Contents

Abstract

Autism spectrum disorder (ASD) is a complex heterogeneous neurodevelopmental disorder. Macrocephaly frequency in ASD is higher than in typically developing peers and one of the most consistent findings. We performed a systematic review and meta-analysis of studies measuring head circumference in ASD children samples.

We identified 196 studies through searching strategy and selected 28 studies to include in the meta-analyses. We performed a meta-analysis from a total of 828 children (out of 5185 with ASD) founded with macrocephaly in those 28 studies. The percentage of macrocephaly in the ASD children sample was significantly higher than the expected to general population (95% confidence interval found for ASD children was [14.7, 21.2] *versus* 3%, respectively). This result supports macrocephaly as a potential biomarker of ASD with implications in future clinical research.

Keywords

Autism Spectrum Disorder, Autism, Macrocephaly, Head circumference

Introduction

Autism spectrum disorder (ASD) is a complex heterogeneous neurodevelopmental disorder characterized by deficits in social communication and social interaction, with repetitive and restrictive patterns of behaviour and interests. (1-4) It has an extremely variable intensity and combination of these features. The prevalence of ASD has increased significantly over the past decade (3,5), affecting about 1% of the population, with a male predominance. (4)

Although the accurate aetiology of ASD remains elusive (3,6) there is a strong genetic component (6) with environmental influences. Even though the symptoms of ASD are usually present in the first two years of life, the diagnosis is frequently made after the age of three. Methods to facilitate the early diagnosis of ASD are crucial, so these children can benefit from an early and intensive intervention. (5) Many researchers have attempted identify potential markers that serve as early signs, which can help to improve the understanding, diagnosis and treatment of ASD. (1,5,7-8)

Macrocephaly is one of the most consistent findings in ASD (1-5) and defined as a head circumference greater than 2 standard deviations above the mean for age and gender or greater than the 97^{th} percentile. Since Kanner's original paper in 1943 (5 of the 11 children had relatively large heads) (7) numerous studies indicate the presence of macrocephaly in children with ASD, with rates of approximately 20% (5,9) being higher than the expected value of 3%. However, results have been inconsistent, not only about the percentage of children with macrocephaly, but also about when it becomes noticeable. Most studies reported an average or even smaller head circumference at birth in the ASD children compared to the typically developing peers, followed by an accelerated growth in head circumference within the first 12 months of life. (5,8) The role of weight and height as a variable also remains unclear, some studies considering an association and others refer head circumference as an independent parameter. (1,9)

Since head circumference is correlated to the whole brain volume and weight (5) head growth is an indicator of brain growth. An increased head size in children with ASD is suggestive of early abnormal brain growth with age. (1,2,7)

It remains unclear if macrocephaly represents a different subtype of ASD. (1,7) Macrocephaly could be associated to an endophenotype pointing towards specific etiopathogenic factors, or it could be the tip of iceberg of a more general tendency toward increased head circumference. (1)

Our aim is to compile and synthesize the existing literature, by conducting a systematic review and meta-analysis to determine the prevalence of macrocephaly in children with ASD.

Methods

Data sources and literature search

A systematic review was undertaken based on the MOOSE guideline for review of observational studies. Publications were searched on MEDLINE, via PubMed, using the search string "autism AND ((macrocephaly) OR (head AND size) OR (head AND circumference) OR (megalencephaly) OR (cranial AND circumference))". No restrictions were placed on date of publication. Filters were used to restrict the search to studies published in English and including only children and adolescents (<18 years old). The search is updated to January 6, 2016.

Eligibility criteria

To be eligible, each study had to meet all of the following criteria:

1. Its participants were children (0 – 18 years old) with ASD diagnosis;
2. It indicated the numbers of children with ASD and macrocephaly, or it is possible to compute those numbers;
3. It defined macrocephaly as the head circumference being greater than 2 standard deviations above the mean for age and gender;
4. Its participants with macrocephaly have an idiopathic ASD;
5. It had to be published in English;
6. It included new results (e.g., thus excluding review articles, case reports and commentaries).

Study selection and Data extraction

The study selection was processed according to the following steps:

1. Publications were searched on MEDLINE, via PubMed;
2. The titles and abstracts retrieved were screened and assessed for eligibility, according to the criteria described above;
3. The remaining records were re-analysed based on the full article;
4. The final selected studies were included in the systematic review ad meta-analyses. For each selected study, six aspects were considered in order to group and analyse data: first author identifier, date of publication, age of the participants (median age, mean age ± SD or age range), gender of the participants, sample size and percentage of ASD children with macrocephaly.

Statistical analysis

MedCalc 12.7.2.0 was used to perform the meta-analysis of the data. The heterogeneity of the data was analysed using I^2 statistic and Cohen's Q test. A random effect model was then used to estimate a global effect measure for the proportion of children with macrocephaly.

Results

A total of 196 studies were identified through PubMed searching. The titles and abstracts of the 196 records were screened and assessed for eligibility, leading to the exclusion of 134 studies, due to lack of head circumference measurements, age of the participants falling outside of the range of 0 to 18 years, participants not having the diagnosis of autism spectrum disorder or macrocephaly not being idiopathic. Review articles, commentaries and animal model studies were also excluded (see Appendix 1). The remaining 62 articles were revaluated for eligibility according the criteria described above, being excluded 34 studies. There were selected 28 studies to include in the systematic review and meta-analyses (see Appendix 2). Figure 1 describes the different phases of the study selection. Information about the 28 references is detailed in the Table 1.

