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MATERNAL EXPOSURE TO STRESSFUL/TRAUMATIC EVENTS AND AUTISM SPECTRUM DISORDERS IN OFFSPRING: PRELIMINARY FINDINGS OF A CASE-CONTROL PILOT STUDY

Rosaria Nardello, Valeria Tullio, Alessandra Viviano, Fulvio Guccione , Corinne La Spina, Stefania Zerbo, Antonina Argo

Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialities "G. D'Alessandro", University of Palermo, Italy

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ABSTRACT

The correlation between maternal exposure to stressful and traumatic events during pregnancy and autism spectrum disorder (ASD) in offspring has been studied in the literature. Fewer studies, however, have considered the mother's exposure to traumatic events during childhood. This work focuses on maternal exposure to these events in childhood and/or adulthood, relating it to autism spectrum disorder in offspring. A questionnaire was used to assess whether and to what type of event the mothers have been exposed, and to assess eventual peri-traumatic dissociation related to the traumatic event. The mothers involved in this study were recruited at the Child Neuropsychiatry Outpatient Clinic of the University Hospital of Palermo. 22 mothers (natural mothers) gave their time to participate in this pilot study, and all who were considered have the characteristics required to be enrolled in this study. The control group consists of 50 mothers of children with diagnosis of language disorder (LD). The difference between maternal exposure to stressful and traumatic events in the group of cases compared to the control group is statistically significant ($p = 0.03$); the median value is 7 in the cases vs 4.5 in controls. The finding of a greater number of stressful and traumatic events in mothers of children with autism spectrum disorder compared to mothers of children with language disorder could suggest the existence of a correlation between maternal exposure to stress and trauma and the risk of developing autism in offspring.

1. Introduction

It is known in the literature that an adequate level of well-being in mothers favors the establishment of a positive mother-child bond and facilitates the mental, emotional and social development of children [1].
Many studies have also shown that a poor mental health condition in mothers exposes their children to a greater risk of psychosocial disorders, personality disorders, as well as low levels of growth and/or IQ [2-4].
The correlation between maternal exposure to stressful and traumatic events during pregnancy and the presence of autism spectrum disorder in the offspring has been widely investigated by several works [5,6,7]. These studies have shown how maternal exposure to these events not only correlates to a high risk of ASD for offspring, but also, in relation to the type of stressful event, to the different level of severity the autistic condition can occur with [7].

Fewer studies, however, considered maternal exposure to stressful and traumatic events during the mother's childhood which focus on the highest forms of stress and trauma, such as mistreatment and abuse (emotional, physical, and sexual) [8-11].
As demonstrated by emerging theories on the intergenerational transmission of trauma, exposure to stressful and traumatic events would seem to have repercussions not only on the neurobiological systems of the exposed subjects, but also on the neurodevelopment of subsequent generations [12-14]. Complex levels of regulation, involving immune dysregulations, endocrinological alterations and epigenetic changes affecting the maternal and paternal germ lines would be called into question [5,12, 14].

* *Corresponding author*: Corinne La Spina, *corinne.laspina93@gmail.com*
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A different role seems to be played by the different maternal susceptibility to stress, in relation to the maternal genotype of the serotonin transporter (SERT) [5, 15].

Psychoanalytic studies have shown that a mother's trauma, even more an unresolved (unintegrated) trauma, may interfere with her ability to sensitively respond to her child, negatively affecting the development of secure attachment in her own child, and potentially contributing to the intergenerational transmission of trauma [16,17].

Based on the evidence proposed by international literature, this work aims at assessing maternal exposure to stressful and traumatic events in childhood and/or adulthood, and relating it to the onset of autism spectrum disorder in offspring. Autism spectrum disorder (ASD) is a neuropsychiatric disorder, onset in childhood, characterized by persistent deficits in communication and social interaction in multiple contexts, as well as a pattern of restricted and repetitive behaviors, interests or activities. Symptoms cause clinically significant impairment of functioning in the social, occupational, or other important areas, and should not be better explained by intellectual disability or global developmental delay [19].

