All analyses were completed using Stata statistical software (Stata version 12.0; Stata Corp LP, College Station, Tex).

All statistical tests were 2-tailed and significance was set at P <0.05.

2 Results

The means and standard deviations (SD) of RSE scores for all subgroups, categorized according to gender were presented. The overall mean RSE score for girls was slightly higher than that of boys (girls: 30.245.07; boys: 29.795.04) in rural Chinese children, and the scores were slightly higher for girls than for boys at almost each age between 10 to 16 years. In addition, there were significant differences of mean scores among levels of characteristics include economic status in boys, academic achievement in girls and boys and height Z-scores for girls by ANOVA. T test was performed to compare the difference of mean scores in the same level of each characteristic between girls and boys, Table 1.

For regression analyses, RSE scores as a continuous outcome variable and age, economic status, academic achievement, Z-scores of height, weight and BMI were entered on model, and the regression coefficients were presented to compare the amount of impact of independent variables on RSE scores. It can be seen that older age, and weight Z-scores more than 1 could significantly contribute higher RES scores, but high economic status and medium-level academic achievement were just the contrary in boys. Girls with height Z-scores less than 1 and BMI Z-scores more than 1 had significant lower RSE scores (1.31, 1.04 scores decreased compared with average height Z-scores and average BMI Z-scores, P<0.05, respectively), and economic status had no significant impact on that scores. To our surprise, results of regression showed that higher level academic achievement didnt resulted in higher RSE scores in girls and boys, Table 2.

In multivariate analyses, using self-esteem as a binary variable according to the cutoff of the RSE score, results showed that older age was a protective factor of dissatisfactory self-esteem in boys and girls after controlling for other factors. Dissatisfactory self-esteem was significantly associated with medium level of academic achievement compared with low level of that (boys: OR=1.49, 95% CI 1.13-1.97; girls: OR=2.32, 95% CI 1.75-3.08). Dissatisfactory self-esteem was also significantly associated with the height Z-scores less than -1 compared with normal height (the height Z-scores more than -1 and less than 1) in girls (OR=1.69, 95% CI 1.19-2.38, P=0.003), but no significant association in boys.

Figure 1, 2, 3 presented the changes of self-esteem scores with age by different levels of Z-scores height, weight and BMI in boys and girls. The figures suggested significantly decreased scores of self-esteem in the boys with the height Z-scores less than -1 compared with boys with the height Z-scores more than -1 after the age of 13, and it also can be seen that lower height Z-scores, lower self-esteem scores in girls between ages of 10 to 16. Similarly, the decreases of RSE scores for weight appeared at the years of age 12 and 16 for boys, and at the years of age 10,13 and 16 for girls compared with the same two levels.

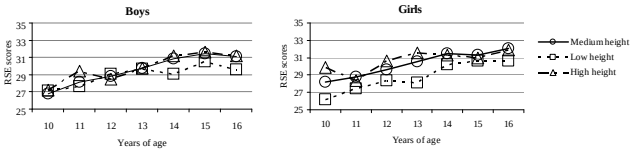

Figure 1. Mean level of self-esteem by Z-scores of height for boys and girls across the years of age

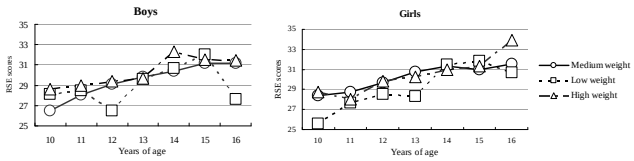

Figure 2. Mean level of self-esteem by Z-scores of weight for boys and girls across the years of age

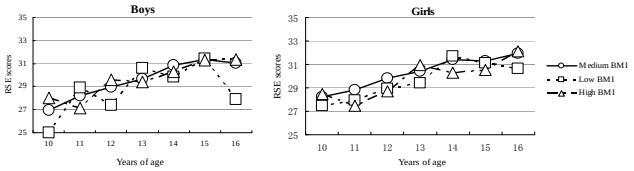

Figure 3. Mean level of self-esteem by Z-scores of BMI for boys and girls across the years of age

3 Discussion

We examined the association between self-esteem and economic status, academic achievement, height, weight and BMI in rural school-aged children in China. In this study, we found that the RSE scores of girls were slightly higher than that of boys in rural China. Low socioeconomic status had been reported to be a risk factor of low self-esteem, but our findings suggested that only the self-esteem scores of boys were associated with SES, and there was no significant difference for prevalence rate of dissatisfactory self-esteem among different economic status in boys. In addition, the self-esteem was not associated with SES in girls. The reason for this result may lie in the fact that theres only a marginal difference among economic status especially in rural China.

Although prior studies had demonstrated that only a modest correlation was discovered between general self-esteem and academic achievement, despite popular beliefs that high self-esteem facilitates academic achievement,[36] we found a unpredictable result that higher aca-

Table 1. Means and Standard Deviations of Self-Esteem Scores According Gender

	Boys						Girls					
	Grade 3 to 6		Grade 7 to 9		Grade 10 to 12		Grade 3 to 6		Grade 7 to 9		Grade 10 to 12	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	F value	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	F value
Economic status														
Rich	64	28.45 -4.52	33	32.48 -5.26	4	31.8 -7.79	7.68**	43	29.45 -5.07	22	30.22 -4.68	3	32 -4.87	0.48
Moderate	454	28.51 -4.72	637	30.89 -4.95	110	31.97 -4.96	40.74**	484	28.54 -4.56	615	31.44 -4.69	103	30.35 -5.35	51.79**
Poor	240	27.47 -4.76	296	30.37 -4.79	122	32.09 -4.92	43.61**	273	28.42 -4.66	301	31.01 -4.98	101	31.47 -4.34	26.62**
F value		3.94*		3.2*		0.02			0.93		1.36		45.16**	
Academic achievement														
Top Level	165	28.76 -4.86	210	30.67 -4.82	52	32.48 -4.47	14.33**	157	29.68 -4.58	205	32.17 -4.19	47	32.32 -4.43	16.13**
Medium Level	245	27.41 -4.43	293	29.74 -4.7	96	31.93 -4.86	37.16**	268	27.45 -4.45	285	30 -4.3	88	30.62 -4.67	29.84**
Low Level	342	28.47 -4.83	462	31.52 -4.99	88	31.86 -5.37	41.4**	372	28.87 -4.63	448	31.67 -5.17	71	30.57 -5.08	32.7**
F value		3.56*		8.94**		0.28			9.1**		15.64**		38.13**	
Height Z-score														
Less than -1	124	28.54 -4.87	125	29.7 -5.05	14	30.74 -4.92	2.41	122	27.43 -3.95	118	30.37 -4.53	29	29.27 -4.79	14.12**
-1 to 1	538	28.06 -4.73	683	30.97 -4.99	182	32.05 -4.9	71.97**	569	28.71 -4.71	667	31.36 -4.77	139	31.65 -6.89	48.93**
More than 1	96	28.38 -4.62	158	30.86 -4.42	40	32.38 -5.29	13.56**	109	28.95 -4.72	153	31.6 -5	40	30.98 -4.36	9.75**
F value		0.61		3.54*		0.57			4.37*		2.55		1.79	
Weight Z-score														
Less than -1	122	27.43 -3.95	118	30.37 -4.53	29	29.27 -4.79	9.09**	107	27.9 -4.18	137	31.08 -4.53	27	30.04 -4.47	15.87**
-1 to 1	569	28.71 -4.71	667	31.36 -4.77	139	31.65 -6.89	63.83**	595	28.69 -4.65	654	31.3 -4.78	149	30.81 -5.05	48.62**
More than 1	109	28.95 -4.72	153	31.6 -5	40	30.98 -4.36	11.91**	98	28.39 -4.89	147	31.34 -5.05	32	33.93 -10.58	13.14**
F value		0.7		0.94		0.79			1.4		0.14		3.9*	
BMI Z-score														
Less than -1	96	27.81 -4.46	106	30.72 -5.08	26	31.97 -5.74	12.14**	101	28.61 -4.54	130	31.1 -4.91	31	30.43 -4.38	8.01**
-1 to 1	578	28.24 -4.77	728	30.82 -4.87	175	32.08 -4.92	64.82**	596	28.6 -4.55	662	31.44 -4.7	148	31.09 -5.07	60.41**
More than 1	84	28.17 -4.86	132	30.65 -5.12	35	31.82 -4.71	9.13**	103	28.15 -5.12	146	30.7 -5.02	29	32.55 -11.4	8.44**
F value		0.35		0.08		0.04			0.44		1.53		0.94	

* P<0.05; ** P<0.001

Table 2. Summary of Multiple Regression Analyses Predicting Self-Esteem in Girls and Boys

	Model 1		Model 2		Model 3		Model 4	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
	β		β		β		β	
Grade	0.3176	0.246	0.3144	0.241	0.314	0.241	0.3142	0.241
Economic status	-0.08	0.201	-0.078	0.202	-0.077	0.203	-0.076	0.203
Academic achievements	-0.031	0.045	-0.031	0.043	-0.031	0.043	-0.031	0.044
Height			0.0355	0.089	0.021	0.111	-0.051	0.091
Weight					0.02	-0.037	0.1409	-0.003
BMI							-0.087	-0.028
R^2	0.1021	0.122	0.1034	0.13	0.104	0.131	0.1038	0.131
$\triangle R^2$			0.0013	0.008	1E-04	9E-04	0.0003	0
F	74.22	89.83	56.4	72.36	45.19	58.32	37.72	48.59

demic achievement didnt contribute higher RSE scores in rural China. The cause may be include: 1) The high cost of Higher Education to poor people in China. 2) Nowadays, college students' low employment becomes an undisputable reality in China. 3) Going to college didnt necessarily bring about a dramatic transformation in the quality of life for poor people in China. These notions may change the learning attitude and motivation of children in rural China, and a good school perfermance is not still an important learning target for them. Moreover, this result was supported by previous studies. For example, Crocker and Major found that stigmatized groups may compare their outcomes with those of the in-group, rather than with the relatively advantaged outgroup,[37] and an other study found that children with low self-esteem seem to focus on self-protection; rather than trying to achieve gains for their self-esteem, they try to avoid losses.[38]

A number of previous studies had explored the relationship between body image (height, weight, BMI) and self-esteem in adolescent[39–41] and had produced conflicting results.[42,43] Previous studies had found that taller adults tend to enjoy better mental health than their counter parts of average.[42,43] Our results showed a lower self-esteem score and a higher prevalence rate of dissatisfactory self-esteem in girls with lower height Z-score, but there was no significant difference of self-esteem scores among different height Z-scores in boys. This results may be explained as follows: 1) Body image may be affected and partly determined by cultural beliefs and values regarding beauty and attractiveness. 2) Girls who express greater dissatisfaction with their height and body shape tend to have lower self-esteem scores than girls who have a healthier body image.[44,45] 3) The greater body dissatisfaction (discrepancy between current and ideal figures) displayed by adult females has since been replicated in adolescents. 4) Body shape satisfaction and self-esteem mbe significantly and more strongly related in females than males. Previous study about height and adolescent psychological well-being found that one percentile point increase in height is associated with only a 0.006−0.007 increase in RSE scores among American male students aged 12 to 19 years,[46] and this result was consistent with ours. In addition, a large amount of previous studies has demonstrated that overweight or obesity was a risk factor of low self-esteem,[47] but we found the factors of weight and BMI were not significantly associated with self-esteem in our findings. The reason might be derived from the difference of the investigated population. In our study, only 2.78% (93/3344) of participants were obesity (BMI Z-scores2), and the prevalence rate of obesity was much lower than that in urban China or developed countries.

It was easy to understand that the years of age when self-esteem was influenced by the height, weight and BMI was was earlier for girls than boys because of early puberty in girls than boys.

Further elucidation of the mechanisms through which characteristics related self-esteem will be necessary to guide families, clinicians, and public health workers in their efforts to preserve healthy self-esteem levels during adolescence and ensure a successful transition to adulthood, especially in China.