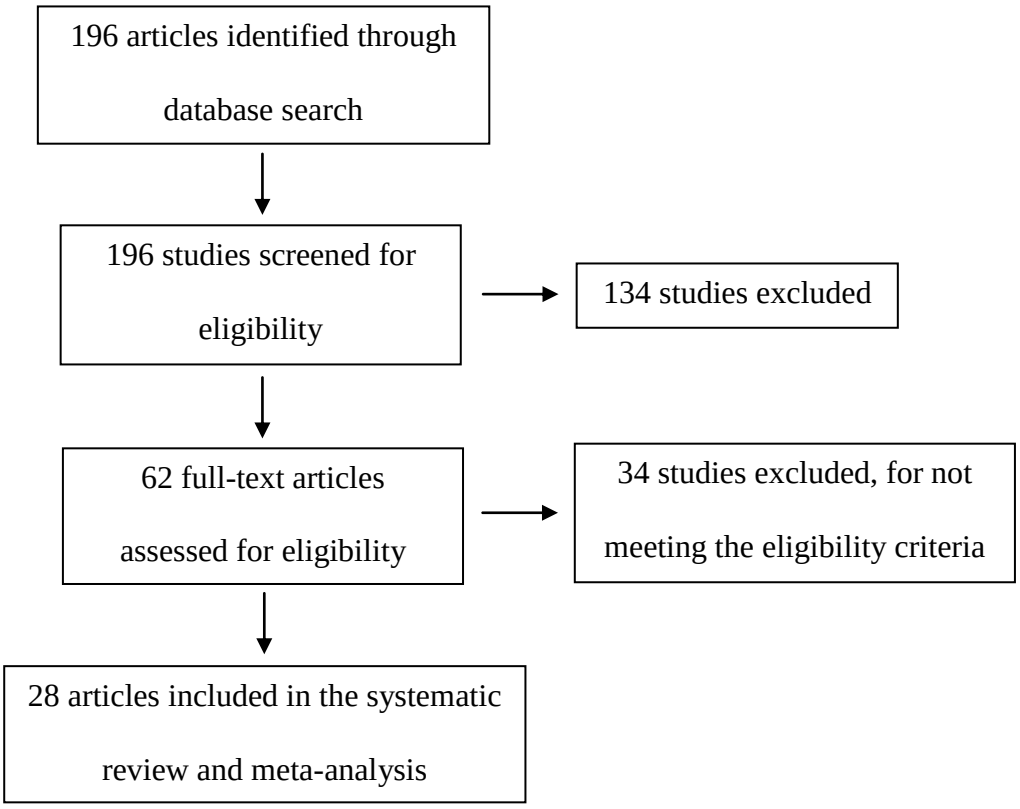

Figure 1: Flow-chart depicting the different phases of the systematic review

Table 1: studies included in the meta-analysis

Reference	Nº	Age (median or mean age ± SD or age range)	Gender	Sample size	Macrocephaly %
Bailey et al., 1995 (10)	1	2 - 16Y	M	21	42,8%
Davidovitch et al., 1995 (11)	2	47,68m	M; F (4,9:1)	148	18,2%
Woodhouse et al., 1996 (12)	3	2 - 16Y		37	29,7%
Lainhart et al., 1997 (13)	4	< 16Y	M ; F	60	11,7%
Rodier et al., 1997 (14)	5	6 – 14Y	M; F (4,6:1)	61	13,1%
Fombonne et al., 1999 (15)	6	2,2 – 16Y	M; F	109	18,3%
Ghaziuddin et al., 1999 (16)	7	10.9Y± 3.9	M	20	20%
Fidler et al., 2000 (17)	8	13,5Y ± 8,9	M; F (4,1:1)	41	12,2%
Miles et al., 2000 (18)	9	1 - 18Y	M; F	123	23,6%
Gillberg and Souza, 2002 (19)	10	1 – 16Y	M; F (18:1)	100	15%
Deutsch and Joseph, 2003 (20)	11	4 – 14Y	M; F (6:1)	63	14,3%
Riikonen et al., 2006 (21)	12	1 – 15Y	M; F (4:1)	25	0%
Lainhart et al., 2006 (22)	13	3 – 18Y	M; F	200	17%
Tripi et al., 2007 (23)	14	7Y	M; F (11:1)	24	20,8%
Sacco et al., 2007 (24)	15	3 – 16Y	M; F (6:1)	241	31,1%
Webb et al., 2007 (25)	16	3 – 4Y	M	28	21,4%
Van Daalen et al., 2007 (2)	17	4Y ± 8	M; F (4,9:1)	53	11,3%
White et al., 2009 (26)	18	7 – 12Y	M; F (11,3:1)	49	24,5%
Bigler et al., 2010 (27)	19	14,43Y	M	42	31%
Davidovitch et al., 2010 (28)	20	29,3m	M ; F (5,7:1)	317	4,4%
Froehlich et al., 2013 (7)	21	4 – 18Y	M; F (5,9:1)	255	21%
Morhardt et al., 2014 (29)	22	12 – 36m	M; F	59	32,2%
Grandgeorge et al., 2013 (5)	23	18m – 18Y	M; F (4,1:1)	422	5,7%
Chaste et al., 2013 (1)	24	8,9Y ± 3,5	M; F (6,6:1)	1889	14,7%
Ben-Itzchak et al., 2013 (4)	25	18m – 15Y	M; F (6,7:1)	659	18,1%
O'Reilly et al., 2013 (30)	26	6 – 12Y	M; F (5,5:1)	39	20,5%
Valvo et al., 2013 (31)	27	2,2 – 17,5Y	M; F	67	20,9%
Cederlund et al., 2014 (32)	28	3Y	M; F (5,6:1)	33	12,1%

Legend: Y-year; m-month; M- male; F - female

The meta-analysis was performed applying a random effect model due to the amount of heterogeneity found (Q-value=189.63, 27 df; p-value <0.0001; I^2=85.76%). The 95% confidence interval found for ASD children was [14.7, 21.2], resulting from a total of 828 children (out of 5185) being found with macrocephaly in the 28 studies (Figure 2).