Although the etiopathogenesis of ASD is only partially understood, a genetic and an environmental component is certainly involved in the onset of this neurodevelopmental disorder. In addition to the risk factors known as gestational diabetes, hypertension, preeclampsia, viral infections and the use of certain drugs, an increasing attention by the scientific community has been placed on maternal exposure to stressful and traumatic events, agents both in the pre-conceptional period and during pregnancy [5-9, 17, 18]. The term stress indicates any physical or mental stress, capable of altering the homeostatic balance and triggering a series of behavioral and neuroendocrine responses in the body [12]. Stress acts in a continuum, ranging from appropriate responses meant to face and overcome the stressful event, to the onset of psychosomatic pathological pictures.

Trauma is an individual's emotional and subjective response to a distressing experience. To discuss about trauma, however, two conditions must occur. The first corresponds to the experience of events that led to death, death threat, serious injury or threat to personal or physical integrity of the self and others. The second corresponds to the response to stressors, to the overwhelming feelings of fear and horror, of helplessness or denial [20]. It is also necessary to keep in mind that unfavorable events (generally associated with chronic neglect, trauma and abuse in childhood) that occur between birth and adulthood, capable of interfering with the optimal development process, may leave deep psychic wounds in those who have suffered, making them vulnerable adults as consequence of stressful events. This form of trauma (developmental or complex) compromises the identity, the self-esteem, the personality, the emotional regulation, and ability to relate to others and to engage in intimate relationships of the individual [21]. The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of the self or others. In response to these stressors, the person's reaction involves fear and horror (emotions), helplessness (a learned behavior) or denial (cognitive alterations and ego defenses) [20].

Many bodies of research on the intergenerational transmission of trauma have recently attempted to understand how highly stressful and traumatic maternal events could affect subsequent generations.

According to the dominant paradigm, the transmission of trauma would occur through indirect mechanisms related to the child's post-natal environment and the effects of maternal exposure to the trauma itself, such as depression, reduction of parenting skills (suboptimal parenting) and substance use/abuse capable of influencing maternal sensitivity, the quality of the mother-child relationship and, consequently, the temperament of the newborn [14,22, 23].

The "Attachment Theory" research found that the maternal exposure to trauma had negative effects on attachment (the fundamental bond that is established, from birth, between the child and the caregiver and which is maintained throughout his life), such that disturbances in the caregiver-child relationship were associated with the maternal perception of the "child as threat" [24]. The trauma, an unintegrated trauma no less, may interfere with a mother's expectations and perceptions of her child, compromising the development of secure attachment in her infant [16].

Maternal exposure to childhood trauma seems to significantly predict total behavioral disorders - both internalizing and externalizing in offspring and to associate alterations of emotional regulation (emotional reactivity, emotional regulation) in children of mothers exposed to highly stressful events during their childhood [24-28].

In contrast, there are several biological mechanisms involved in the intergenerational transmission of trauma agents before conception and during intrauterine life. Exposure to stressful and traumatic events is associated with epigenetic changes affecting the maternal and paternal germ lines, maternal immune dysregulations responsible for a pro-inflammatory state and endocrinological alterations, especially concerning an altered responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis, capable of conditioning the placental environment and, consequently, fetal neurodevelopment [5,12,14].

Maternal exposure to childhood trauma has been associated with changes in the physiological systems of response to fetal-placental stress during pregnancy, in particular with changes in the levels of cortisol and pCRH (placental Corticotropin Releasing Hormone), a hormone produced by placenta, having a fundamental role in initiating and maintaining pregnancy, in the regulation of the HPA axis of the fetus, whose production is also stress-related [12,22, 29, 30].

Compared to the unexposed, women exposed to childhood trauma in particular show an increase of about 25% of the pCRH levels in the final stages of pregnancy and an increase in its trajectory of about two times steeper (two-fold steeper) than at the deflection point in the 19th week of gestation [22].

Studies about women with stories of child sexual abuse (CSA), women with stories of abuse, but non-sexual (CA, Childhood Abuse) and non-abused women (NA, No Abuse) also found that women with CSA stories showed significantly higher levels of cortisol awakening response (CAR) at the end of the third quarter than CAs and NAs. On the contrary, in typical pregnancies, the levels of cortisol awakening response decrease with the progress of pregnancy [31].

2. Material and methods

Objective

According to the literature, maternal exposure to stress and trauma, both in the preconceived period and during pregnancy, can constitute a risk factor for the development of ASD in offspring [5,8,9,18]. Authors considered both perspectives, psychological (psychodynamic approach) and biogenetics.