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References

[1] Cribb VL, Haase AM. Girls feeling good at school: School gender environment, internalization and awareness of sociocultural attitudes associations with self-esteem in adolescent girls. *J Adolesc*, 2016, **46**:107−114 http://dx.doi.org/10.1016/j.adolescence.2015.10.019

[2] Benson PE, Da'as T, Johal A,*et al.* Relationships between dental appearance, self-esteem, socio-economic status, and oral health-related quality of life in UK schoolchildren: A 3-year cohort study. *Eur J Orthod*, 2015, **37**(5):481−490 https://dx.doi.org/10.1093/ejo/cju076

[3] Hosseini SN, Mirzaei Alavijeh M, Karami Matin B, *et al.* Locus of Control or Self-Esteem; Which One is the Best Predictor of Academic Achievement in Iranian College Students. *Iran J Psychiatry Behav Sci*, 2016, **10**(1): e2602 https://dx.doi.org/10.17795/ijpbs-2602

[4] Mullis RL, Chapman P. Age, gender, and self-esteem differences in adolescent coping styles. *J Soc Psychol*, 2000, **140**(4): 539−541 https://dx.doi.org/10.1080/00224540009600494

[5] Danielsen YS, Stormark KM, Nordhus IH,*et al.* Factors associated with low self-esteem in children with overweight. *Obes Facts*, 2012, **5**(5): 722−733 https://dx.doi.org/10.1159/000338333

[6] Huang L, Tao FB, Wan YH,*et al.* Self-reported weight status rather than BMI may be closely related to psychopathological symptoms among Mainland Chinese adolescents. *J Trop Pediatr*, 2011, **57**(4): 307−311
https://dx.doi.org/10.1093/tropej/fmp097

[7] Hesketh K, Wake M, Waters E. Body mass index and parent-reported self-esteem in elementary school children: evidence for a causal relationship. *Int J Obes Relat Metab Disord*, 2004, **28**(10): 1233−1237
https://dx.doi.org/10.1038/sj.ijo.0802624

[8] Aspinwall LG, Taylor SE. Effects of social comparison direction, threat, and self-esteem on affect, self-evaluation, and expected success. *J Pers Soc Psychol*, 1993, **64**(5): 708−722
https://dx.doi.org/10.1037/0022-3514.64.5.708

[9] Bailey SD, Ricciardelli LA. Social comparisons, appearance related comments, contingent self-esteem and their relationships with body dissatisfaction and eating disturbance among women. *Eat Behav*, 2010, **11**(2): 107−112
https://dx.doi.org/10.1016/j.eatbeh.2009.12.001

[10] Patrick H, Neighbors C, Knee CR. Appearance-related social comparisons: the role of contingent self-esteem and self-perceptions of attractiveness. *Pers Soc Psychol Bull*, 2004, **30**(4): 501−514
https://dx.doi.org/10.1177/0146167203261891

[11] Mullis AK, Mullis RL, Normandin D. Cross-sectional and longitudinal comparisons of adolescent self-esteem. *Adolescence*, 1992, **27**(105): 51−61
http://www.ncbi.nlm.nih.gov/pubmed/1539501

[12] Bachman JG, O'Malley PM, Freedman-Doan P, *et al.* Adolescent Self-Esteem: Differences by Race/Ethnicity, Gender, and Age. *Self Identity*, 2011, **10**(4): 445−473
https://dx.doi.org/10.1080%2F15298861003794538

[13] Reynolds MW, Wallace J, Hill TF, *et al.* The relationship between gender, depression, and self-esteem in children who have witnessed domestic violence. *Child Abuse Negl*, 2001, **25**(9): 1201−1206
http://dx.doi.org/10.1016/S0145-2134(01)00269-1

[14] Calzo JP, Roberts AL, Corliss HL, *et al.* Physical activity disparities in heterosexual and sexual minority youth ages 12-22 years old: roles of childhood gender nonconformity and athletic self-esteem. *Ann Behav Med*, 2014, **47**(1): 17−27
https://dx.doi.org/10.1007/s12160-013-9570-y

[15] Alpert-Gillis LJ, Connell JP. Gender and sex-role influences on children's self-esteem. *J Pers*, 1989, **57**(1): 97−114
http://dx.doi.org/10.1111/j.1467-6494.1989.tb00762.x

[16] Ng JYY, Tam SF, Man DWK,*et al.* Gender difference in self-esteem of Hong Kong Chinese with cardiac diseases. *Int J Rehabil*, 2003, **26**(1): 67−70
https://dx.doi.org/10.1097/01.mrr.0000054803.81886.8b

[17] Israel AC, Ivanova MY. Global and dimensional self-esteem in preadolescent and early adolescent children who are overweight: age and gender differences. *Int J Eat Disord*, 2002, **31**(4): 424−429
https://dx.doi.org/10.1002/eat.10048

[18] Watkins D, Dong Q, Xia Y. Age and gender differences in the self-esteem of Chinese children. *J Soc Psychol*, 1997, **137**(3): 374−379
https://dx.doi.org/10.1080/00224549709595448

[19] Conte HR, Plutchik R, Picard S,*et al.* Gender differences in recalled parental childrearing behaviors and adult self-esteem. *Compr Psychiatry*, 1996, **37**(3): 157−166
http://dx.doi.org/10.1016/S0010-440X(96)90032-2

[20] Sahlstein EA, M. Sex differences in self-esteem: A meta-analytic assessment. In: Interpersonal Communication Research: Advances through meta-analysis. New Jersey: Lawrence Erlbaum Associates, 2002: 59−72
http://dx.doi.org/10.1037/0033-2909.125.4.470

[21] Booth MZ, Gerard JM. Self-esteem and academic achievement: a comparative study of adolescent students in England and the United States. *Compare*, 1996, **41**(5): 629−648
https://dx.doi.org/10.1080/03057925.2011.566688

[22] Kristjansson AL, Sigfusdottir ID, Allegrante JP. Health behavior and academic achievement among adolescents: the relative contribution of dietary habits, physical activity, body mass index, and self-esteem. *Health Educ Behav*, 2010, **37**(1): 51−64
https://dx.doi.org/10.1177/1090198107313481

[23] Marsh HW, O'Mara A. Reciprocal effects between academic self-concept, self-esteem, achievement, and attainment over seven adolescent years: unidimensional and multidimensional perspectives of self-concept. *Pers Soc Psychol Bull*, 2008, **34**(4): 542−552
https://dx.doi.org/10.1177/0146167207312313

[24] Gordon DA. Children's beliefs in internal-external control and self-esteem as related to academic achievement. *J Pers Assess*, 1977, **41**(4): 383−386
https://dx.doi.org/10.1207/s15327752jpa4104_8

[25] Marsh HWY, A S. Longitudinal structural equation models of academic self-concept and achievement: Gender differences in the development of math and English constructs. *American Educational Research Journal*, 1998, **35**(4): 705−738
https://dx.doi.org/10.3102/00028312035004705

[26] Valentine JC, Dubois DL, Cooper H. The Relation between Self-Beliefs and Academic Achievement: A Systematic Review. *Educational Psychologist*, 2004, **39**(2): 111−133
http://dx.doi.org/10.1207/s15326985ep3902_3

[27] Fernandes N, Khubchandani J, Seabert D, *et al.* Overweight status in Indian children: prevalence and psychosocial correlates. *Indian Pediatr*, 2015, **52**(2): 131−134
http://dx.doi.org/10.1007/s13312-015-0587-0

[28] Rankin J, Matthews L, Cobley S, *et al.* Psychological consequences of childhood obesity: psychiatric comorbidity and prevention. *Adolesc Health Med Ther*, 2016, **7**: 125−146
https://dx.doi.org/10.1097/HCR.0000000000000202

[29] De Bourdeaudhuij I, Lefevre J, Deforche B, *et al.* Physical activity and psychosocial correlates in normal weight and overweight 11 to 19 year olds. *Obes Res*, 2005, **13**(6): 1097−1105
https://dx.doi.org/10.1038/oby.2005.128

[30] Backes V, Olinto MT, Henn RL, *et al.* Association between psychosocial factors and self-reported overweight in Brazilian adults. *Cad Saude Publica*, 2011, **27**(3): 573−580
http://dx.doi.org/10.1590/S0102-311X2011000300017

[31] Osika W, Montgomery SM. Physical control and coordination in childhood and adult obesity: longitudinal birth cohort study. *BMJ*, 2008, **337**: a699
https://doi.org/10.1136/bmj.a699

[32] Booth D. Learned Role of Tastes in Eating Motivation. In: Taste, experience, and feeding. Washington,DC, USA: American Psychological Association, 1990. 179−194
http://sro.sussex.ac.uk/id/eprint/56324

[33] Triandis HC. Cross-cultural studies of individualism and collectivism. *Nebr Symp Motiv*, 1989, **37**: 41−133
https://doi.org/10.1177/0022022190212001

[34] Guo J, Chen L, Wang X, *et al.* The Relationship Between Internet Addiction and Depression Among Migrant Children and Left-Behind Children in China. *Cyberpsychology Behav Soc Netw*, 2012, **15**(11): 585−590
https://dx.doi.org/10.1089/cyber.2012.0261

[35] Macola L, do Vale IN, Carmona EV. Assessment of self-esteem in pregnant women using Rosenberg's Self-Esteem Scale. *Rev Esc Enferm USP*, 2010, **44**(3): 570−577
http://dx.doi.org/10.1590/S0080-62342010000300004

[36] Marsh HW, Yeung AS. An extension of the internal/external frame of reference model: A response to Bong (1998). *Multivar Behav Res*, 2001, **36**(3): 389−420
https://dx.doi.org/10.1207/S15327906389-420

[37] Crocker J, Major B. Social stigma and self-esteem: the self-protective properties of stigma. *Psychol Rev*, 1989, **96**(4): 608−630
https://dx.doi.org/10.1037/0033-295x.96.4.608

[38] Wood JV, Giordano-Beech M, Taylor KL, *et al.* Strategies of social comparison among people with low self-esteem: Self-protection and self-enhancement. *J Pers Soc Psychol*, 1994, **67**(4): 713−731
https://dx.doi.org/10.1037/0022-3514.67.4.713

[39] Al-Halabi S, Garcia-Portilla MP, Saiz PA, *et al.* Psychometric properties of the Spanish version of the Body Weight, Image and Self-Esteem Evaluation questionnaire in patients with severe mental disorders. *Compr Psychiatry*, 2012, (): 1237−1242
https://dx.doi.org/10.1016/j.comppsych.2012.04.001

[40] Wolfradt U, Neumann K. Depersonalization, self-esteem and body image in male-to-female transsexuals compared to male and female controls. *Arch Sex Behav*, 2001, **30**(3): 301−310
https://dx.doi.org/10.1023/A:1002752214526

[41] Furnham A, Badmin N, Sneade I. Body image dissatisfaction: gender differences in eating attitudes, self-esteem, and reasons for exercise. *J Psychol*, 2002, **136**(6): 581−596
https://dx.doi.org/10.1080/00223980209604820

[42] Grubb HJ, Sellers MI, Waligroski K. Factors related to depression and eating disorders: self-esteem, body image, and attractiveness. *Psychol Rep*, 1993, **72**(3): 1003−1010
https://dx.doi.org/10.2466/pr0.1993.72.3.1003

[43] Rubin R. Body image and self-esteem. *Nurs Outlook*, 1968, **16**(6): 20−23
https://www.ncbi.nlm.nih.gov/pubmed/5185153

[44] Cooper PJ, Fairburn CG. Binge-eating and self-induced vomiting in the community: A preliminary study. *Br J Psychiatry*, 1983, **142**(): 139−144
https://dx.doi.org/10.1192/bjp.142.2.139

[45] Furnham A, Calnan A. Eating disturbance, self-esteem, reasons for exercising and body weight dissatisfaction in adolescent males. *Eur Eat Disorders Rev*, 1998, **6**(1): 58−72
http://dx.doi.org/10.1002/(SICI)1099-0968(199803)6:1⟨58::AID-ERV184⟩3.0.CO;2-V

[46] McClure AC, Tanski SE, Kingsbury J, *et al.* Characteristics Associated with Low Self-Esteem among US Adolescents. *Acad Pediatr*, 2010, **10**(4): 238−244
https://dx.doi.org/10.1016%2Fj.acap.2010.03.007

[47] Franklin J, Denyer G, Steinbeck KS, *et al.* Obesity and risk of low self-esteem: a statewide survey of Australian children. *Pediatrics*, 2006, **118**(6): 2481−2487
https://dx.doi.org/10.1542/peds.2006-0511

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RESEARCH ARTICLE

Sleep Less, myopia more

Xiaoxin Xu[1*] Dafang Wang[2] Gexing Xiao[3] Kang Yu[4] Yanhong Gong[1]

Abstract: The data through 15,316 Chinese school students aged 6 to 18 years from 19 randomized schools inside Beijing city including the cycloplegic refractor and also the possible genetic, environmental as well as behavioural habit risk factors were examined to explore the key risk aspects for myopia. Univariate along with multiple logistic regression analysis were carried out, and receiver operator characteristic (ROC) curves generated.The results showed that myopia was associated with short sleeping time (lowest time span) versus long sleeping time (highest time span) (odds ratio=3.37; 95%CI 3.07-3.70). Controlling for the same factors, children with shorter sleeping time had significantly more myopic refractions (-1.69D for children with the shortest sleeping time compared with -1.29D for children with the longest sleeping time per day). Analysis of the areas under the ROC curves showed five variables with predictive values better than chance: age, sleeping time, reading or writing distance, hours of studying, and parent's myopia.The findings indicated that Sleeping time may be an independent risk factor of myopia, and this relationship may not be explained merely by increased hours of studying or hours of watching TV. An interesting observation is that sleeping time may be an important risk factor for myopia compared with other near work factors. The complexity of the relationship between sleeping time and myopia need additional studies to clarify any cause-effect relationship.