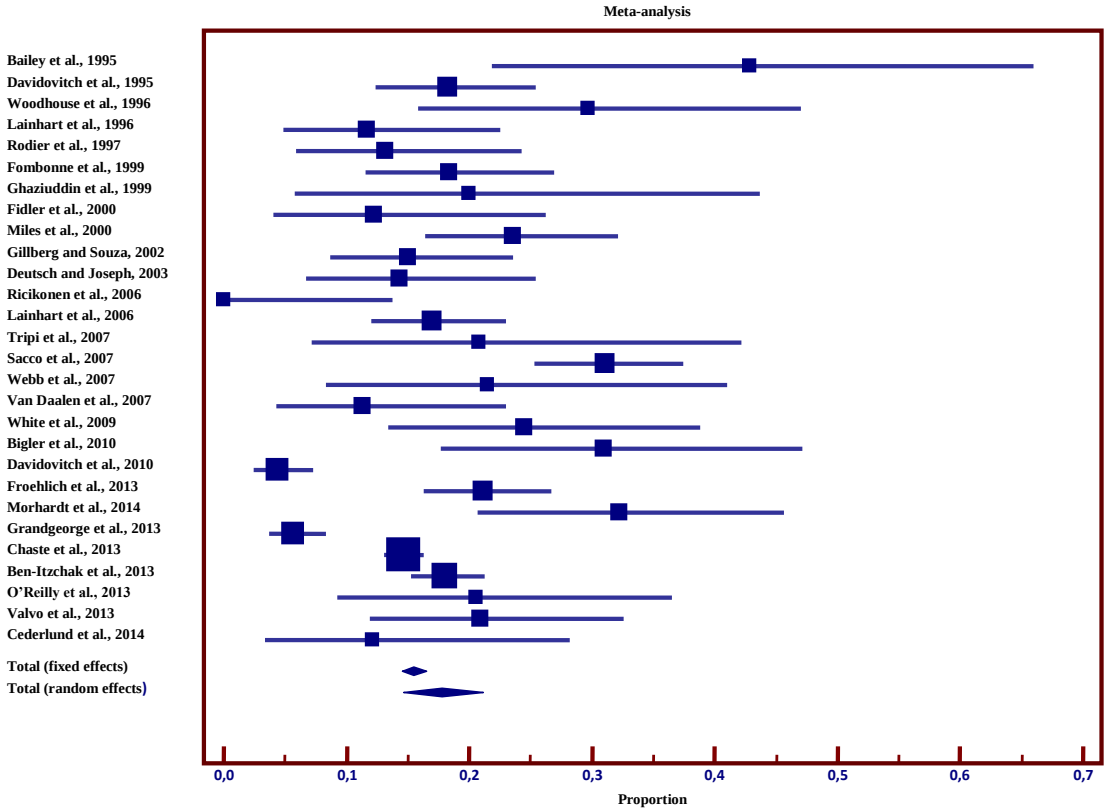

Figure 2: Forest plot of the prevalence of macrocephaly in ASD children, with 95% confidence intervals.

Discussion

The current study aimed to investigate the frequency of macrocephaly in ASD published in literature. It was performed a systematic review of studies measuring head circumference in autistic children samples.

ASD is a complex and heterogeneous disorder, not only clinically but also etiologically. Therefore, it will be useful defining endophenotypes to delineate more homogeneous subtypes of ASD, which can help to clinical and research purposes. (2,7,24) Macrocephaly is the most consistent finding in ASD, with a prevalence that varies between 11 to 42% in previous studies.

We confirmed that the presence of macrocephaly in children with ASD is higher than the expected value of the general population (95% confidence interval of [14.7%, 21.2%] *versus* 3%, respectively). It was detected between-study heterogeneity. That could be explain by the different age range of the ASD children that varied between 1 to 18 years, the percentage of each gender in the different studies and the different nationalities of the children of which study (Europe, Asia and USA).

In our analyse we excluded studies where macrocephaly was not idiopathic (e.g. children with tuberous sclerosis, fragile X syndrome or *PTEN* mutation), so it would not over-bias the result.

Sacco et al. published in September 2015 a systematic review and meta-analysis about the effect size and statistical significance for head circumference and total brain volume in autism. We obtain similar range results with their prevalence of macrocephaly among autistic individuals of 15,7%. (33) However, there are differences, regarding eligibility criteria between their study and ours: the age range, since we only included children and they did not have an age restriction; the presence of group control, because in their study was required the existence of data from both cases and controls comparable.

The knowledge of increased prevalence of macrocephaly in ASD suggests the possibility of an accelerated head growth in early childhood (2,4) which is supported by post-mortem and neuroimaging findings. (4,12)

Most of the studies suggest that the acceleration of head growth occurs during the first year of life, which precedes the onset of clinical symptoms and the head circumference at birth is smaller or normal compared to the average for general population. (13,25) The low rate of macrocephaly at birth and the higher rates in children and adults suggest that rates of head growth increase during postnatal life, implying that pathogenic processes underlying autism continue postnatally and last for several years. (22,24) Nevertheless, Grandgeorge et al. (2013) observed 11% of children latter diagnosed with ASD had relative macrocephaly at birth, which supports the hypothesis that the increase in head circumference may begin during pregnancy. (5)

Some authors consider head circumference growth an isolated finding (1,13,18,22,26) but others enhanced an association between weight and length/height and macrocephaly. Still remains inconclusive, although it has been proposed macrocephaly associated to an overgrowth syndrome. (7,11,19,24,32)

It also exist some discrepancy in the results about the relation between head circumference and IQ, with some studies finding a relationship between macrocephaly and a behavioural or cognitive feature of ASD, (1,11,20,22,24) and others report no association. (7,12,13,15,17-19,30)

ASD is strongly genetically determined, supported by twin and family studies. That raise the possibility that increased head circumference also may be a familial trait, (1,7,10,12,17,18,22) which could lead to an overestimated result of the prevalence of macrocephaly related to ASD. Research in future should take into account parents head circumference.

Although macrocephaly appears to be a finding that is non-specific to ASD (17) it could be an early sign that allows a valuable time window to diagnosis and intervention.

There are limitations in the present systematic review. It did not consider head circumference information of parents and siblings, weight and height were not collected and compared with the head circumference (excluding that way the cases of general body overgrowth). Also the measurements of head circumference are intrinsically associated with error, because it is measurer-dependent. Also, it did not evaluate head circumference chart used in each study, since Morhardt et al (2013) did not find significant differences in identification of macrocephaly in ASD children related to head circumference chart used. (29)

Measuring head circumference during child development is routine practice in many countries (5) macrocephaly can be a valuable marker in ASD. Indeed, the consistency of macrocephaly rates in ASD across studies performed in different nations raises confidence in the reliability of the overall estimates provided by the present meta-analysis.

Conclusion

Our results reliably confirm the consistent association of macrocephaly (i.e. head circumference above the 97^{th} percentile) with autism. The prevalence of macrocephaly in ASD group was largely higher than the predicted in controls (3%).

Our study demonstrated the 95% confidence interval of macrocephaly in ASD children was [14.7%, 21.2%]. This result highlights future inclusion of macrocephaly as potential biomarker in ASD.