The main goals of our research have been: assess the existence of a statistically significant difference between the case and control group; evaluate the differences between the two groups for each single event; evaluate the possible protective role of external support, both professional

and non-professional; evaluate the differences between the groups on type of event felt as most important, and the responses relating to this event concerning the possible peritraumatic dissociation, during the event or immediately later.

The peritraumatic dissociation is defined "as a complex array of reactions at the time of the trauma that include depersonalization, derealization, dissociative amnesia, out-of-body experiences, emotional numbness, and altered time perception"[32].

Sampling

The exposure to stressful and traumatic events was assessed in a population consisting of mothers of children with diagnosis of autism spectrum disorder (ASD) compared to a control population made of mothers of people with language disorder (LD). Both sample and controls were enrolled consecutively.

The research was carried out in the Child Neuropsychiatry Outpatient Clinic of the University Hospital of Palermo where the children of the interviewees (both the case and control group) received the diagnosis and check-ups.

Out of 50 mothers of children who received a diagnosis of ASD and were monitored in our clinic, only 22 mothers (natural mothers) gave their time to participate in this pilot study, and all who were considered have the characteristics required to be enrolled in this study. All mothers signed informed consent for participation in the study.

The control group consists of 50 mothers of children with diagnosis of language disorder (LD): this choice makes sense in the view of the same time of diagnostic offspring of DL and ASD.

The case group and the control group were comparable and homogeneous regarding some variables such as maternal age and SES (socio-economic status: housewife, middle school degree, two or more children).

In both samples women were excluded who did not want to participate in the research and mothers of children with a genetic syndrome (Trisomy 18, Fragile X, Down Syndrome, Angelman, Jacobsen and Rett Syndrome).

Tools

A brief preliminary interview checked the mothers' availability to take part in the interview and the absence of genetic syndromes in the children. We used both ADI-R and ADOS Scales for ASD diagnosis in children, TPL and TVL Scales for LD diagnosis, WIPPSI- IV and Bayley-III Scales to assess cognitive development. To assess the maternal exposure to stressful and traumatic events, we used a questionnaire, created for this research, divided in two sections. The first one, an adaptation of "Life Stressor Checklist – Revised" [33-36] consists of 32 questions, evaluating stressful and traumatic events experienced by the interviewees during their life (29 questions), the potential use or abuse of substances and psychotropic drugs (1 question) and the eventual support received by professionals, relatives or friends (2 questions).

In the event that the answer to the question was "yes", therefore if the mother reported that she had experienced that specific stressful and traumatic event, the interviewee was also asked to quantify through a 5-point scale, 1 corresponding to "not at all" and 5 to "extremely", how disturbing the event was and how much it continued to be when evoked.

The second section, an adaptation of the "Peritraumatic Dissociative Experiences Questionnaire" [20,37] consists of ten questions, aimed at assessing the eventual peritraumatic dissociation in coincidence or in the immediate proximity of the traumatic event. Mothers are asked to consider, among all the stressful events indicated in the first part of the questionnaire, those that have especially scared her, selecting a maximum of two; for each question, the interviewee can select an answer in a range from 1 to 5, 1 corresponding to "not true" and 5 to "extremely true".

It should be noted that the questionnaire was proposed as a structured interview in order to facilitate the grouping, the analysis and the evaluation of the reply, and to increase the reliability of the responses of the interviewed subjects.

Particular attention was paid to the choice of the place for the interview and to the evaluation, step by step, of any emotional reactions evoked by the questions proposed through the questionnaire. In one case, for this reason, it was preferred not to complete the interview. Questionnaires were administered by two health professionals (psychologist and children psychiatric).

Analysis

The answers obtained through the questionnaire were collected on an excel sheet and the statistical analysis of the data was performed with the "Open Source Software R" [35].

We used the "chi square" test for independence to compare the categorical variables, while for numerical variables in groups mean, standard deviation, median and range were given, and a non-parametric test, the "Wilcoxon test" for independent samples, was used for comparison between the two groups.

To obtain a general quantitative assessment of all stressful and traumatic events reported by the interviewed mothers, a simple summary parameter was calculated, counting all the positive answers to the questions in the first part of the questionnaire (the total number of experienced events) for each individual patient.