Keywords: Sleeping time, Myopia, Social Medicine, Children

The prevalence of myopia of Chinese school-aged students has been one of the highest[1–3] in the world according to the Report of Student Physical Health Monitoring by Ministry of Education of China in 2010, and which in Beijing city (31.10% of primary school students, 62.12% of middle school students, 77.88% of high school students) is higher than the average of whole country and shows an upward trend. Considering myopias high prevalence, being able to slow or stop myopia progression and ultimately prevent the occurrence of myopia is important especially in China.

An extensive literature on the possible environmental, behavioural habit and genetic risk factors for myopia exists, but the strength of many associations is often weak, and some prior results are often contradictory. Commonly investigated risk factors include environmental risk factors such as parental education, family income, illumination condition, and behavioural risk factors such as reading distance, hours of sports, hours of watching TV or using computer, sleeping time, as well as parental myopia, a possible indicator of genetic susceptibility.[4] Studies focusing on reducing the progression of myopia have had limited success. Trials using progressive addition lenses,[5] bifocals,[6] and rigid gas permeable contact lenses[7] found small, statistically significant reduction in myopic progression when compared to relevant control groups. As a main measurement for preventing and controlling myopia of school students in China, Eye Exercises (a method of massage for eye) has been carried out for near 30 years in school, but that doesn't make the prevalence of myopia lower.

In this article we use mass data of school-age students about potential risk factors of myopia from primary and middle schools in Beijing city to explore the prior or sensitive factors and evaluate the association with myopia.

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*Correspondence to: Xiaoxin Xu, School of Social Development and Public Policy, Beijing Normal University, Beijing 100875, China; Email: xuxiaoxin@bnu.edu.cn

[1] School of Social Development and Public Policy, Beijing Normal University, Beijing 100875, China

[2] Department of Pediatrics, Tsinghua University YuQuan Hospital, Beijing 100040, China

[3] Center of Information, Chinese Center for Disease Control and Prevention, Beijing 102206, China

[4] School of Chemical and Biomedical Engineering, Nanyang Technological University, 70 Nanyang Drive, Singapore 637457

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1 Materials and methods

1.1 Subjects

The sample of this study came from a multistage stratified random sampling, in which 18 districts in Beijing were divided into three strata of developed region, developing region and undeveloped region according to the economic indicator of GDP; six schools of 3 primary schools and 3 middle schools were randomly selected from each stratum; and a total of 900 students from each school were randomly drawn in 2008. Parents and students were provided an explanation of the study, and the parents gave their consents for their children's participation in the study if the study protocol was approved by Beijing Municipal Commission of Education. Finally, 15316 school-aged students (response rate is 94.5%) from grade 1 in primary school to grade 3 in high school located in different districts in Beijing were invited to participate in the survey (primary school students:5643 (36.8%), middle school students:4378 (28.6%), and high school students:5295 (34.6%); male students:7434 (48.5%) and female students:7882 (51.5%); urban areas:6230 (40.7%) and suburban areas:9086 (59.3%)).

1.2 Questionnaire survey

A questionnaire designed to evaluate the genetic, environmental and behavioral risk factors risk factors of myopia ,which included several parts, the first part: general characteristic (gender, age, parent's education, parent's profession, family income, etc); the second part: near work questions (reading or writing distance, studying time per day, hours of watching TV and using computer per day, distance to TV and computer per day, etc); the third part: sports, sleeping and nutrition questions (hours of sports per day, sleeping time per day , quantity of sweet foods, fruit, vegetable and high protein foods, etc); the forth part: parent's myopia. By the reliability and validity test about the questionnaire, the Crosspatch's alpha,the Guttman split half correlation coefficient and the Scale reliability coefficient are 0.71,0.654, 0.704, respectively.

1.3 Measurements

Myopia was defined as at least -0.75D of myopia in both the horizontal and vertical meridians on cycloplegic auto refraction. An auto keratorefractometer (model RM A7000, Topcon, Ltd, Japan) was used to obtain the average of five consecutive refraction readings (all readings <0.25D apart) and average of two corneal curvature readings in the flatter and steeper meridians was calculated.[8,9] Parents provided information through a survey on parental myopia,parental education level and the number of hours per day of watching TV or using computer a child performed and the children provided information of years of birth, gender, the distance of reading or writing, hours of sports (not include outdoor leisure activities), and hours of sleeping.

1.4 Data analysis

Refraction was analyzed as (spherical equivalent [SE]: sphere + half negativecylinder power). Myopia was defined as SE at least -0.75D. Data (SE) from the right and left eye were similar (Pearson correlation coefficient=0.88), and thus the left eye results were presented. To count the univariate odds ratio(OR) and multivariate OR after adjusting other variables for myopia by logistic regression models with refraction as the dependent variable and sleeping time, age, gender, parental myopia, parental education, reading or writing distance, hours of sports, hours of watching TV or using computers the explanatory variables.To count the adjusted mean refraction in different sleeping time span by multiple linear regression models after adjusting other risk factors. The linear trend tests were performed by assigning consecutive integers to each sleeping time span. The areas under the ROC curves (AUC) was used to compare the specificity and sensitivity to myopia among the main risk factors include age, hours of sleeping, father's education, parent's myopia and reading distance.Data analysis was conducted using the commercially available software (Stata, Ver.10.0; Stata, College Station, TX).[10]

2 Results

2.1 Characteristics of the subjects

The mean refractive error was -1.45 D (SD 2.50; range -14.78 to 14.37), and the prevalence rate of myopia was 8178/15316 (53.40%; 95% confidence interval (CI), 52.60%-54.19%).The median number of hours of watching TV or use computer and hours of studying was 1 to 2 hours and 7 to 9 hours per day, respectively.

There were 278 (4.95%) and 1141 (25.16%)childrenin the highest sleeping time span whose hours of studying greater than 10 hours per day compared with the lowest sleeping time span (P<0.001; Table1).The spearman correlation coefficient of sleeping time and hours of studying per day was -0.26(P<0.001).Children with sleeping time in the highest span were more likely to spend hours of watching TV or use computer more than 2h (33.32%) compared with children with sleeping time in the lowest sleeping time span (18.08%;P<0.001).

Table 1. Hours of studying per day of Chinese children by sleeping time span

		Hours of Studying per Day				
Sleeping time	n	6 Hours or Less	6 to 8 Hours	8 to 10 Hours	10 Hours or	P
7Hoursor less	4535	679 (14.97%)	1512 (33.34%)	1203 (26.53%)	1141(25.16%	<0.001
About 8 hours	4809	929 (19.32%)	2046 (42.55%)	1189 (24.72%)	645 (13.41%)	
9Hoursor more	5618	1692(30.12%)	2819 (50.18%)	829 (14.76%)	278 (4.95%)	

2.2 Risk factors associated with myopia

In univariate analyses, myopia was associated with older age (17 or more years) compared with younger age (6 to 9 years; odds ratio [OR]=11.24; 95% CI 9.99-12.63; Table 2), but not associated with female versus male (OR=1.33; 95% CI 1.25-1.42), and marginally associated with maternal tertiary education versus primary education (OR=1.71; 95%CI 1.40-2.10). Myopia was associated with two versus no myopia parents (OR=1.88; 95%CI 1.69-2.10), and myopia was not associated with the hours of sports, and hours of watching TV or using computer per day in the highest level versus in the lowest level (OR=1.17, 0.86; 95%CI 1.07-1.27, 0.79-0.94, respectively). Myopia was associated with reading or writing distance and hours of studying per day in the highest level versus in the lowest level (OR=2.51, 3.06; 95%CI 2.21-2.84, 2.72-3.44), and associated with hours of sleep more than 9 hours versus less than 7 hours (OR=4.07; 95%CI 3.74-4.43). A final multivariate model was constructed with myopia as the outcome variable and age, gender, parental myopia, father's education, reading or writing distance, hours of sports per day, hours of watching TV or using computer per day, hours of studying per day, and hours of sleep as explanatory variables. Myopia did not remain associated with gender, hours of sports per day, hours of watching TV or using computer per day, and the association with hours of studying was marginally significant (OR=1.43; 95%CI 1.25-1.64 for more than 10h vs. less than 6h) in multivariate analyses.

2.3 Unadjusted and adjusted refraction changes by sleeping time

The prevalence rates of myopia in children with the lowest sleeping time span were 68.45%, 56.08% in the second highest sleeping time span, 34.80% in the highest sleeping time span. Myopia associated with sleeping time more than 9h vs. less than 7h (OR=3.37; 95%CI 3.07-3.70) after controlling for age, gender, parental myopia, father's education, reading or writing distance, hours of sports per day, hours of watching TV or using computer per day, hours of studying per day (Table 2).Myopia was also associated with unit increases in sleeping time (OR=1.95; 95%CI 1.86-2.04;P<0.001), after controlling for the same factors. Similar significant univariate (OR=2.05; 95%CI 1.96-2.13;P<0.001) and multivariate (OR=1.94; 95%CI 1.85-2.04;P<0.001) associations between myopia and sleeping time were found. The relationship between sleeping time and myopia remained significantly positive within each strata of hours of watching TV or using computer per day. There was no interaction between hours of studying or hours of sports per day and sleeping time. Moreover, there was no interaction between father's education or parental myopia and sleeping time.The multivariate adjusted mean refractive error for children with sleeping time in the highest span was -1.69 D compared with -1.29 D for children with sleeping time in the lowest span (P<0.001; Table 3). For every point increase in sleeping time, there is a 0.09 D shift in refraction toward less myopia values (P<0.001; Table 3).