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Appendix 1

Table 2: Screening of the 196 records based on titles and abstracts

Nº	Authors	Year	Title	Verdict
1	Migliavacca et al.	2015	A Potential Contributory Role for Ciliary Dysfunction in the 16p11.2 600 kb BP4-BP5 Pathology.	No (1)
2	Meguid et al.	2014	Anthropometric assessment of a Middle Eastern group of autistic children.	Yes
3	McKeague et al.	2015	Autism with intellectual disability related to dynamics of head circumference growth during early infancy.	Yes
4	Pyhälä et al.	2014	Very low birth weight, infant growth, and autism-spectrum traits in adulthood.	No (2)
5	Brooks et al.	2014	A novel ribosomopathy caused by dysfunction of RPL10 disrupts neurodevelopment and causes X-linked microcephaly in humans.	No (1,3)
6	Bay	2014	Fertility treatment: long-term growth and mental development of the children.	No (6)
7	Prontera et al.	2014	Recurrent ~100 Kb microdeletion in the chromosomal region 14q11.2, involving CHD8 gene, is associated with autism and macrocephaly.	No (8)
8	Campbell et al.	2014	Early generalized overgrowth in autism spectrum disorder: prevalence rates, gender effects, and clinical outcomes.	Yes
9	Zwaigenbaum et al.	2014	Early head growth in infants at risk of autism: a baby siblings research consortium study.	No (6)
10	Qureshi et al.	2014	Opposing brain differences in 16p11.2 deletion and duplication carriers.	No (6)
11	Bernier et al.	2014	Disruptive CHD8 mutations define a subtype of autism early in development.	No (5)
12	Allely et al.	2014	Neurobiological abnormalities in the first few years of life in individuals later diagnosed with autism spectrum disorder: a review of recent data.	No (7)

13	Keown et al.	2014	Nutritional implications of selective eating in a child with autism spectrum disorder.	No (8)
14	Cederlund et al.	2014	Pre-schoolchildren with autism spectrum disorders are rarely macrocephalic: a population study.	Yes
15	Marchese et al.	2014	Autism-epilepsy phenotype with macrocephaly suggests PTEN, but not GLIALCAM, genetic screening.	No (6)
16	Sarasua et al.	2014	Clinical and genomic evaluation of 201 patients with Phelan-McDermid syndrome.	No (6)
17	Al-Kateb et al.	2014	Scoliosis and vertebral anomalies: additional abnormal phenotypes associated with chromosome 16p11.2 rearrangement.	No (6)
18	Piras et al.	2014	Anti-brain antibodies are associated with more severe cognitive and behavioral profiles in Italian children with Autism Spectrum Disorder.	No (9)
19	Vanderver et al.	2014	Characteristic brain magnetic resonance imaging pattern in patients with macrocephaly and PTEN mutations.	No (6)
20	Ewing et al.	2013	Reduced face aftereffects in autism are not due to poor attention.	No (4)
21	Okamoto et al.	2014	A clinical study of patients with pericentromeric deletion and duplication within 16p12.2-p11.2.	No (6)
22	Le Fevre et al.	2013	FOXP1 mutations cause intellectual disability and a recognizable phenotype.	No (5)
23	O'Reilly et al.	2013	Is macrocephaly a neural marker of a local bias in autism?	Yes
24	Sarasua et al.	2013	22q13.2q13.32 genomic regions associated with severity of speech delay, developmental delay, and physical features in Phelan-McDermid syndrome.	No (6)
25	Valvo et al.	2013	Somatic overgrowth predisposes to seizures in autism spectrum disorders.	Yes
26	Davis et al.	2013	Mode of genetic inheritance modifies the association of head circumference and autism-related symptoms: a cross-sectional study.	No (6)
27	Shuvarikov et al.	2013	Recurrent HERV-H-mediated 3q13.2-q13.31 deletions cause a syndrome of hypotonia and motor, language, and cognitive delays.	No (4, 6)
28	Moss et al.	2014	Increased risk of very low birth weight, rapid postnatal growth, and autism in underweight and obese mothers.	No (4, 6)

29	Ben-Itzchak et al.	2013	Specific neurological phenotypes in autism spectrum disorders are associated with sex representation.	Yes
30	Surén et al.	2013	Early growth patterns in children with autism.	Yes
31	Bardsley et al.	2013	47,XYY syndrome: clinical phenotype and timing of ascertainment.	No (6)
32	Chaste et al.	2013	Adjusting head circumference for covariates in autism: clinical correlates of a highly heritable continuous trait.	Yes
33	Raznahan et al.	2013	Compared to what? Early brain overgrowth in autism and the perils of population norms.	No (7)
34	Hobert et al.	2014	Biochemical screening and PTEN mutation analysis in individuals with autism spectrum disorders and macrocephaly.	Yes
35	Capo-Chichi et al.	2013	Disruption of TBC1D7, a subunit of the TSC1-TSC2 protein complex, in intellectual disability and megalencephaly.	No (8)
36	Grandgeorge et al.	2013	Autism spectrum disorders: head circumference and body length at birth are both relative.	Yes
37	Napolioni et al.	2013	Plasma cytokine profiling in sibling pairs discordant for autism spectrum disorder.	Yes
38	Granados et al.	2013	Brothers with germline PTEN mutations and persistent hypoglycemia, macrocephaly, developmental delay, short stature, and coagulopathy.	No (6)
39	Klein et al.	2013	Macrocephaly as a clinical indicator of genetic subtypes in autism.	No (10)
40	Morhardt et al.	2014	Head circumference in young children with autism: the impact of different head circumference charts.	Yes
41	Froehlich et al.	2013	Head circumferences in twins with and without Autism Spectrum Disorders.	Yes
42	Langridge et al.	2013	Maternal conditions and perinatal characteristics associated with autism spectrum disorder and intellectual disability.	No (6)
43	Ewing et al.	2013	Atypical updating of face representations with experience in children with autism.	No (4)
44	Flore et al.	2012	Updates in the genetic evaluation of the child with global developmental delay or intellectual disability.	No (6,7)
45	O'Roak et al.	2012	Multiplex targeted sequencing identifies recurrently mutated genes in autism spectrum disorders.	No (4)
46	Busa et al.	2013	Novel PTEN germline mutation in a family with mild phenotype: difficulties in genetic counseling.	No (5,6)
47	Zufferey et al.	2012	A 600 kb deletion syndrome at 16p11.2 leads to energy imbalance and neuropsychiatric disorders.	No (6)