We evaluated a total of 28 events, excluding from this analysis the answers to questions 5, 14, 31, 32, for the following reasons:

- question n° 5 was excluded because there was no positive answer, in both groups.
- question n° 14 was not considered because it was asking about severe physical or mental disabilities of their children, without specifying that the child with ASD was not to be included. In fact, all mothers of the Case Group replied "Yes" to this question, having at least one child with ASD, which was of course the criterion which defined the group itself, while all mothers of control group, instead, answered "No" to the same question.
- questions n° 31 and 32 asked whether the interviewee had received support from professionals or relatives and friends. These two questions, therefore, were not about exposure to stressful and traumatic events, but represent "positive" factors. Therefore, they were evaluated separately.

A comparison of the rate of positive answers in the two groups was then performed individually for each of the 28 questions.

In the end, we evaluated the distribution of the event considered as the most significant in the two groups and the distribution of the score relative to the 10 questions regarding this event in the second part of the questionnaire. Statistical significance was analyzed with the "Wilcoxon test".

3. Results

Table 1 shows the mean, standard deviation, median and range of mother's age in the group of cases and in the group of controls. As shown, the age was comparable in the two groups. Cases and controls were also comparable for other variables such as SES (Socio-Economic Status), use of alcohol, drugs of abuse or psychotropic drugs.

The use of psychotropic drugs was slightly more frequent in cases than in controls, but the difference was not statistically significant. In almost all cases the use was sporadic, limited in time and related to events (grief), not accompanied by a psychiatric diagnosis in the mother interviewed.

The first goal of our research was to assess whether there was a statistically significant difference between maternal exposure to stressful and traumatic events in the two groups, using the answers to the questions in the first part of the questionnaire.

A first analysis was performed using the general summary parameter (the total number of positive responses to the questions for each patient in the 28 questions considered). Figure 1 shows how the distribution of that parameter (and therefore of the total number of experienced events) is higher in the group of cases. The median value is 7 in the cases vs 4.5 in controls, and the difference is significant (p = 0.03).

Groups	Mean	DS	Median	Range	p-value
Case	40.6	7.4	41.5	26 - 57	0.82
Control	40.1	6.6	39.5	26 - 53	

Table 1. Main characteristics of the two samples: age in years.

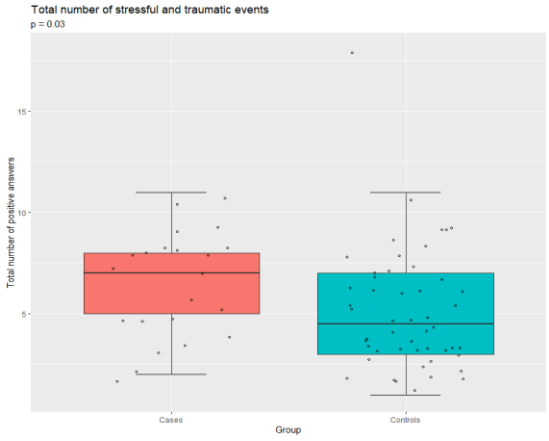

Figure 1. Boxplots of the distribution of the general score for the first part of the questionnaire in the two groups.

Then we analyzed the answers to each individual question in both groups to assess how each of them was related to the different distribution of the total number of events in the two groups.

For this purpose, we considered the rate of positive answers for each question, and Table 2 summarizes the results.

In this analysis, some questions (number 5, 14, 31, and 32) do not appear, because they have been excluded from the calculations, according to the criteria already mentioned.

For many questions a higher rate of events was observed in cases than in controls, in accord with the general trend observed in the previous global analysis. The only significant p values, however, were observed for the following questions:

- 4 (close relative imprisoned);
- 24 (sexual touching, as a minor);
- 29 (events experienced by a person close to the interviewed).

Many other questions showed some detectable higher rate of events in cases, with p values not significant, but < 0.15:

- 20 (having suffered a robbery or a physical assault by someone the interviewee did not know);
- 22 (having been mistreated or physically assaulted - not sexually - by someone the interviewee knew, as an adult);
- 23 (having suffered sexual harassment in the workplace or at school);
- 25 (having been forced in sexual touching when interviewee was of age);
- 30 (use of alcohol, drugs or psychiatric drugs to deal with on one or more occasions).