The areas under the ROC curves (AUC) associated with univariate logistic predictive models are presented in Table 4. The variable of age has the largest AUC (0.72), and sleeping time, reading distance, and hours of studying are the next closest variables (0.65, 0.57, 0.57). The remainder activities had AUCs between 0.50 and 0.55.[11,12]

The R^2, or coefficient of multiple determinations, that estimate the proportion of variance in refraction explained in several models.[13] Explanatory variables were added to a baseline model (model 1) in a stepwise fashion, whereby the explanatory variables that explained the greatest variance in refraction were added first. The baseline model include age, gender, and parental myopia (R^2=0.155). Model 2 included the addition of sleeping time, the explanatory variable that explained the greatest variance in refractive error, in addition to the base model (R^2=0.157). Model 2 was statistically significant improvement in the explanation of variables for refractive error compared with the base model, model 1 (partial F test: P<0.001). Model 3 included reading or writing distance in addition to all the explanatory variables in model 2 (R^2=0.161), and model 4 included father's

Table 2. Risk factors associated with myopia

	n	Univariate OR for Myopia (95%CI)	P	Multivariate OR for Myopia (95%CI)	P
Age (y)					
6 to 9	3107	1 (referent)		1 (referent)	
10 to 13	4120	3.60(3.21, 4.02)	<0.001	4.05 (3.59, 4.58)	<0.001
14 to 16	4547	7.84 (7.01,8.77)	(trend)	7.87 (6.89, 8.98)	(trend)
17 or More	3542	10.87 (9.65, 12.24)		11.27 (9.74,13.05)	
Gender					
Male	7434	1 (referent)			
Female	7882	1.33(1.25 1.42)	<0.001	1.27(1.18 1.36)	
Number of parent with myopia					
0	9893	1 (referent)			
1	3883	1.53(1.42 1.65)	<0.001	1.91(1.75 2.10)	<0.001
2	1540	1.88(1.69 2.10)	(trend)	2.83(2.47 3.24)	(trend)
Father's education level					
Primary education	425	1 (referent)			
Secondary education	3969	1.16(0.94 1.43)	0.17	1.27(1.00 1.60)	0.044
Polytechnic education	4004	1.43(1.16 1.76)	<0.001	1.54(1.22 1.94)	<0.001
Tertiary education	6644	1.71(1.40 2.10)	(trend)	1.70(1.342.14)	(trend)
Reading or writing distance					
Greater than 33cm	1374	1 (referent)			
About 33cm	7280	1.67(1.48 1.89)	<0.001	1.39(1.21 1.60)	<0.001
Less than 33cm	6556	2.51(2.21 2.84)	(trend)	1.95(1.69 2.24)	(trend)
Hours of sports per day					
30 Min or less	4448	1 (referent)		1 (referent)	
30 Min to 1 hour	6990	1.15(1.06 1.24)		1.05(0.96 1.15)	0.181
1 Hour or more	3708	1.17(1.07 1.27)		0.97(0.88 1.08)	0.753
Hours of watching TV per day					
2 Hours or more	6400	1 (referent)			
1 to 2 Hours	5680	0.83(0.77 0.89)	<0.001	0.94(0.86 1.02)	0.453
1 Hour or less	2974	0.86(0.79 0.94)	<0.001	0.88(0.790.97)	0.473
Hours of studying per day					
10 Hours or more	3365	1 (referent)		1 (referent)	
8 to10 Hours	6457	1.30(1.20 1.42)	<0.001	1.14(1.04 1.26)	0.015
6 to 8 Hours	3265	2.37(2.15 2.62)	(trend)	1.39(1.241.56)	<0.001
6 Hours or less	2085	3.06(2.72 3.44)		1.43(1.251.64)	(trend)
Hours of sleep per day					
9 Hours or more	5675	1 (referent)			
About 8 hours	4859	2.39(2.21 2.59)	<0.001	2.12(1.94 2.31)	<0.001
7 Hours or less	4567	4.07(3.74 4.43)	(trend)	3.37(3.073.70)	<0.001

education in addition to all the explanatory variables in model 3 (R^2=0.164). Model 5 included studying time per day in addition to all the explanatory variables in model 4 (R^2=0.165), and model 6 included hours of watching TV or using computer per day in addition to all the explanatory variables in model 5 (R^2=0.166), and model 7 included hours of sports per day in addition to the explanatory variables in model 6 (R^2=0.166). The R^2 values for model 3 were significantly higher than those in model 2, and the R^2 values were also higher for model

Table 3. Unadjusted and Adjusted Mean Refraction by Sleeping Time

Sleeping Time	n	Refractive Error (D)			
		Unadjusted Mean (SD)	95%CI	Adjusted Mean (SD)	95%CI
9 Hours or more	5061	-0.76(1.82)	-0.81, -0.71	-1.29(0.03)	-1.36, -1.23
About 8 hours	4423	-1.57(3.23)	-1.67, -1.48	-1.49(0.02)	-1.54, -1.45
7 Hours or less	4208	-2.28(2.27)	-2.35, -2.21	-1.69(0.04)	-1.77,-1.62
P(trend)		<0.001		<0.001	
Regression model results					
Regression coefficient		-0.71		-0.09	
P(regression)		<0.001		<0.001	

Table 4. AUC associated with variables of risk factors for myopia

Variable	AUC	SE	95%CI
Age	0.72	0.01	0.71- 0.73
Parent's myopia	0.56	0.01	0.55- 0.56
Father's education	0.55	0.01	0.54- 0.55
Reading distance	0.57	0.01	0.56- 0.58
Hours of sleeping	0.65	0.01	0.64- 0.66
Hours of sports/ outdoor	0.52	0.01	0.51- 0.53
Hours of studying	0.57	0.01	0.56- 0.58
Hours of TV	0.5	0.01	0.49- 0.51

4 than model 3, model 5 than model 4, model 6 than model 5 (all partial F test: $P<0.001$), but the R^2 values for model 7 were similar to those in model 6 (partial F test: P=0.976).[14–16]

3 Discussion

As an important risk factor for myopia, sleeping time was often ignored in some prior studies,[17–26] maybe the sleeping time is enough for school-aged children in some countries, but which is not enough yet in China. Our data suggest that the mean hours of sleep is 9 hours per day for primary school students, 8 hours per day for middle school students, and 7 hours per day for high school students in Beijing city. Chinese children aged 6 to 18 years with less sleeping time in Beijing city were more likely to be myopia, after controlling for age, gender, parental myopia, father's education, reading or writing distance, hours of sports per day, hours of watching TV or using computer per day, and hours of studying per day. Our data suggest that sleeping time has an association with myopia independent of near work in Chinese school-aged students, though the mechanism underlying the sleeping time-myopia relationship is not well understood. An interesting observation is that myopia (SE at least -0.75 D) is not significantly associated with hours of watching TV or using computer, hours of studying, hours of sports per day after controlling for other con-founders, including sleeping time, however, remains associated with number of parent with myopia, reading or writing distance after controlling other factors, including sleeping time. The number of hours of sports(not include any outdoor leisure activities) was not a significant factor in the logistic models. Myopia was not associated with hours of sports less than 30 minutes versus greater than 1 hour per day after controlling for age, gender, parental myopia, father's education, reading or writing distance, hours of watching TV or using computer per day, hours of studying per day, and sleeping time per day (OR=0.97; 95%CI 0.88-1.08).This is similar to the results of Parssinen and Lyyra,[27] but is contrast with the results of Lisa and Loraine,[28] who evaluated factors associated with myopic progression in a survey from Orinda Longitudinal Study of Myopia subjects from 1989 to 2001. They assessed parental history of myopia, near work factors, and sports per week (include outdoor activities) to predict the future myopia and concluded that greater weekly participation in sports was associated with reduced odds of having myopia. Prior studies suggest that several hours of sports or outdoor activities per day are required for myopia protection, but only the hours of sports(without hours of outdoor activities) was collected in our study because it is difficult to record the hours of outdoor activities of the large number of participations. Likewise, there is no body of literature addressing the relation between sleeping time and myopia. A possible explanation about the effect of sleeping for myopia could be to re-

lieve ciliary muscle to be tired and prevents or alleviates the myopic progression. Confounding effects must also be considered. Myopia has been associated with other characteristic such as IQ[29–31] and personality.[32,33] Perhaps increased sleeping time can be a surrogate for more extroverted personality from psychological characteristics.There have been a few previously published reports of ambient lighting during sleep and the association of myopia, and concluded that night-time light exposure during infancy is not a major risk factor for myopia development in most population groups.[34]Maybe hours of sleep, ambient lighting during sleep, and quality of sleep should be considered all together to analysis the association between sleep and myopia. In assessing these results, it is possible that using a questionnaire asking the number of hours of the sleeping time per day may present difficulties. The questionnaire may not be the most appropriate information to target the amount of near work or other activities actually completely. The results may also be affected by deleting the missing data during data analysis, though the sample size is large. In conclusion, sleeping time per day may be associated with myopia, independent of near work factors in school-aged children. Sleeping time contributes to a greater variance in refraction compared with near work. Enough sleeping time will benefit to myopia for school-aged children.

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References

[1] Lin LL, Shih YF, Tsai CB, *et al.* Epidemiologic study of ocularrefraction among schoolchildren in Taiwan in 1995. *Optom VisSci*, 1999, **76**:275*C*281 https://doi.org/10.1097/00006324-199905000-00013

[2] Quek TP, Chua CG, Chong CS, *et al.* Prevalence of refractive errors in teenage high school students in Singapore. *Ophthalmic Physiol Opt*, 2004,**24**:47C55 http://dx.doi.org/10.1046/j.1475-1313.2003.00166.x

[3] Lam CS, Goldschmidt E, Edwards MH. Prevalence of myopia inlocal and international schools in Hong Kong.*Optom Vis Sci*,2004,**81**(5):317C223 http://dx.doi.org/10.1097/01.opx.0000134905.98403.18

[4] Saw SM,Katz J, Schein OD, *et al.* Epidemiology of myopia. *Epidemiol Rev*, 1996,**18**:175-187 http://dx.doi.org/10.1093/oxfordjournals.epirev.a017924

[5] Gwiazda J, Hyman L, Hussein M, *et al.* A randomized clinical trialof progressive addition lenses versus single vision lenses on theprogression of myopia in children. *Invest Ophthalmol Vis Sci*,2003, **44**(4):1492-1500 http://dx.doi.org/10.1167/iovs.02-0816

[6] Fulk GW, Cyert LA, Parker DE. A randomized trial of the effect ofsingle-vision vs. bifocal lenses on myopia progression in childrenwith esophoria. *Optom Vis Sci*, 2000, **77**(8):395-401

[7] Walline JJ, Jones LA, Mutti DO, *et al.* A randomized trial of theeffects of rigid contact lenses on myopia progression. *Arch Ophthalmol*, 2004,**122**(12):1760-1766 http://dx.doi.org/10.1001/archopht.122.12.1760

[8] Rudnicka AR, Steele CF, Crabb DP, *et al.* Repeatability, reproducibilityand intersession variability of the Allergan Humphreyultrasonic biometer. *Acta Ophthalmol* ,1992, **70**(3):327-334 http://dx.doi.org/10.1111/j.1755-3768.1992.tb08573.x

[9] Hyman L, Gwiazda J, Marsh-Tootle WL, *et al.* The Correction of Myopia Evaluation Trial(COMET): design and general baseline characteristics.*Control Clin Trials*, 2001 **22**(5):573-592 http://dx.doi.org/10.1016/S0197-2456(01)00156-8

[10] Stata Statistical Software: Release 7.0. College Station, TX: StataCorporation.; 2001

[11] Hanley JA, McNeil BJ. The meaning and use of the area under areceiver operating characteristic (ROC) curve. *Radiology*, 1982,**143**(1):29-36 http://dx.doi.org/10.1148/radiology.143.1.7063747

[12] Campbell G. Advances in statistical methodology for the evaluationof diagnostic and laboratory tests. *Stat Med*, 1994, **13**(5-7):499-508 http://dx.doi.org/10.1002/sim.4780130513

[13] Mutti DO, Mitchell GL, Moeschberger ML, *et al.* Parental myopia, near work, school achievement, and childrensrefractive error.*Invest Ophthalmol Vis Sci*, 2002, **43**(12):3633-3640 http://iovs.arvojournals.org/article.aspx?articleid=2162292

[14] Schmid KL, Wildsoet CF. Effects on the compensatory responsesto positive and negative lenses of intermittent lens wear and ciliarynerve section in chicks. *Vision Res*, 1996, **36**(7):1023-1036 http://dx.doi.org/10.1016/0042-6989(95)00191-3

[15] Rosner M, Belkin M. Intelligence, education, and myopia in males. *Arch Ophthalmol*,1987,**105**(11):1508-1511 http://dx.doi.org/10.1001/archopht.1987.01060110054030

[16] Teasdale TW, Fuchs J, Goldschmidt E. Degree of myopia in relationto intelligence and educational level.*Lancet*,1988, **2**(8624):1351-1354 http://dx.doi.org/10.1016/S0140-6736(88)90880-X

[17] Zadnik K, Satariano WA, Mutti DO, *et al.* The effectof parental history of myopia on childrens eye size.*JAMA*,1994, **271**(17):1323-1327 http://dx.doi.org/10.1167/iovs.06-1097