48	Dolcetti et al.	2013	1q21.1 Microduplication expression in adults.	No (4, 6, 7)
49	Schrieken et al.	2013	Head circumference and height abnormalities in autism revisited: the role of pre- and perinatal risk factors.	Yes
50	Gamliel et al.	2012	Minor fetal sonographic findings in autism spectrum disorder.	No (7)
51	Aoki et al.	2012	Age-related change in brain metabolite abnormalities in autism: a meta-analysis of proton magnetic resonance spectroscopy studies.	No (7)
52	Barber et al.	2013	16p11.2-p12.2 duplication syndrome; a genomic condition differentiated from euchromatic variation of 16p11.2.	No (6)
53	Luo et al.	2012	Genome-wide transcriptome profiling reveals the functional impact of rare de novo and recurrent CNVs in autism spectrum disorders.	No (5)
54	Onore et al.	2012	Levels of soluble platelet endothelial cell adhesion molecule-1 and P-selectin are decreased in children with autism spectrum disorder.	No (4)
55	Hazlett et al.	2012	Brain volume findings in 6-month-old infants at high familial risk for autism.	No (6)
56	Zhou et Parada	2012	PTEN signaling in autism spectrum disorders.	No (7)
57	Schaaf et al.	2012	Phenotypic spectrum and genotype-phenotype correlations of NRXN1 exon deletions.	No (5)
58	Lynch et al.	2012	Broadening the phenotype associated with mutations in UPF3B: two further cases with renal dysplasia and variable developmental delay.	No (8)
59	Saugstad et al.	2012	Further evidence that infantile autism is a chronic psychosis distinguished by a deficient delayed response function affecting the connections between hippocampus and singulum in its center, the SMA and the inhibitory Purkinje cells in cerebellum.	No (6)
60	Wyer et al.	2012	Individual differences in (non-visual) processing style predict the face inversion effect.	No (4)
61	Ververi et al.	2012	Clinical and laboratory data in a sample of Greek children with autism spectrum disorders.	No (6)

62	Nordahl et al.	2011	Brain enlargement is associated with regression in preschool-age boys with autism spectrum disorders.	Yes
63	Gray et al.	2012	Could head circumference be used to screen for autism in young males with developmental delay?	Yes
64	Sarasua et al.	2011	Association between deletion size and important phenotypes expands the genomic region of interest in Phelan-McDermid syndrome (22q13 deletion syndrome).	No (6)
65	Chawarska et al.	2011	Early generalized overgrowth in boys with autism.	Yes
66	Conti et al.	2012	Phosphatase and tensin homolog (PTEN) gene mutations and autism: literature review and a case report of a patient with Cowden syndrome, autistic disorder, and epilepsy.	No (6, 7, 8)
67	Cheon et al.	2011	Involvement of the anterior thalamic radiation in boys with high functioning autism spectrum disorders: a Diffusion Tensor Imaging study.	No (4)
68	Jacquemont et al.	2011	Mirror extreme BMI phenotypes associated with gene dosage at the chromosome 16p11.2 locus.	No (6)
69	Southwick et al.	2011	Memory functioning in children and adolescents with autism.	No (4)
70	Gardener et al.	2011	Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis.	No (7)
71	Cheung et al.	2011	MRI study of minor physical anomaly in childhood autism implicates aberrant neurodevelopment in infancy.	No (4)
72	Davidovitch et al.	2011	Israeli children with autism spectrum disorder are not macrocephalic.	Yes
73	Barnard-Brak et al.	2011	Macrocephaly in children with autism spectrum disorders.	Yes
74	Adamsen et al.	2011	Autism associated with low 5-hydroxyindolacetic acid in CSF and the heterozygous SLC6A4 gene Gly56Ala plus 5-HTTLPR L/L promoter variants.	No (8)
75	Stigler et al.	2011	Structural and functional magnetic resonance imaging of autism spectrum disorders.	No (7)
76	Moreno-De-Luca et al.	2010	Deletion 17q12 is a recurrent copy number variant that confers high risk of autism and schizophrenia.	No (5, 6)
77	Schaaf et al.	2011	Expanding the clinical spectrum of the 16p11.2 chromosomal rearrangements: three patients with syringomyelia.	No (5, 6)

78	Fukumoto et al.	2011	Head circumference and body growth in autism spectrum disorders.	Yes
79	Wallace et al.	2010	Age-related temporal and parietal cortical thinning in autism spectrum disorders.	No (2, 4)
80	Sacco et al.	2010	Principal pathogenetic components and biological endophenotypes in autism spectrum disorders.	Yes
81	Stein et al.	2010	Autistic spectrum disorder in a 9-year-old girl with macrocephaly.	No (8)
82	Malinger et al.	2011	Can syndromic macrocephaly be diagnosed in utero?	No (2)
83	Grafodatskaya et al.	2010	Autism spectrum disorders and epigenetics.	No (7)
84	Baron-Cohen	2010	Neonatal free testosterone and head circumference: need for replication.	No (6)
85	McBride et al.	2010	Confirmation study of PTEN mutations among individuals with autism or developmental delays/mental retardation and macrocephaly.	No (5, 10)
86	Bigler et al.	2010	Volumetric and voxel-based morphometry findings in autism subjects with and without macrocephaly.	Yes
87	Indredavik et al.	2010	Perinatal risk and psychiatric outcome in adolescents born preterm with very low birth weight or term small for gestational age.	No (6)
88	Rommelse et al.	2010	A pilot study of abnormal growth in autism spectrum disorders and other childhood psychiatric disorders.	Yes
89	Whitehouse et al.	2011	Brief report: a preliminary study of fetal head circumference growth in autism spectrum disorder.	No (2)
90	Alliman et al.	2010	Clinical and molecular characterization of individuals with recurrent genomic disorder at 10q22.3q23.2.	No (6)
91	Monk et al.	2010	Neural circuitry of emotional face processing in autism spectrum disorders.	No (4)
92	Fletcher et al.	2010	Microstructural connectivity of the arcuate fasciculus in adolescents with high-functioning autism.	No (4)
93	Kosaka et al.	2010	Smaller insula and inferior frontal volumes in young adults with pervasive developmental disorders.	No (2)
94	Shinawi et al.	2010	Recurrent reciprocal 16p11.2 rearrangements associated with global developmental delay, behavioural problems, dysmorphism, epilepsy, and abnormal head size.	No (5, 6)