Positive answers			
Question number	**Cases**	**Controls**	**p-value**
1	2 (9.1%)	14 (28%)	**0.08**
2	5 (22.7%)	5 (10%)	0.15
3	5 (22.7%)	11 (22%)	0.94
4	9 (40.9%)	7 (14%)	0.01
6	0 (0%)	1 (2%)	0.50
7	2 (9.1%)	9 (18%)	0.33
8	5 (22.7%)	8 (16%)	0.49
9	4 (18.2%)	11 (22%)	0.71
10	7 (31.8%)	20 (40%)	0.51
11	0 (0%)	1 (2%)	0.50
12	7 (31.8%)	20 (40%)	0.51
13	0 (0%)	3 (6%)	0.24
15	10 (45.5%)	21 (42%)	0.78
16	7 (31.8%)	17 (34%)	0.86
17	19 (86.4%)	41 (82%)	0.65
18	3 (13.6%)	5 (10%)	0.65
19	7 (31.8%)	14 (28%)	0.74
20	5 (22.7%)	4 (8%)	**0.08**
21	2 (9.1%)	1 (2%)	0.16
22	5 (22.7%)	4 (8%)	**0.08**
23	6 (27.3%)	6 (12%)	**0.11**
24	4 (18.2%)	2 (4%)	0.04
25	1 (4.5%)	0 (0%)	**0.13**
26	0 (0%)	1 (2%)	0.50
27	1 (4.5%)	1 (2%)	0.54
28	8 (36.4%)	13 (26%)	0.38
29	9 (40.9%)	7 (14%)	0.01
30	8 (36.4%)	9 (18%)	**0.09**

Legenda: 1. Involvement in a serious disaster (earthquake, fire or explosion); **2.** Have witnessed a serious accident; **3.** Involvement in a serious accident;**4.** Close relative imprisoned; **7.** Separation or divorce; **8.** Have had serious economic problems; **9.** Have had serious physical or mental problems; **10.** Emotional mistreatment; **11.** Been physically neglected;**12.** Interruption of pregnancy; **13.** Forced separation from a child (loss of custody or kidnapping); **15.** Take care of someone close (not a child) with severe physical or mental problems; **16.** Sudden death of a close person; **17.**Death of a close person; **18.** Have witnessed violence between family members as a minor; **19.** Have witnessed robbery or a physical assault; **20.** Have been robbed or physically assaulted by someone the interviewee didn't know; **21.** Maltreatment or physical assault when the interviewee was a minor, by someone the interviewee knew; **22.** Maltreatment or physical assault when the interviewee was of age, by someone the interviewee knew; **23.**Having been bothered or tormented by observations of a sexual nature, jokes, requests for sexual performances at work or at school; **24.** Have been forced in sexual touching when interviewee was a minor; **25.** Have been forced in sexual touching when interviewee was of age; **26.** Have experienced sexual violence when interviewee was a minor; **27.** Have experienced sexual violence when interviewee was of age; **28.**Other events; **29.** Events experienced by a person close to the interviewee; **30.** Use of alcohol, drugs or psychiatric drugs (with or without a prescription) to deal with one or more of the events.

Table 2. Question number and corresponding stressing and traumatic event.

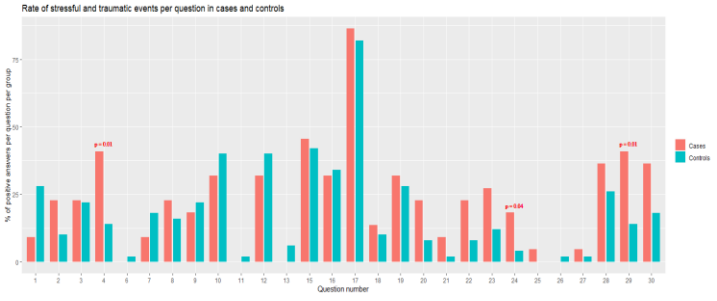

Figure 2. Rate of positive answers for each question, and the significant p-values.

In many other questions the effect is small.

Finally, in a few cases an opposite effect can be detected, even if not significantly, with a higher rate of events in controls, for example in the following questions:

- 1 (involvement in a serious disaster (earthquake, fire or explosion);
- 7 (separation or divorce);

- 10 (emotional mistreatment);
- 12 (interruption of pregnancy).