[18] Tan CSH , ChanYH, Wong TY, *et al.* Prevalence and risk factors for refractive errors and ocular biometry parameters in an elderly Asian population: the Singapore Longitudinal Aging Study (SLAS).*EYE*, 2011, **25**(10):1294-1301 https://doi.org/10.1038/eye.2011.144

[19] Konstantopoulos A,Yadegarfar G, et al. Near work, education, family history, and myopia in Greek conscripts. *EYE*, 2008, **22**(4):542-546
https://doi.org/10.1038/sj.eye.6702693

[20] Gwiazda J, Deng L, et al. Association of Education and Occupation with Myopia in COMET Parents. *Optom Vis Sci*,2011, **88**(9): 1045-1053
https://doi.org/10.1097/OPX.0b013e31822171ad

[21] Grosvenor T. Refractive state, intelligence test scores, and academicability. *Am J Optom Arch Am AcadOptom*, 1970, **47**(5):355-361
https://doi.org/10.1097/00006324-197005000-00003

[22] Douglas JW, Ross JM, Simpson HR. The ability and attainment ofshort-sighted pupils.*J R Statist Soc A* 1967, **130**(4):479-504
https://doi.org/10.2307/2982520

[23] Mutti DO, Mitchell GL, Moeschberger ML, Jones LA, ZadnikK.Parental myopia, near work, school achievement, and childrensrefractive error. *Invest Ophthalmol Vis Sci*, 2002,**43**(12):3633-3640
http://iovs.arvojournals.org/article.aspx?articleid=2162292

[24] Wensor M, McCarty CA, Taylor HR. Prevalence and risk factors of myopia in Victoria, Australia. *Arch Ophthal*, 1999, **117**(5):658-663
https://doi.org/10.1001/archopht.117.5.658

[25] Saw SM, Hong CY, ChiaKS, Stone RA, Tan D. Nearwork andmyopia in young children. *Lancet*, 2001,**357**(9253):390
https://doi.org/10.1016/S0140-6736(05)71520-8

[26] Saw SM, Chua WH, Hong CY, et al. Nearwork in early onsetmyopia.*Invest Ophthalmol Vis Sci*, 2002, **43**(2):332-339
http://iovs.arvojournals.org/article.aspx?articleid=2162578

[27] Parssinen O, Lyyra AL. Myopia and myopic progression amongschoolchildren: a three-year follow-up study.*Invest OphthalmolVis Sci*, 1993,**34**(9):2794-2802
http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933175/

[28] LisaA.Jones, Loraine T, et al. Parental history of myopia, sports and outdoor activities, and future myopia.*Invest Ophthalmol Vis Sci*,2007, **48**(8):3524-3532
https://doi.org/10.1167/iovs.06-1118

[29] Schmid KL, Wildsoet CF. Effects on the compensatory responsesto positive and negative lenses of intermittent lens wear and ciliarynerve section in chicks. *Vision Res*, 1996, **36**(7):1023-1036
http://dx.doi.org/10.1016/0042-6989(95)00191-3

[30] Rosner M, Belkin M. Intelligence, education, and myopia in males. *Arch Ophthalmol*,1987,**105**(11):1508-1511
http://dx.doi.org/10.1001/archopht.1987.01060110054030

[31] Teasdale TW, Fuchs J, Goldschmidt E. Degree of myopia in relation to intelligence and educational level. *Lancet*,1988, **2**(8624):1351-1354
http://dx.doi.org/10.1016/S0140-6736(88)90880-X

[32] Beedle SL, Young FA. Values, personality, physical characteristics,and refractive error. *Am J OptomPhysiol Opt*, 1976, **53**(11):735-739
https://www.ncbi.nlm.nih.gov/pubmed/998715

[33] Gawron VJ. Ocular accommodation, personality, and autonomicbalance. *Am J OptomPhysiol Opt*, 1983, **60**(7):630-639
https://doi.org/10.1097/00006324-198307000-00011

[34] Guggenheim JA, Hill C, Yam TF. Myopia, genetics, and ambient lighting at night in a UK sample. *Brit J Opt*,2003,**87**(5): 580-582
http://dx.doi.org/10.1136/bjo.87.5.580

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RESEARCH ARTICLE

Toxic metals and autism

Giulio Filippo Tarro[1*] Renato Minguzzi[2] Franco Verzella[3]

Abstract: Toxic metals (MT) are the major pollution to the land (37.3% in Europe), which are produced mainly by industrial activities, entering a far part of our life cycle, through the skin, breathing, ingestion of foods and water. Especially children in the first three years of life are biologically more vulnerable. The spreading epidemic of Autism and developmental disorders, that has been recorded in industrialized countries during the last 20 years is a sensitive thermometer of the pollution. Tests were carried out on 20 MT in a group of 73 subjects diagnosed with autism, the mean age of 8 years old. All 73 patients were over threshold for at least one metal. Seven metals (mercury, lead, antimony, tin, arsenic, thallium, cesium) had values over 50% (thirty-seven patients). The 26% (nineteen patients) exceeded the threshold for ten or more metals. Gadolinium 1521.21 exceeds threshold times. Mercury (x 379.95), tin (x 118), lead (x 108): presenting the coefficients more elevated. The average values exceed the threshold a lot: Mercury (x 28.14), Lead (x 10.56), Tin (x 9.98). With age increases the threshold exceeded for a lower number of metals. The analysis shows that gender has no significant difference, possibly results from the reduced number of females (18%). A future comparison research remains. We will explore the detoxification capacity difference between two genders affected by autism.

Keywords: Toxic metals, Autism

Consistent scientific research in the past thirty years shows progressive environmental toxicity signals,[1–3] which affect and threaten life on the planet, such as the decrease in the number and variety of plant and animal species and the spread of chronic degenerative diseases in a globalized society. Over 40 years, autism has risen from an incidence of 1 in 2,500 (1975) to 1 in 68, while learning and developmental disorders affecting 1 in 6 children (Center for Disease Control: Surveillance Summaries / April 1, 2016/65 (3); 1-23). The level of toxicity that characterizes every aspect of our daily lives systematically exceeds the analytical limits of the most sophisticated technologies available to us for five basic reasons:

1) The astronomical number of pollutants produced by humans and released to the environment: more than 126 million new substances, organic and inorganic, produced by the industry since 1957; currently, average 12,000 new substances are added each day (www.CAS Registry; home page).

2) The incomplete certification relating to health risks.[4]

3) The inability to evaluate the detoxifying power of the individual, against specific toxins.[5]

4) The inability to assess over time the biological action summation exerted by different toxic substances in the individual.[6,7]

5) The lack of a practice dedicated to the detoxification of metals by the Public Health. AAA/BBB

Environmental pollution, food toxicity and drug addiction are largely characterized by the presence of heavy metals (MP).[8,9] The Heavy Metals have higher atomic numbers than iron, a density greater than 5 g/cm^3, and are a common cause of pollution and toxicity in biological organisms.[10] The formation of salts behave as cations. They tend to form complex bonds and show great affinity for the sulfides in different oxidation states depending on the pH, they bind proteins in the blood, and then distributed to the different compartments depending on their properties. MP essential at very low doses become toxic at high doses: chromium, manganese, iron, cobalt, copper and zinc.[11] Metals toxic anyway (MT) include: beryllium, aluminum, antimony, thallium, tin, uranium, tungsten, nickel, arsenic, cadmium, mercury, lead, uranium, gadolinium.[12] Sources Man-made include: electrical installations (Hg, As, Tl),

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*Correspondence to: Giulio Filippo Tarro, Committee on Biotechnologies and Virus-Sphere World Academy Biomedical Technologies, UNESCO, Italy; Email: giuliotarro@gmail.com

[2] Comune di Bologna, 40129 Bologna, Italy

[3] Medicina Funzionale, 40069 Zola Pedrosa, Italy

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vehicles (Cd), diesel engines (Ni), metallurgical industries and foundries (Pb, As, Cu, Al, Co, Zn, Fe), agriculture (Cu, As , Al, Zn), of waste disposal systems (Hg, Cd, Pb, as) paints (Hg, Cd, Pb), insecticides, rodenticides, fungicides (Hg, as, Cd, Ti), cookware (Al, Cu), wood protection products (As, Cu), disinfectants (Cu, Hg, Ag), vaccines (Hg, Al), dental materials (Hg, Al, Au, Ag, Ni), contrast medium for the resonance nuclear magnetic (Gd).[13] Since 2003, in EU countries it is applied a protocol for monitoring air emissions of cadmium, lead and mercury and a detailed report of the situation was published in 2007 by a task force of experts selected by European governments, which describes the technologies as available to control the emission of these metals, pointing to plans, strategies and policies to curb emissions within agreed limits. The emissions resulting from industrial activities, traffic of vehicles and from energy production. Between 1990 and 2003, emissions to air in Europe decreased on average by 50%. However, this significant reduction is not able to counteract the continuous and progressive accumulation in soils, where the MT constitute the main pollutant (37.3%).[14]

The toxicological research has recently demonstrated the extreme danger of chronic low-dose exposure, because the MT will slowly accumulate in our tissues, which do not participate in any biological functional activity and their action is to block the many complex active enzyme, with cumulative effect and mutual reinforcement over time.[15] In particular, the MT inhibit enzymes and molecules which provide antioxidant activity, by blocking the sulfhydryl groups (glutathione, metallothioneins, cysteine, alpha-lipoic acid) with a consequent increase of oxidative stress, alter the ionic homeostasis (calcium, sodium, potassium) , mitochondrial function, in a selective manner by interfering with the Krebs cycle and with the methylation- Sulfoxidation circuit.[16] It should be noted that by the latter circuit it depends on the synthesis of creatine (for energy charging processes), neuromediators, melatonin, the blockade of histamine (allergic reactions), the modulation of DNA (protein synthesis), synthesis myelin (nerve impulse conduction) and finally the synthesis of cysteine and glutathione (antioxidant and detoxifying activity). In other words, the MT enter our metabolism and profoundly alter, so the formulation of security lapses is always purely conventional.[17,18] In the brain, liver, kidney, immune system, bones, lungs, MT create localized inflammatory reactions and generalized reactions with toxic genesis and / or immune, predisposing us to a long series of disorders and diseases.[19,20]

The absorption of MT at the gastrointestinal level and in lung level varies depending on the host condition, the composition (inorganic or organic) and the state of valence (elementary or ionic) of the metal.[21] The blood is the primary means of transport of the metals according kinetics dependent on: diffusibility, the form of bonding, speed of processing and bio-availability of intracellular ligands.[22] The main streets of metal excretion are renal and biliary-intestinal. Minimally elimination can happen for salivation, sweating, exhalation, breast, skin exfoliation and loss of hair and nails.[23,24] Some organs (bone, brain, liver and kidney) sequester certain metals in relatively high concentration and chronically for years.

The absorption of labor origin takes place mainly through the respiratory route; the digestive tract is secondary, and generally linked to poor hygiene measures or accidents.[25] The percutaneous absorption has been demonstrated for the hexavalent chromium and certain organo-metallic compounds, such as tetraethyl lead and methylmercury.[26] The distribution of metals in the organism can occur in free form or bound to plasma proteins, such as albumin, transferrin, metallothionein, ceruloplasmin, to reach the critical concentration, at which there are early toxic effects.[27] Each metal is deposited in a specific way in different organs and tissues based on selective affinity. In general, the metals do not undergo metabolic processes, except that the organometallic forms, such as alkyl lead and the organo-mercurials.

Autism occurs between the first and the third year, children in 90% of cases are free of genetic diseases. but frequent polymorphisms (SNPs) that affect oxidative stress (GSTT1, GSTM1, SOD 2), and the detoxifying capacity (CYP2D6, CYP2C9, CYP2C19, NAT 2).[28,29] Clinically, this syndrome multifactorial and multisystemic, appears with a slowing of cognitive behavioral development (isolation, indifference, loss of contact with peers and family members) regression of the word, self behaviors and hetero aggressive and a long line of organic disorders, affecting intestinal function, immune and energy metabolism.[30] Since 1995 it is stated in the international arena the multidisciplinary approach for the prevention and treatment of developmental disorders (Defeat Autism Now, DAN!), Which made it possible to investigate the molecular biological and clinical aspects of this syndrome and to start integrated programs and personalized therapy and rehabilitation.[31,32] The research and clinical practice that have resulted in multidisciplinary autistic child represented a ”successful model”, which promoted new diagnostic and therapeutic acquisitions to numerous systemic multi adult chronic diseases.