95	O'Shea et al.	2009	The ELGAN study of the brain and related disorders in extremely low gestational age newborns.	No (6)
96	Coffin et al.	2009	Lipoblastoma (LPB): a clinicopathologic and immunohistochemical analysis of 59 cases.	No (6)
97	Dammann et al.	2009	SNAP-II and SNAPPE-II and the risk of structural and functional brain disorders in extremely low gestational age newborns: the ELGAN study.	No (6)
98	Mraz et al.	2009	Accelerated head and body growth in infants later diagnosed with autism spectrum disorders: a comparative study of optimal outcome children.	Yes
99	White et al.	2009	Big heads, small details and autism.	Yes
100	Langen et al.	2009	Changes in the developmental trajectories of striatum in autism.	No (2)
101	Sajdel-Sulkowska et al.	2009	Increase in cerebellar neurotrophin-3 and oxidative stress markers in autism.	No (4)
102	Lynch et al.	2009	Bannayan-Riley-Ruvalcaba syndrome: a cause of extreme macrocephaly and neurodevelopmental delay.	No (6, 10)
103	Varga et al.	2009	The prevalence of PTEN mutations in a clinical pediatric cohort with autism spectrum disorders, developmental delay, and macrocephaly.	No (5, 6)
104	Molloy et al.	2009	Differences in the clinical presentation of Trisomy 21 with and without autism.	No (6)
105	Hallahan et al.	2009	Brain morphometry volume in autistic spectrum disorder: a magnetic resonance imaging study of adults.	No (2)
106	Orrico et al.	2009	Novel PTEN mutations in neurodevelopmental disorders and macrocephaly.	No (5, 6)
107	Kilian et al.	2008	Regional callosal morphology in autism and macrocephaly.	No (10)
108	Cleavinger et al.	2008	Quantitative magnetic resonance image analysis of the cerebellum in macrocephalic and normocephalic children and adults with autism.	No (2)
109	Elder et al.	2008	Head circumference as an early predictor of autism symptoms in younger siblings of children with autism spectrum disorder.	No (6)

110	Buxbaum et al.	2007	Mutation analysis of the NSD1 gene in patients with autism spectrum disorders and macrocephaly.	No (5, 10)
111	Zafeiriou et al.	2008	L-2-Hydroxyglutaric aciduria presenting with severe autistic features.	No (6)
112	van Daalen et al.	2007	Body length and head growth in the first year of life in autism.	Yes
113	Webb et al.	2007	Rate of head circumference growth as a function of autism diagnosis and history of autistic regression.	Yes
114	Cusmano-Ozog et al.	2007	22q13.3 deletion syndrome: a recognizable malformation syndrome associated with marked speech and language delay.	No (6)
115	Ben Itzchak et al.	2008	Cognitive, behavior and intervention outcome in young children with autism.	No (4)
116	Lahuis et al.	2008	MRI-based morphometry in children with multiple complex developmental disorder, a phenotypically defined subtype of pervasive developmental disorder not otherwise specified.	Yes
117	Gan et al.	2008	Epilepsy associated with a cerebellar arachnoid cyst: seizure control following fenestration of the cyst.	No (6, 8)
118	Fukumoto et al.	2008	Growth of head circumference in autistic infants during the first year of life.	Yes
119	Sacco et al.	2007	Clinical, morphological, and biochemical correlates of head circumference in autism.	Yes
120	Mraz et al.	2007	Correlates of head circumference growth in infants later diagnosed with autism spectrum disorders.	Yes
121	Tate et al.	2007	The relative contributions of brain, cerebrospinal fluid-filled structures and non-neural tissue volumes to occipital-frontal head circumference in subjects with autism.	No (4)
122	Tripi et al.	2008	Minor physical anomalies in children with autism spectrum disorder.	Yes
123	Mills et al.	2007	Elevated levels of growth-related hormones in autism and autism spectrum disorder.	Yes
124	Hughes	2007	Autism: the first firm finding = underconnectivity?	No (4, 7)
125	Tan et al.	2007	The spectrum of vascular anomalies in patients with PTEN mutations: implications for diagnosis and management.	No (6)
126	Tsuchiya et al.	2007	Decreased serum levels of platelet-endothelial adhesion molecule (PECAM-1) in subjects with high-functioning autism: a negative correlation with head circumference at birth.	No (6)

127	Miles et Takahashi	2007	Lack of association between Rh status, Rh immune globulin in pregnancy and autism.	No (2)
128	Herman et al.	2007	Genetic testing in autism: how much is enough?	Yes
129	Bigler et al.	2007	Superior temporal gyrus, language function, and autism.	No (2)
130	Buxbaum et al.	2007	Mutation screening of the PTEN gene in patients with autism spectrum disorders and macrocephaly.	No (10)
131	Chiu et al.	2007	Early acceleration of head circumference in children with fragile x syndrome and autism.	No (6)
132	Herman et al.	2007	Increasing knowledge of PTEN germline mutations: Two additional patients with autism and macrocephaly.	No (8)
133	Neeley et al.	2007	Quantitative temporal lobe differences: autism distinguished from controls using classification and regression tree analysis.	No (9)
134	Muscarella et. al	2007	HOXA1 gene variants influence head growth rates in humans.	No (6)
135	Dawson et al.	2007	Rate of head growth decelerates and symptoms worsen in the second year of life in autism.	Yes
136	Alexander et al.	2007	Diffusion tensor imaging of the corpus callosum in Autism.	No (4)
137	Lainhart et al.	2006	Head circumference and height in autism: a study by the Collaborative Program of Excellence in Autism.	Yes
138	Riikonen et al.	2006	Cerebrospinal fluid insulin-like growth factors IGF-1 and IGF-2 in infantile autism.	Yes
139	Dissanayake et al.	2006	Growth in stature and head circumference in high-functioning autism and Asperger disorder during the first 3 years of life.	Yes
140	Hazlett et al.	2005	Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years.	Yes
141	Redcay et al.	2005	When is the brain enlarged in autism? A meta-analysis of all brain size reports.	No (7)
142	Wassink et al.	2005	A case of autism and uniparental disomy of chromosome 1.	No (8)
143	Butler et al.	2005	Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations.	No (10)
144	Rice et al.	2005	Macrocephaly, corpus callosum morphology, and autism.	No (10)
145	Dementieva et al.	2005	Accelerated head growth in early development of individuals with autism.	Yes