Figure 2 shows a bar plot with the rate of positive answers for each question, and the significant p-values.

Table 3 summarizes, in order of statistical significance, the questions and related events in which a p-value < 0.15 was observed.

Questions 31 and 32 evaluated the support received by professionals (question number 31) or relatives and friends (32).

Table 4 shows the results: as it can be seen, there is no significant difference between cases and controls for either of the two questions. The support received by relatives and friends appears to be much more frequent than the support received by professionals in both groups.

NN	Question	Event rate	p-value
4	Close relative imprisoned	Higher in Cases	0.01
29	Events experienced by a person close to the interviewee	Higher in Cases	0.01
24	Sexual touching when interviewee was a minor	Higher in Cases	0.04
20	Robbery or physical assault by someone the interviewee didn't know	Higher in Cases	0.08
22	Maltreatment or physical assault when the interviewee was of age, by someone knew	Higher in Cases	0.08
1	Involvement in a serious disaster	Higher in Controls	0.08
30	Use of alcohol, drugs or psychiatric drugs (with or without a prescription) to deal with one or more of the events	Higher in Cases	0.09
23	Having been bothered or tormented by observations of a sexual nature, jokes, requests for sexual performances at work or at school	Higher in Cases	0.11
25	Having been forced in sexual touching when interviewee was of age	Higher in Cases	0.13

Table 3. Questions and events in which a p-value < 0.15 was observed.

N°	Question	Cases	Controls	p-value
31	Support received by professionals	6 (27.3%)	14 (28.0%)	0.95
32	Support received by relatives or friends	20 (90.9%)	42 (84.0%)	0.43

Table 4. Questions about support received by others.

Finally, each mother was asked to indicate which of the events she experienced was the most stressful. Table 5 shows the events indicated by at least three people and the percentages of each in the two groups. Overall, the distribution is similar in the two groups (p = 0.5059). Only three events were indicated more frequently in the cases group, but the differences are very small and not significant.

N°	Event	Total	Case (%)	Controls (%)
17	Death of a close person	21	**36.4**	27.1
28	Other events	14	**27.3**	16.7
16	Sudden death of a close person	8	9.1	12.5
10	Emotional mistreatment	4	4.5	6.2
12	Interruption of pregnancy	4	0	8.3
29	Events experienced by a person close to the interviewee	3	**4.5**	4.2

Table 5. Events experienced as most stressful or traumatic by the interviewed women.

In the second part of the questionnaire, the interviewee gave an answer about the possible dissociative response to the event she considered most significant, in a semi-quantitative scale ranging from 1 to 5. No significant differences were observed in this part of the analysis.

Figure 3 shows the boxplots and p-values for each of the ten questions relating to the second part of the questionnaire.

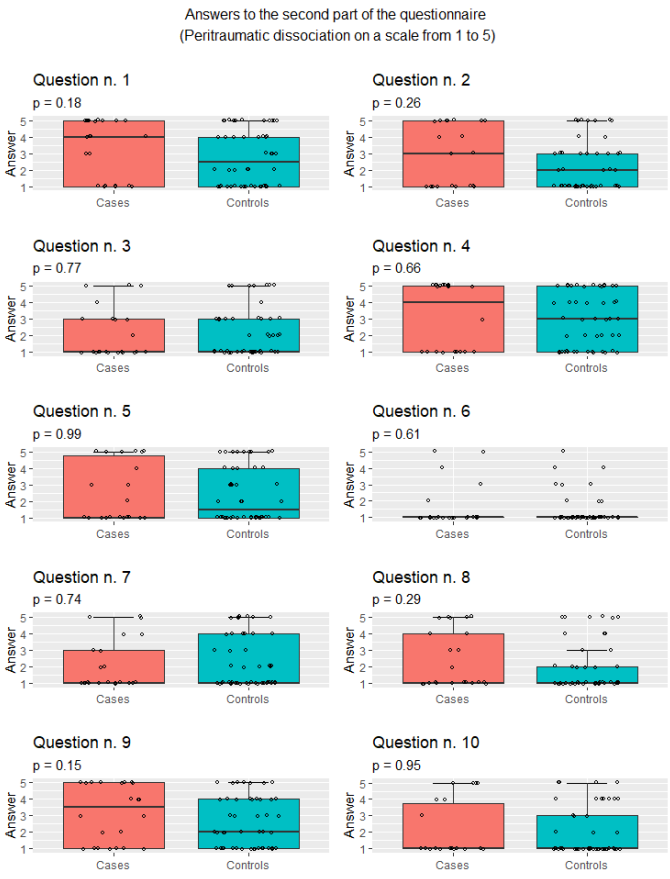

Figure 3. Boxplots and p-values for each of the ten questions relating to the second part of the questionnaire.