1 Materials and methods

From 2010 to 2016, 73 patients, mainly from central and northern Italy, with a diagnosis of autism, including 13 females (18%) and 60 males (82%), the average age of 8 years (2 to 23 years old), were subjected to a test for the analysis of toxic metals. The test involves the administration of an oral powder DMSA (meso-2-3- dimercaptosuccinic acid) <30 mg/kg of body weight, in a single intake, and in the collection of urine of the next six hours, the end of which is extracted to be as the urine sample, which is analyzed in the laboratory. The dosage of toxic metals is read in micrograms/gram of creatinine. The beds metals include lead (Pb), mercury (Hg), aluminum (Al), antimony (Sb), arsenic (As), barium (Ba), bismuth (Bi), cadmium (Cd), cesium (Cs) gadolinium (Gd), gallium (Ga), nickel (Ni), niobium (Nb), platinum (Pt), rubidium (Rb), tellurium (Tl), thorium (Th), tin (Sn), tungsten (W), uranium (U).

The DMSA is a water soluble molecule, such chelating action, with its two sulfhydryl groups (SH) manifests a great affinity for mercury and lead, cadmium, arsenic, tin, thallium, antimony, uranium and nickel, the lower the affinity with aluminum. It increases the excretion of potassium and chromium. For oral absorption, approximately 20% and the highest values are found in the circulation after 2 to 4 hours, excretion occurs mainly via the urine. In 1991, due to its low toxicity, DMSA has been approved by the FDA (Food and Drug Administration, USA) for the treatment of pediatric poisoning Lead from 1 year old.

2 Results

The results are presented through a series of tables and charts(Table 1,2,3,4,5,6; Figure 1,2,3,4).

1. Number of metal for patients: All 73 patients are suprathreshold for at least one metal; Mercury (95.89%) and lead (94.52%) are suprathreshold for the higher number of patients; Seven metals: mercury, lead, antimony, tin, arsenic, thallium, cesium suprathreshold values present in over 50% of patients (37 patients); Three metals are suprathreshold in over 80% of patients: Hg (95.89%); Pb (94.52%); Sb 83.56%); The average theoretical value for the metal suprathreshold patients is equal to 31% (23 patients); Thorium and niobium involving only one patient; No detectable: thorium (98.63%), bismuth (97.26%), niobium (91.78%).

2. Number of patient metals: Nineteen patients (26%) below the threshold for 10 or more metals; The patient 71 exceeds the threshold for 14 metals; The patient 46 exceeds the threshold for only two metals (Hg and U); The theoretical mean value is 38.3%, equivalent to 8 metals above for patient threshold.

3. Maximum Value / Value Threshold: Gadolinium exceeds the threshold of 1521.21 times; Hg (x379.95), Sn (x118), Pb (x108); Thorium exceeds the threshold of 1.67 times and has the lowest coefficient; Excluding the Gadolinium, the average of the maximum values exceeds the 42% threshold.

4. Medium / Threshold value: The average value of Gadolinium is 254.98 times higher than the threshold; The highest average values: Hg (x28.14), Pb (x10.56), Sn (x9.98); The average theoretical value for the 19 metals is 4 times higher than the threshold; The lowest coefficient is observed for the Cadmium, which is lower than the threshold.

It is a statistical model which is estimated to relate the number of metals that exceed the threshold with the age of patients. It appears to be an inverse relationship between the two variables, ie with increasing age the threshold is exceeded for a lower number of metals. This statistical model (Poisson model) is having a very good fit to the data (P value = 0.9038). The coefficient for the years made variable = 0.2157, P value = 0.031.

The analysis in relation to the gender did not produce any meaningful result, possibly also in relation to the small number of females.

The correlations between pairs of metals have a double interest: environmental and metabolic.

The Table 1 shows the associations between metals, which were statistically more significant.

Table 1. The associations between metals

Associated metals	r value[1]	P value
Bi Th	r=0.6922	p=0.0000**
Rb Tl	r=0.6503	p=0.0000**
Rb Cs	r=0.5588	p=0.0000**
Cs Tl	r=0.5554	p=0.0000**
Sb Sn	r=0.4812	p=0.0000**
Al Ba	r=0.4697	p=0.0000**
Pb Tl	r=0.4138	p=0.0003**
Sb Cd	r=0.3866	p=0.0007**
Hg Sn	r=0.3806	p=0.0009**
Cd Sn	r=0.3783	p=0.0010**

Note:**P<0.001 *P<0.05

The Spearman r value also allows to work on very low numerosity, as in the case of the correlation between Bi and Th, with very few detectable observations.The corre-

lations between the seven metals that are suprathreshold in over 50% of patients, include in descending order for metal couple:

- •Pb con: Tl, As, Hg, Cs.
- •Hg con: Sn, Al, As.
- •Sb con: Sn, Cd, As, Ni.
- •As con: Cs, Cd, Sn, Tl, Ni.
- •Cs con: Tl.

The pervasive developmental disorder is a heterogeneous group of neurodevelopmental conditions that are manifested at an early age, characterized by difficulties in social interaction and communication and the presence of restricted and repetitive behaviors and interests. These disorders debut in the early years of life, but they involve the whole mental development of the individual. The terminology used by the new diagnostic classification of the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-S) (American Psychiatric Association, 2013) refers to a dimensional view of disease that appears at the ideal moment to represent the continuity between autism and other disorders included in the same category. According to this perspective, the symptoms of Autism Spectrum Disorder would represent the final extreme, with pathological significance, of a continuum of difficulties which may also be highlighted within the general population.

The most recent interpretations attribute a fundamental role to autism in neurophysiological and genetic factors. This interpretive approach has been gradually replacing the initial psychodynamic and environmental hypotheses, mainly incurred by the authors to psychodynamic.

Compared to the etiology of autism, the theory commonly accepted today is that genetic and environmental elements act in the early stages of child development, during pregnancy, or during the first years of life. The current hypothesis is that autism are involved no fewer than three and no more fifteen to twenty genes. Each of these acts as a risk factor, which is due to the onset of the disease, unless there are other risk factors (genetic or environmental, favoring expression of genes ”sick”). According to this theory, in the general population there exist many normal subjects, carriers of genes predisposing to autism, who have not developed Autism, because there have been no other ”precipitating factors”.

The first evidence of a genetic basis of autism comes from the observation that identical twins have a much higher chance (from 36% to 90% according to various studies) of disease recurrence compared to dizygotic twins. Except for a minority of cases (less than 10%), in which autism was associated with chromosomal abnormalities or diseases in Mendelian transmission, for the remaining 90% of cases the most likely pattern of inheritance is not what monogenic, but a multilocus model, where multiple genes contribute to predisposition to the disorder. The complexity of the picture, adding the influence of environmental factors. Among the biochemical factors which appear to be mainly involved in the genesis of autism are the dopaminergic, serotonergic and noradrenergic; glial protein and ganglioside; brain metabolism (Ciaccio et al., Conference A.G.S.A.S.2003). The alteration of these systems leads to an alteration of neuromodulators, which leads to an alteration of neurotransmission. Among the neuromodulators involved is dopamine, serotonin, the gaba, glutamate, glycine. The dopamine system is invoked in having a role in autism because functions such as perception, attention, etc., which are regulated by dopamine, are compromised in individuals with autism; Furthermore, because dopamine agonists, such as amphetamines, aggravate the symptoms; Finally, because neuroleptic drugs with a competitive mechanism on specific receptors for dopamine, causing an improvement in the symptomatology. Instead, Lambiase (2004) states that a deficiency of serotonin in the frontal lobes may be related to impulsivity, and obsessive-compulsive symptoms may be related to a deficiency of serotonin in the basal ganglia.

On the relationship between serotonin and autism it is based on the theory of De Long (1999). This theory assumes two types of autism: 1. The first is characterized by an early brain damage, usually of the temporal lobes, predominantly of the side, which prevents the achievement of the basic semantic structures of language, social skills and intentional activities organized. These children can not build a structure of meaning and are usually low-functioning. In this case of autism with bilateral temporal sclerosis post epileptic, those of herpes simplex encephalitis, infantile spasms, tuberous sclerosis with thunderstorms tubers, cases of congenital rubella, etc.

The second group is not associated with brain damage. This would be the most common idiopathic form and not accompanied by neurological signs or alterations of any kind to the instrumental investigations. Usually, it has a family-based, or genetic roots. Initially, it begins with phenomena of regression in the second year of life, there is some language development and cognitive activities with some normal functions islands, while the affective symptoms are prominent. The prognosis would be better than the first group.

Other studies have been conducted in neurobiology and showed the existence of deficits at the level of the limbic system, cerebellum, hippocampus, amygdala, frontal lobe and cerebellum.

Recent studies have focused on the role of mirror neurons. Between the 80s and 90sWelsh and Rizzolatti coli.discovered the existence of mirror neurons in monkeys. These neurons are activated in the moment in which the individual performs an action or sees someone else perform an action allowing the understanding of the action or the "ability to recognize that an individual is performing an action, this action to differentiate from another similar to it, and to use this information in order to act in such a way appropriate "(Welsh, 1996, p.606). In 1995 Fogassi, Welsh et al., we demonstrated the presence in humans. These neurons are involved not only in the moment in which an individual observes an action implemented by another person but also when observing the expression of emotion.

Again the data are controversial. The research that questions the report is conducted by a group of researchers at New York University (2010) who published a paper in Neuron in 2010. In the paper they have refuted the hypothesis of a link with autism-mirror neurons demonstrating an experiment that autistic people do not show differences compared to the control group.

Today we can say that the causes of autism, despite the proliferation of various theories about them, are unknown. I think it's anachronistic reference to the work of Wakefield because it is well established that there is no correlation between the trivalent vaccine and autism. In fact in the journal Journal of the American Medical Association (JAMA): April 21, 2015-313 (15) 1534-40, the MMR (measles, rubella, anti, anti mumps) was not found associated with an increased risk of the disorder autism spectrum, after a study of 95,000 children with autistic siblings more.

The conclusion is therefore to be found in the epidemiology of autism spectrum disorders when it can be stated that: the pathologies autism spectrum represent an example of multifactorial disease, ie a situation of disease that when it comes to producing a genetic predisposition meets with noxious stimuli which may be of chemical nature, a physical nature, of immunologic origin or other origin, for example infectious.

Figure 2 shows: Seven metals are suprathreshold in 20% of patients: Ni (17.81); Ga (8.22); Cd (5.48); Gd (4.11); Bi (2.74); Nb 1.37); Th (1.37); Fourteen metals are suprathreshold in 50% of patients: Cs (53.42); Rb (46.58); W (43.84); At (35.62); Pt (30.14); U (26.03); Ba (23.29); Ni (17.81); Ga (8.22); Cd (5.48); Gd (4.11); Bi (2.74); Nb 1.37); Th (1.37); Seven metals are suprathreshold in over 50% of patients: Hg (95.89); Pb (94.52); Sb 83.56); Sn 79.45; As 57.53; Tl 54.79; Cs 53.42); Three metals are suprathreshold in over 80% of patients: Hg (95.89); Pb (94.52); Sb 83.56).