146	Torrey et al.	2004	Autism and head circumference in the first year of life.	Yes
147	Courchesne et al.	2004	Brain development in autism: early overgrowth followed by premature arrest of growth.	No (7)
148	Courchesne et al.	2003	The autistic brain: birth through adulthood.	No (7)
149	Wallace et Treffert	2003	Head size and autism.	No (7)
150	Herbert et al.	2004	Localization of white matter volume increase in autism and developmental language disorder.	No (4)
151	Pescucci et al.	2003	Chromosome 2 deletion encompassing the MAP2 gene in a patient with autism and Rett-like features.	No (8)
152	Conciatori et al.	2004	Association between the HOXA1 A218G polymorphism and increased head circumference in patients with autism.	No (5)
153	Bigler et al.	2003	Temporal lobe, autism, and macrocephaly.	Yes
154	Geerts et al.	2003	The XYY syndrome: a follow-up study on 38 boys.	No (6)
155	Steiner et al.	2003	On macrocephaly, epilepsy, autism, specific facial features, and mental retardation.	Yes
156	Courchesne et al.	2003	Evidence of brain overgrowth in the first year of life in autism.	Yes
157	Deutsch et Joseph	2003	Brief report: cognitive correlates of enlarged head circumference in children with autism.	Yes
158	Thompson et Bolton	2003	Case report: Angelman syndrome in an individual with a small SMC(15) and paternal uniparental disomy: a case report with reference to the assessment of cognitive functioning and autistic symptomatology.	No (6, 8)
159	Cohen	2003	Mental deficiency, alterations in performance, and CNS abnormalities in overgrowth syndromes.	No (6)
160	Bartholomeusz et al.	2002	Relationship between head circumference and brain volume in healthy normal toddlers, children, and adults.	No (2, 6)
161	Casanova et al.	2002	Neuronal density and architecture (Gray Level Index) in the brains of autistic patients.	No (4)
162	Aylward et al.	2002	Effects of age on brain volume and head circumference in autism.	Yes
163	Hultman et al.	2002	Perinatal risk factors for infantile autism.	Yes
164	Gillberg et Souza	2002	Head circumference in autism, Asperger syndrome, and ADHD: a comparative study.	Yes

165	Zappella et al.	2001	Preserved speech variants of the Rett syndrome: molecular and clinical analysis.	No (6)
166	Bolton et al.	2001	Association between idiopathic infantile macrocephaly and autism spectrum disorders.	Yes
167	Goffin et al.	2001	PTEN mutation in a family with Cowden syndrome and autism.	No (6, 8)
168	Hardan et al.	2001	Posterior fossa magnetic resonance imaging in autism.	No (2, 4)
169	Stoll	2001	Problems in the diagnosis of fragile X syndrome in young children are still present.	No (6)
170	Miles et al.	2000	Head circumference is an independent clinical finding associated with autism.	Yes
171	Persico et al.	2000	Adenosine deaminase alleles and autistic disorder: case-control and family-based association studies.	No (5)
172	Fidler et al.	2000	Macrocephaly in autism and other pervasive developmental disorders.	Yes
173	Fombonne	2000	Is a large head circumference a sign of autism?	Yes
174	Naqvi et al.	2000	Cole-Hughes macrocephaly syndrome and associated autistic manifestations.	No (6)
175	Starkstein et al.	2000	SPECT findings in mentally retarded autistic individuals.	No (4)
176	Ghaziuddin et al.	1999	Is megalencephaly specific to autism?	Yes
177	Fombonne et al.	1999	Microcephaly and macrocephaly in autism.	Yes
178	Rutter et al.	1999	Quasi-autistic patterns following severe early global privation. English and Romanian Adoptees (ERA) Study Team.	No (4)
179	Courchesne et al.	1999	Brain weight in autism: normal in the majority of cases, megalencephalic in rare cases.	No (4)
180	Skjeldal et al.	1998	Childhood autism: the need for physical investigations.	Yes
181	Pascual-Castroviejo et al.	1998	Hypomelanosis of ITO. A study of 76 infantile cases.	No (6)
182	Orstavik et al.	1997	Macrocephaly, epilepsy, autism, dysmorphic features, and mental retardation in two sisters: a new autosomal recessive syndrome?	No (6, 8)
183	Stevenson et al.	1997	Autism and macrocephaly.	Yes

184	Rodier et al.	1997	Minor malformations and physical measurements in autism: data from Nova Scotia.	Yes
185	Lainhart et al.	1997	Macrocephaly in children and adults with autism.	Yes
186	Woodhouse et al.	1996	Head circumference in autism and other pervasive developmental disorders.	Yes
187	Davidovitch et al.	1996	Head circumference measurements in children with autism.	Yes
188	Bailey et al.	1996	Autism and megalencephaly.	Yes
189	Courchesne et al	1994	The brain in infantile autism: posterior fossa structures are abnormal.	No (4)
190	Laxova	1994	Fragile X syndrome.	No (6)
191	Tirosh et Canby	1993	Autism with hyperlexia: a distinct syndrome?	No (6)
192	Wang et al.	1992	Specific neurobehavioral profile of Williams' syndrome is associated with neocerebellar hemispheric preservation.	No (6)
193	Gaffney et al.	1987	Cerebellar structure in autism.	No (4)
194	Rolando	1985	Rett syndrome: report of eight cases.	No (6, 8)
195	Nomura et al.	1984	Rett syndrome--clinical studies and pathophysiological consideration.	No (6)
196	Walker	1977	Incidence of minor physical anomaly in autism.	No (4)

Legend:

(1): study on animal models

(2): participants aren´t children (age range isn´t between 0 and 18 years)

(3): deals only with microcephaly

(4): study without head circumference measurement

(5): macrocephaly isn´t idiopathic

(6): children without ASD diagnosis or with syndromic forms of ASD

(7): review article

(8): case report

(9): excluded participants with macrocephaly

(10): selected only participants with macrocephaly

Appendix 2

Table 3: Screening of the 62 studies based on full article

Nº	Authors	Year	Title	Verdict
1	Meguid et al.	2014	Anthropometric assessment of a Middle Eastern group of autistic children.	No (1)
2	McKeague et al.	2015	Autism with intellectual disability related to dynamics of head circumference growth during early infancy.	No (4)
3	Campbell et al.	2014	Early generalized overgrowth in autism spectrum disorder: prevalence rates, gender effects, and clinical outcomes.	No (2)
4	Cederlund et al.	2014	Pre-schoolchildren with autism spectrum disorders are rarely macrocephalic: a population study.	Yes
5	O'Reilly et al.	2013	Is macrocephaly a neural marker of a local bias in autism?	Yes
6	Ben-Itzchak et al.	2013	Specific neurological phenotypes in autism spectrum disorders are associated with sex representation.	Yes
7	Surén et al.	2013	Early growth patterns in children with autism.	No (2)
8	Chaste et al.	2013	Adjusting head circumference for covariates in autism: clinical correlates of a highly heritable continuous trait.	Yes
9	Hobert et al.	2014	Biochemical screening and PTEN mutation analysis in individuals with autism spectrum disorders and macrocephaly.	No (3)
10	Grandgeorge et al.	2013	Autism spectrum disorders: head circumference and body length at birth are both relative.	Yes
11	Napolioni et al.	2013	Plasma cytokine profiling in sibling pairs discordant for autism spectrum disorder.	No (4)
12	Morhardt et al.	2014	Head circumference in young children with autism: the impact of different head circumference charts.	Yes
13	Froehlich et al.	2013	Head circumferences in twins with and without Autism Spectrum Disorders.	Yes
14	Schrieken et al.	2013	Head circumference and height abnormalities in autism revisited: the role of pre- and perinatal risk factors.	No (2)