4. Discussion

Our study examined the possible correlation between maternal exposure to stressful and traumatic events and the presence of autism spectrum disorder (ASD) in offspring. The results showed that the mothers of children with ASD were apparently exposed to a greater number of stressful and traumatic events during their lifetime, compared to the mothers of children with language disorders (LD) in the control group. Indeed, a significant difference was observed using the global number of events mentioned by each interviewed as a global parameter (median number = 7 in cases and 4.5 in controls, p = 0.03).

The evaluation of the individual stressful and traumatic events showed a statistically significant difference between the two groups only for three questions (4, 24 and 29) of the questionnaire, i.e. those assessing the imprisonment of a close relative, having been forced in sexual touching as a minor; and one or more indirect stressful and traumatic events experienced by a close person. A few other questions showed some (not significant) effect, as shown in Table 3, and in many other questions the difference was small or even opposite (with a higher rate of events in controls). Of course, this analysis of the individual effects is based on a small number of observations, and no difference would remain significant if adjusted for the high number of comparisons.

However, the observed results seem to show that only some specific traumatic events are truly responsible for the global significant difference in the two groups. Even if further studies with a larger number of observations are certainly necessary to confirm our data, a few comments can be proposed here.

For example, "having a close relative in prison" is in our sample one of the most significant risk factors involved in the etiology of ASD in offspring, and there could be at least two explanations for that. Firstly, this event, when experienced by the mothers, is considered stressful and could configure that set of psychological, relational, social, environmental, economic, etc. dimensions attributable to a "complex" traumatic condition [21].

Secondly, subjects with history of imprisonment often present characteristic personality traits and psychiatric disorders with an important genetic background which, therefore, are more likely to be found in relatives (in our case the mothers interviewed); as several studies suggest, the genetic risk for autism may overlap the genetic risk for other neuropsychiatric disorders; thus, these elements would constitute "indicators" of the risk of ASD [9].

Another significant effect was also observed for the event corresponding to question 29 (events experienced by a person close to the interviewee) and 24 (sexual touching as a minor).

Some minor effect was also present for questions 20 (having undergone a direct assault or robbery), 22 (having been physically abused by a known person when the interviewee was of age), 30 (use of alcohol, drugs or psychotropic drugs to deal with one or more events), 23 (having suffered sexual harassment in the workplace or school) and 25 (having been forced in sexual touching when interviewee was of age).

It is interesting to note that a limited number of stressful events, with some common elements, seem to affect the total score difference between the two groups, while others have apparently no effect, or even an opposite effect (for example, events related to question 1, involvement in a serious disaster, are more frequent in controls). In fact, the events apparently related to ASD offspring seem to be more “personal”, events in which the mother was subjected to physical or emotional violence in the first person or experienced such violence through a person very close.

It seems that the type of traumatic event definitely has some relevance, and that violence related to the physical and sexual sphere has a greater impact than other, more impersonal events, like a generic disaster like earthquake, a flood, a fire or an explosion.

Therefore, the dominant theme here seems to be the violence suffered: the event must be perceived as serious and personally relevant, and above all as violent and unjustifiable. It is no coincidence that the accidental event, as far as possible, is understood and accepted, while the violence suffered, whether it is purely physical or even emotional, is not.

Other works in the literature confirm the correlation between maternal exposure to different forms of abuse (emotional, physical and sexual) and the increased risk of ASD for offspring [8,9]. Although in these studies all perinatal adverse circumstances such as smoking, alcohol abuse, previous abortions, gestational diabetes, preeclampsia, SSRI therapy and maternal age were more prevalent in mothers exposed to abuse, this would only partially justify the increased risk of ASD for offspring, suggesting the involvement of other mechanisms [8,9]. It is possible that exposure to child abuse induces the activation of inflammatory and autoimmune processes in the mother, with consequences also during pregnancy [8,14].