Table 2. Percentage of patients above the threshold for metal

Metal	Patients above threshold
Pb	94.52%
Hg	95.89%
Al	35.62%
Sb	83.56%
As	57.53%
Ba	23.29%
Bi	2.74%
Cd	5.48%
Cs	53.42%
Gd	4.11%
Ga	8.22%
Ni	17.81%
Nb	1.37%
Pt	30.14%
Rb	46.58%
Tl	54.79%
Th	1.37%
Sn	79.45%
W	43.84%
U	26.03%

3 Conclusion

MT is the major pollutant to the environment we live, which are the result of industrial and market activities. MT affect every aspect of our daily lives, as a permanent tax on health, starting from conception. Thermometer sensitive for this condition is the child population, with particular regard to the first three years, in relation to the fragility, complexity, dynamism, that characterize this stage of development. MT and developmental disorders are two antibiological sensitive marker of the quality of the environment in which we live. In Italy and Europe health care is long overdue on both fronts. The MT is treated from a few dozen "alternative" doctors in private practice and autistic children under the care of a Neuropsychiatry, pronouncing the verdict incurable and simultaneously denies the multidisciplinary dialogue with the biological person-centered medicine. The current trend in the epidemic of autism (1 child in 50) and developmental disorders (1 in 6 children) is an absolute alarm to our species, when the statistical confirmation projection that over 30 years the autism affect half of the child population. Toxic Metals source ia-

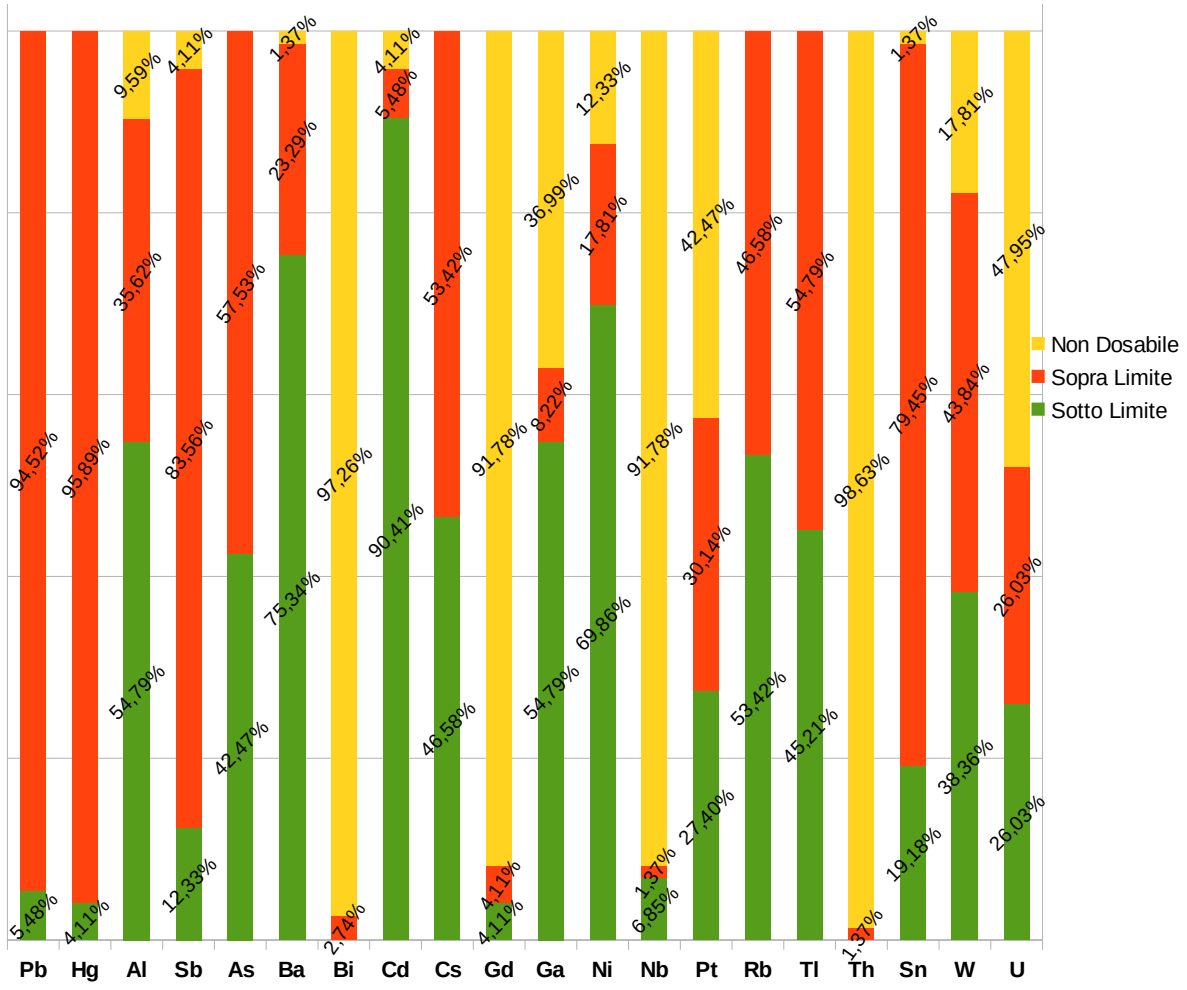

Figure 1. Records for each metal, the percentage of patients

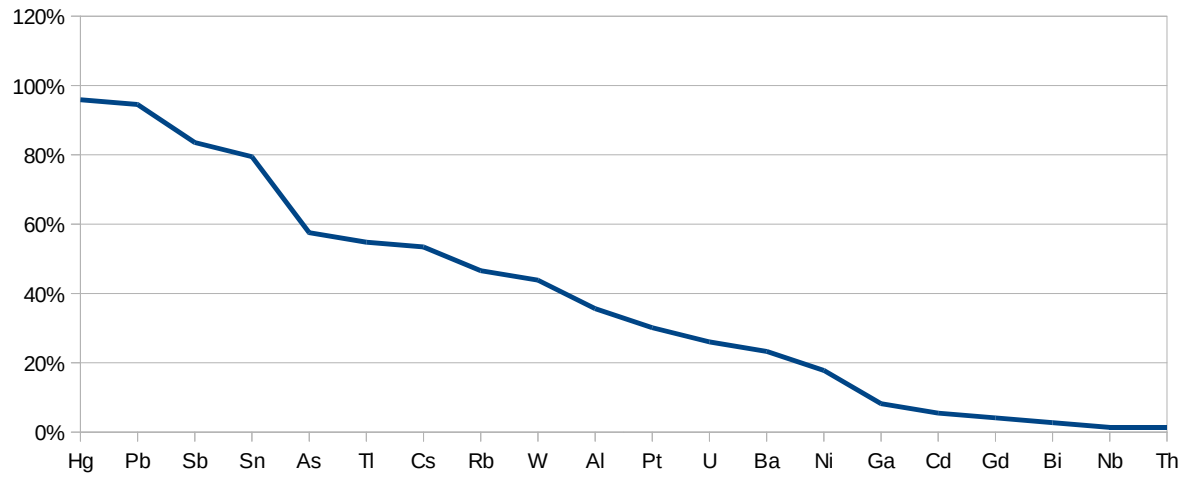

Figure 2. Percentage of patients suprathreshold for each metal

trogenic include vaccines (ethyl mercury and aluminum) and dental amalgams (mercury, silver and tin), affecting a large percentage of the population over age 35 and are properly removed in a narrow minority of cases from a

Table 3. Percentage of metals above for patient threshold

Case	Suprathreshold metals	Case	Suprathreshold metals
Patient 1	30%	Patient 38	55%
Patient 2	40%	Patient 39	30%
Patient 3	15%	Patient 40	55%
Patient 4	45%	Patient 41	55%
Patient 5	35%	Patient 42	40%
Patient 6	45%	Patient 43	45%
Patient 7	55%	Patient 44	20%
Patient 8	30%	Patient 45	35%
Patient 9	35%	Patient 46	10%
Patient 10	50%	Patient 47	45%
Patient 11	35%	Patient 48	45%
Patient 12	20%	Patient 49	45%
Patient 13	40%	Patient 50	15%
Patient 14	30%	Patient 51	30%
Patient 15	50%	Patient 52	35%
Patient 16	55%	Patient 53	25%
Patient 17	25%	Patient 54	20%
Patient 18	35%	Patient 55	45%
Patient 19	40%	Patient 56	60%
Patient 20	30%	Patient 57	55%
Patient 21	25%	Patient 58	35%
Patient 22	50%	Patient 59	35%
Patient 23	50%	Patient 60	50%
Patient 24	60%	Patient 61	30%
Patient 25	25%	Patient 62	20%
Patient 26	50%	Patient 63	40%
Patient 27	25%	Patient 64	45%
Patient 28	40%	Patient 65	25%
Patient 29	30%	Patient 66	45%
Patient 30	50%	Patient 67	45%
Patient 31	30%	Patient 68	50%
Patient 32	40%	Patient 69	30%
Patient 33	60%	Patient 70	30%
Patient 34	25%	Patient 71	70%
Patient 35	35%	Patient 72	45%
Patient 36	30%	Patient 73	50%
Patient 37	20%		

Note: All patients appear to be above the threshold for at least a metal; 19 patients (26%) exceeded the threshold for 10 or more metals; The patient 71 exceeds the threshold for 14 metals; The patient 46 exceeds the threshold for only two metals (Hg and U); The theoretical mean value is 38.3%, equivalent to 8 metals above for patient threshold.

Table 4. The maximum value and times exceeds the threshold

Metal	Max value	Times (the max value exceeds threshold)
Pb	151.200	108.000
Hg	832.080	379.950
Al	629.200	28.220
Sb	6.814	45.730
As	700.000	14.000
Ba	57.900	8.640
Bi	9.620	4.220
Cd	3.810	5.950
Cs	44.800	4.270
Gd	28.903	1521.210
Ga	0.081	2.890
Ni	16.740	4.310
Nb	0.303	3.610
Pt	0.684	20.730
Rb	11.013	4.870
Tl	3.776	12.670
Th	6.991	1.670
Sn	240.730	118.000
W	3.304	15.660
U	0.167	6.420

Note: The gadolinium exceeds the threshold of 1521.21 times; Excluding gadolinium, the average value exceeds the 42% threshold; Hg (x379.95), Sn (x118); Pb (x108): these are the metals with the highest coefficients; The thorium exceeds the threshold of 1.67 times and has the lowest coefficient; Below the corresponding graph, in which we have excluded the gadolinium, because its insertion, with the exceptionality of the result, flattens the reliefs, as significant, the other metals.

Table 5. The relationship between metals and threshold

Metal	Average value	Times (the average value exceeds threshold)
Pb	14.786	10.56
Hg	61.624	28.14
Al	37.597	1.69
Sb	0.601	4.03
As	88.565	1.77
Ba	5.946	0.89
Bi	7.860	3.45
Cd	0.306	0.48
Cs	11.317	1.08
Gd	4.845	254.98
Ga	0.016	0.58
Ni	3.108	0.80
Nb	0.092	1.10
Pt	0.070	2.11
Rb	2.619	1.16
Tl	0.487	1.63
Th	6.991	1.67
Sn	20.353	9.98
W	0.396	1.88
U	0.044	1.68

Note: The average value of gadolinium is 254.98 times higher than the threshold; The highest average values: Hg (x28.14); Pb (x10.56); Sn (x9.98); The average theoretical value for the 19 metals is 4 times higher than the threshold; The lowest coefficient is observed for cadmium, which is lower than the threshold.

few dozen dentists. The gadolinium as a contrast agent for Magnetic Resonance Imaging, is deposited in tissues and its removal requires a custom chelation therapy protocol, which is systematically ignored by the Neurology and Neuroradiology and that no public institute now offers.