15	Valvo et al.	2013	Somatic overgrowth predisposes to seizures in autism spectrum disorders.	Yes
16	Nordahl et al.	2011	Brain enlargement is associated with regression in preschool-age boys with autism spectrum disorders.	No (4)
17	Gray et al.	2012	Could head circumference be used to screen for autism in young males with developmental delay?	No (6)
18	Chawarska et al.	2011	Early generalized overgrowth in boys with autism.	No (2)
19	Davidovitch et al.	2011	Israeli children with autism spectrum disorder are not macrocephalic.	Yes
20	Barnard-Brak et al.	2011	Macrocephaly in children with autism spectrum disorders.	No (2)
21	Fukumoto et al.	2011	Head circumference and body growth in autism spectrum disorders.	No (2, 4)
22	Sacco et al.	2010	Principal pathogenetic components and biological endophenotypes in autism spectrum disorders.	No (4)
23	Bigler et al.	2010	Volumetric and voxel-based morphometry findings in autism subjects with and without macrocephaly.	Yes
24	Rommelse et al.	2010	A pilot study of abnormal growth in autism spectrum disorders and other childhood psychiatric disorders.	No (2)
25	Mraz et al.	2009	Accelerated head and body growth in infants later diagnosed with autism spectrum disorders: a comparative study of optimal outcome children.	No (2)
26	White et al.	2009	Big heads, small details and autism.	Yes
27	van Daalen et al.	2007	Body length and head growth in the first year of life in autism.	Yes
28	Webb et al.	2007	Rate of head circumference growth as a function of autism diagnosis and history of autistic regression.	Yes
29	Lahuis et al.	2008	MRI-based morphometry in children with multiple complex developmental disorder, a phenotypically defined subtype of pervasive developmental disorder not otherwise specified.	No (7)
30	Fukumoto et al.	2008	Growth of head circumference in autistic infants during the first year of life.	No (2)
31	Sacco et al.	2007	Clinical, morphological, and biochemical correlates of head circumference in autism.	Yes
32	Mraz et al.	2007	Correlates of head circumference growth in infants later diagnosed with autism spectrum disorders.	No (2)

33	Tripi et al.	2008	Minor physical anomalies in children with autism spectrum disorder.	Yes
34	Mills et al.	2007	Elevated levels of growth-related hormones in autism and autism spectrum disorder.	No (4)
35	Herman et al.	2007	Genetic testing in autism: how much is enough?	No (1)
36	Dawson et al.	2007	Rate of head growth decelerates and symptoms worsen in the second year of life in autism.	No (2)
37	Lainhart et al.	2006	Head circumference and height in autism: a study by the Collaborative Program of Excellence in Autism.	Yes
38	Riikonen et al.	2006	Cerebrospinal fluid insulin-like growth factors IGF-1 and IGF-2 in infantile autism.	Yes
39	Dissanayake et al.	2006	Growth in stature and head circumference in high-functioning autism and Asperger disorder during the first 3 years of life.	No (2)
40	Hazlett et al.	2005	Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years.	No (4)
41	Dementieva et al.	2005	Accelerated head growth in early development of individuals with autism.	No (2)
42	Torrey et al.	2004	Autism and head circumference in the first year of life.	No (2)
43	Bigler et al.	2003	Temporal lobe, autism, and macrocephaly.	No (3)
44	Steiner et al.	2003	On macrocephaly, epilepsy, autism, specific facial features, and mental retardation.	No (8)
45	Courchesne et al.	2003	Evidence of brain overgrowth in the first year of life in autism.	No (2)
46	Deutsch et Joseph	2003	Brief report: cognitive correlates of enlarged head circumference in children with autism.	Yes
47	Aylward et al.	2002	Effects of age on brain volume and head circumference in autism.	No (4)
48	Hultman et al.	2002	Perinatal risk factors for infantile autism.	No (4)
49	Gillberg et Souza	2002	Head circumference in autism, Asperger syndrome, and ADHD: a comparative study.	Yes
50	Bolton et al.	2001	Association between idiopathic infantile macrocephaly and autism spectrum disorders.	No (5)
51	Miles et al.	2000	Head circumference is an independent clinical finding associated with autism.	Yes
52	Fidler et al.	2000	Macrocephaly in autism and other pervasive developmental disorders.	Yes

53	Fombonne	2000	Is a large head circumference a sign of autism?	No (8)
54	Ghaziuddin et al.	1999	Is megalencephaly specific to autism?	Yes
55	Fombonne et al.	1999	Microcephaly and macrocephaly in autism.	Yes
56	Skjeldal et al.	1998	Childhood autism: the need for physical investigations.	No (6)
57	Stevenson et al.	1997	Autism and macrocephaly.	No (3)
58	Rodier et al.	1997	Minor malformations and physical measurements in autism: data from Nova Scotia.	Yes
59	Lainhart et al.	1997	Macrocephaly in children and adults with autism.	Yes
60	Woodhouse et al.	1996	Head circumference in autism and other pervasive developmental disorders.	Yes
61	Davidovitch et al.	1996	Head circumference measurements in children with autism.	Yes
62	Bailey et al.	1993	Autism and megalencephaly.	Yes

Legend:

(1): macrocephaly is not defined as head circumference greater than 2 standard deviations above the mean for age and sex

(2): there are different head circumference measurements in different ages for each child.

(3): there isn´t indicated the number of children with ASD and macrocephaly and it doesn´t exist a way to obtain that result

(5): selected participants with normocephaly and macrocephaly

(6): macrocephaly ins´t idiophatic or exist children with syndromic forms of ASD

(7): it wasn´t possible to access the full article

(8): research letter, comentarie