In fact, the dysregulation of maternal cytokines-chemokines contributes to the neurodevelopmental alterations of subjects with ASD and the same could be said of maternal autoantibodies capable of crossing the placenta during pregnancy and reacting against fetal brain proteins [5]. Another mechanism involved is represented by epigenetic changes affecting maternal and paternal germ lines, including DNA methylation, post-transduction modification of histones and non-coding RNAs, processes that regulate the expression of some genes involved in the regulation of neuronal function and immune system [12,14,39,40]. Maternal exposure to stressful and traumatic events correlating with an increased risk of the onset of other neurodevelopmental disorders in offspring, such as ADHD, affecting the brain anatomy of the newborn, could influence the choice of the partner by the mother, making her prefer subjects with autistic traits and thus increasing the risk of ASD in the offspring [13,41,42]. A further element to consider in the association between stress and maternal trauma and the onset of ASD in offspring is the maternal susceptibility to stress, in relation to the maternal genotype of the serotonin transporter (SERT). The most common variation of this gene is SLC6A4, an insertion/deletion of 43 base pairs in the promoter region (5-HTTLPR) of the SERT gene, resulting in a long (long allele) or short (short allele) allelic variant [5].

Some studies have shown that mothers of children with ASD who presented the short variant of the 5-HTTLPR allele, compared with mothers with the long allelic variant, had experienced a greater number of stressful events and reported greater severity about it. This finding shows that maternal polymorphism for the gene coding for the serotonin transporter is associated with a higher incidence of stressful events during pregnancy among mothers of children with ASD [15]. Finally, particular attention should be paid to question 30 of the questionnaire assessing "the use of alcohol, drugs or psychotropic drugs to deal with one or more stressful and traumatic events" among the events with considered significant effect [43-45]. However, it is shown to have no statistical significance in this study. This data allows us to hypothesize that women exposed to particularly stressful and traumatic events during their life will assume risky behaviors more likely than those not exposed; behaviors that could influence and compromise not only maternal health, but also fetal development in subsequent pregnancies [46].

Lastly, support from family, friends or professional figures was verified. It has been observed more frequently than the request for help to a professional figure, a phenomenon often attributable to the trauma itself and to the difficulty of having found valid help. The early intervention of professional figures through the application of standardized procedures could help victims of abuse and could improve patient outcomes [12].

Although the sample analyzed is small and excludes the fathers of children with ASD and with typical development, our study differs from others in the literature in several respects. The women interviewed are mothers of children who have received a diagnosis of ASD at our facility.

The questionnaire was administered in the form of a structured interview in order to facilitate the evaluation and analysis of the responses given. In addition, a very large number of stressors, potentially reactive during the entire life of the mother, were taken into consideration.

This is a case-control pilot study based on a small sample. The study does not claim to generalize the results obtained and although the results are only preliminary, they can certainly constitute a starting point for future works.

5. Conclusions

The finding of a greater number of stressful and traumatic events in mothers of children with autism spectrum disorder (ASD) compared to mothers of children with language disorder (LD) suggests the existence of a relation between maternal exposure to stress and trauma and the risk of developing ASD in offspring. Despite the limitations deriving from the small number of cases, our study highlights the presence of this association and analyzes which events, specifically, can be more involved. Among the stressors considered, having a relative in prison, sexual touching as a minor and the indirect experience through a close person of stressful and traumatic events appear to be more related to ASD in offspring in our sample. Other events related to violence suffered, both physical and sexual, do not reach statistical significance, but seem to have some effect. Our results did not reveal any relevant differences in the two groups between the support received from the professional figures or from people emotionally close to them. However, the second type of support was much more frequent than the first in both cases and in controls. Finally, it should be noted that these results are preliminary and preparatory for subsequent works; therefore, results may not to be generalized in the practice. Further research should be aimed at confirming the presence of a correlation between maternal exposure to stress and trauma and the onset of neurodevelopmental disorders in the offspring. It would also be necessary to deepen the role of any protective factors such as the enhancement of personal and coping resources called into question in dealing with highly stressful and traumatic episodes that, in addition to psychological trauma, may condition the life of parents and compromise the physiological neurodevelopment of subsequent generations.

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