In conclusion, toxic metals and autism promote a new medical approach strategy. Not the diagnosis, but the patient is at the center of the investigation, as the only real evidence, that science and conscience are called to

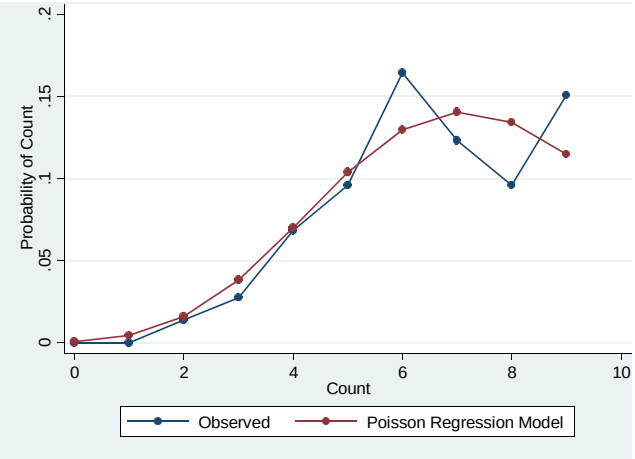

Figure 3. Poisson regression model

Note: Spearman test

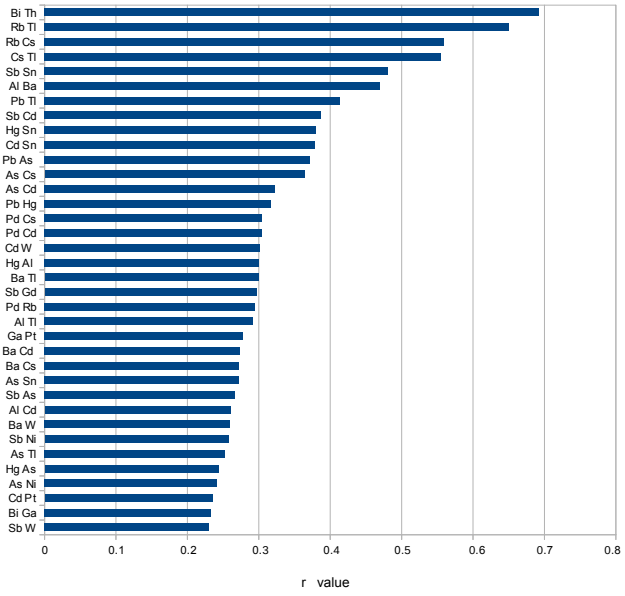

Figure 4. Correlation between metals

Note: 1. The statistical model is estimated to evaluate the number of metals that exceed the threshold with the age of patients. It appears to be an inverse relationship between the two variables. This statistical model (Poisson model) has a very good fit to the data (P value = 0.9038); 2. Coefficient for years is 0.2157; P value = 0.031; 3. The analysis in relation to the gender did not produce any meaningful result, possibly also in relation to the small number of females.

investigate, according to an authentic approach multidisciplinary.

References

[1] Anderlini P, Wu J, Gersten I, *et al.* Cyclophosphamide conditioning in patients with severe aplastic anaemia given unrelated marrow transplantation: a phase 1-2 dose de-escalation study. *Lancet Haematol* , 2015, **2**: 367−375 https://doi.org/10.1016/S2352-3026(15)00147-7

Table 6. Correlations between pairs of metals

Associated metals	r value[1]	P value
Pb Hg	r= 0.3169	p= 0.0063**
Pb As	r= 0.3719	p= 0.0012**
Pb Cd	r= 0.3042	p= 0.0089**
Pb Cs	r= 0.3042	p= 0.0089**
Pb Tl	r= 0.4138	p= 0.0003**
Hg Al	r= 0.3001	p= 0.0099**
Hg As	r= 0.2435	p= 0.0379*
Hg Sn	r= 0.3806	p= 0.0009**
Al Ba	r= 0.4697	p= 0.0000**
Al Cd	r= 0.2605	p= 0.0260*
Al Tl	r= 0.2923	p= 0.0121*
Sb As	r= 0.2662	p= 0.0228*
Sb Cd	r= 0.3866	p= 0.0007**
Sb Gd	r=-0.2968	p= 0.0108*
Sb Ni	r= 0.2576	p= 0.0278*
Sb Sn	r= 0.4812	p= 0.0000**
Sb W	r= 0.2307	p= 0.0497*
As Cd	r= 0.3223	p= 0.0054**
As Cs	r= 0.3639	p= 0.0016**
As Ni	r= 0.2412	p= 0.0398*
As Tl	r= 0.2522	p= 0.0314*
As Sn	r= 0.2725	p= 0.0197*
Ba Cd	r= 0.2738	p= 0.0191*
Ba Cs	r= 0.2725	p= 0.0197*
Ba Tl	r= 0.2995	p= 0.0101*
Ba W	r= 0.2593	p= 0.0268*
Bi Ga	r= 0.2329	p= 0.0474*
Bi Th	r= 0.6922	p= 0.0000**
Cd Pt	r= 0.2351	p= 0.0452*
Cd Sn	r= 0.3783	p= 0.0010**
Cd W	r= 0.3015	p= 0.0095**
Pd Rb	r= 0.2949	p= 0.0113*
Cs Tl	r= 0.5554	p= 0.0000**
Ga Pt	r= 0.2774	p= 0.0175*
Rb Cs	r= 0.5588	p= 0.0000**
Rb Tl	r= 0.6503	p= 0.0000**

Note: 1. Spearman test; 2. $^{**}P<0.001$ $^{*}P<0.05$

[2] Navajas E V, Krema H, Hammoudi D S, *et al.* Retinal toxicity of high-dose hydroxychloroquine in patients with

chronic graft-versus-host disease. *Can J Ophthalmol* , 2016, **50**: 442−450
https://doi.org/10.1016/j.jcjo.2015.08.003

[3] Eaton S A, Jayasooriah N, Buckland M E, *et al.* Roll over Weismann: extracellular vesicles in the transgenerational transmission of environmental effects. *Epigenomics*, 2015, **7**: 1165−1171
https://doi.org/10.2217/epi.15.58

[4] Howe P L, Reichelt-Brushett A J, Clark M W, *et al.* Toxicity estimates for diuron and atrazine for the tropical marine cnidarian Exaiptasia pallida and in-hospite Symbiodinium spp. using PAM chlorophyll-a fluorometry. *J Photochem Photobiol B*, 2017, **171**: 125−132
https://doi.org/10.1016/j.jphotobiol.2017.05.006

[5] Di Cesare Mannelli L, Tenci B, Zanardelli M, *et al.* A alpha7 Nicotinic Receptor Promotes the Neuroprotective Functions of Astrocytes against Oxaliplatin Neurotoxicity. *Neural Plast* , 2015, **2015**: 396908
https://doi.org/10.1155/2015/396908

[6] de Souza J J, Abrahao W A, de Mello J W, *et al.* Geochemistry and spatial variability of metal(loid) concentrations in soils of the state of Minas Gerais, Brazil. *Sci Total Environ* , 2016, **505**: 338−349
https://doi.org/10.1016/j.scitotenv.2014.09.098

[7] Verma M. Toxicoepigenomics and cancer: implications for screening. *Methods Mol Biol* , 2015, **1238**: 355−367
https://doi.org/10.1007/978-1-4939-1804-1_19

[8] Lehmann H and Pabst J Y. Phytovigilance: A medical requirement and a legal obligation. *Ann Pharm Fr* , 2016, **74**: 49−60
https://doi.org/10.1016/j.pharma.2015.06.004

[9] Karila L, Megarbane B, Cottencin O, *et al.* Synthetic cathinones: a new public health problem. *Curr Neuropharmacol* , 2015, **13**: 12−20
https://doi.org/10.2174/1570159X13666141210224137

[10] Iwai C B and Noller B. Ecotoxicological assessment of diffuse pollution using biomonitoring tool for sustainable land use in Thailand. *J Environ Sci (China)*, 2010, **22**: 858−863
https://doi.org/10.1016/s1001-0742(09)60189-3

[11] Kochling J, Rott Y, Arndt S, *et al.* Prevention and synergistic control of Ph(+) ALL by a DNA vaccine and 6-mercaptopurine. *Vaccine* , 2012, **30**: 5949−5955
https://doi.org/10.1016/j.vaccine.2012.07.037

[12] Nyquist R A, Putzig C L and Leugers M A. *Handbook of Infrared and Raman Spectra of Inorganic Compounds and Organic Salts: Infrared Spectra* ,1996, Academic press.

[13] Meuser H. *Contaminated urban soils* , 2010. Springer Science & Business Media

[14] Joint W and Organization W H. *Health risks of heavy metals from long-range transboundary air pollution*, 2007.

[15] Mao G, Zhou Z, Chen Y, *et al.* Neurological Toxicity of Individual and Mixtures of Low Dose Arsenic, Mono and Di (n-butyl) Phthalates on Sub-Chronic Exposure to Mice. *Biol Trace Elem Res* , 2016, **170**: 183−193
https://doi.org/10.1007/s12011-015-0457-6

[16] Bukowska B. Hemoglobin adducts as biomarkers of human exposure to selected xenobiotics. *Postepy Hig Med Dosw (Online)*, 2015, **69**: 668−680
https://doi.org/10.5604/17322693.1156936

[17] Monin A, Baumann P S, Griffa A, *et al.* Glutathione deficit impairs myelin maturation: relevance for white matter integrity in schizophrenia patients. *Mol Psychiatry* , 2015, **20**: 827−838
https://doi.org/10.1038/mp.2014.88

[18] Ljubisavljevic S, Stojanovic I, Pavlovic R, *et al.* The reduced glutathione and S-nitrosothiols levels in acute phase of experimental demyelination–pathophysiological approach and possible clinical relevancy. *Neuroscience* , 2012, **219**: 175−182
https://doi.org/10.1016/j.neuroscience.2012.05.062

[19] Somma F, Castagnola R, Bollino D, *et al.* Oral inflammatory process and general health. Part 1: The focal infection and the oral inflammatory lesion.*Eur Rev Med Pharmacol Sci* , 2010,**14**: 1085−1095

[20] Gulati K, Banerjee B, Lall S B, *et al.* Effects of diesel exhaust, heavy metals and pesticides on various organ systems: possible mechanisms and strategies for prevention and treatment. *Indian J Exp Biol* , 2010, **48**: 710−721

[21] Grand A. Treatment of coronary insufficiency in diabetics: Part 2: acute coronary insufficiency *Ann Cardiol Angeiol (Paris)*, 1999, bf 48: 119−127

[22] Garg S, Pathak K, Philip A, *et al.* Osmotically regulated two-compartment asymmetric membrane capsules for simultaneous controlled release of anti-hypertensive drugs. *Sci Pharm* , 2012, **80**: 229−250
https://doi.org/10.1016/j.fct.2015.12.022

[23] Shin H W, Barletta B, Yoonessi L, *et al.* Quantification of Aerosol Hydrofluoroalkane HFA-134a Elimination in the Exhaled Human Breath Following Inhaled Corticosteroids Administration. *c Clin Transl Sci* , 2015,**8**: 445−450
https://doi.org/10.1111/cts.12305

[24] Scott H A, Latham J R, Callister R, *et al.* Acute exercise is associated with reduced exhaled nitric oxide in physically inactive adults with asthma. *Ann Allergy Asthma Immunol* , 2015,**114**: 470−479
https://doi.org/10.1016/j.anai.2015.04.002

[25] Garland T. Toxicologic disease of the digestive tract.*Vet Clin North Am Food Anim Pract* , 2000, **16**: 187−207

[26] Charalampous N, Kindou A, Vlastos D. A Multidisciplinary Assessment of River Surface Water Quality in Areas Heavily Influenced by Human Activities. *Arch Environ Contam Toxicol* , 2015, **69**: 208−222
https://doi.org/10.1007/s00244-015-0152-9

[27] Aschner M, Syversen T, Souza D O. Metallothioneins: mercury species-specific induction and their potential role in attenuating neurotoxicity. *Experimental Biology and Medicine* , 2006, **231**: 1468−1473
https://doi.org/10.1177/153537020623100904

[28] Aydos S E, Karadag A, Ozkan T. Association of MDR1 C3435T and C1236T single nucleotide polymorphisms with male factor infertility. *Genet Mol Res* , 2015, **14**: 6330−6339
https://doi.org/10.4238/2015.June.11.8

[29] Bag A, Jyala N S and Bag N. Cytochrome P450 1A1 genetic polymorphisms as cancer biomarkers. *Indian J Cancer* , 2015, **52**: 479−489
https://doi.org/10.4103/0019-509X.178380

[30] Grau-Roma L, Fraile L and Segales J. Recent advances in the epidemiology, diagnosis and control of diseases caused by porcine circovirus type 2. *Vet J* , 2011, **187**: 23−32 https://doi.org/10.1016/j.tvjl.2010.01.018

[31] Hinman R S, Delany C M, Campbell P K. Physical Therapists, Telephone Coaches, and Patients With Knee Osteoarthritis: Qualitative Study About Working Together to Promote Exercise Adherence. *Phys Ther* , 2016, **96**: 479−493 https://doi.org/10.2522/ptj.20150260

[32] Chiauzzi E, Rodarte C and DasMahapatra P. Patient-centered activity monitoring in the self-management of chronic health conditions. *BMC Med* , 2015, **13**: 77 https://doi.org/10.1186/s12916-015-0319-2