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Maternal Estrogen Exposure and Autism Risk

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BY

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Abstract

A number of isolated studies have unearthed potential risk factors for Autism Spectrum Disorder (ASD), such as maternal obesity, close birth spacing and conception while taking birth control. These findings are consistent with the idea of a link between maternal endogenous estrogen exposure and ASD risk. The current research seeks to explore whether these risk factors can be best conceptualized in terms of the hormonal milieu that the maternal environment provides, by investigating the above mentioned factors in the same cohort, along with a number of other indicators of maternal hormone profile. The biological mothers of children with ASD (n=253) and the biological mothers of typically developing children (n=221) were asked to complete an online survey designed to delineate maternal hormone profiles both before and during each pregnancy. The survey asked about previously established risk factors for ASD, as well as those yet to be explored in mothers of children with ASD that are expected to be influential, if differences in estrogen profiles is a general risk factor (e.g. breast cancer, hypothyroidism, early age at menarche, etc.) The two groups showed significant statistical differences in their rate of estrogen influenced health indices (breast cancer, rate of hyperthyroidism, Body Mass Index (BMI) and age at menarche), but not other health indices (other types of cancer) suggesting a possible connection between maternal estrogen levels and the pathogenesis of ASD. This is the first study of its kind to hypothesize and explore such a link. The results from this study implicate maternal hormonal profiles as worthy of future study in relation to the etiology of ASD.

Autism Spectrum Disorder (ASD) encompasses a category of neurodevelopmental disorders characterized by two hallmark symptoms: a decrease in the tendency to communicate and socially interact, coupled with an elevation of restricted interests and repetitive behaviors (American Psychological Association, 2013).

Rates of ASD have reached a record high of 1 in every 68 births, which represents a 220% increase since 2002 and an 877% increase since 1993 (The Center for Disease Control, 2016). Recent research indicates that changes in the diagnostic criteria and reporting practices may not completely account for this higher prevalence (King & Bearman, 2009; Polyak, Kubina & Girirajan, 2015), and that an examination of the impact of changing environmental and societal trends is justified (Helt, Bocobo, Bunker, Lasky, in preparation). The current research hopes to expand our understanding of changing risk factors and biological underpinnings for ASD by examining whether maternal estrogen exposure, which has been rising in recent decades (Segovia-Siapco, Pribis, Messina, Oda & Sabate, 2015; e.g. Leddy, Power, Schulkin & 2008), may have a bearing on ASD risk.

Despite the fact that ASD is a genetically loaded developmental disorder (e.g., Geschwind, 2011), genetic research has done little to unearth ASD's specific biological underpinnings; as a result, a definitive pathogenesis remains inconclusive. For instance, there exists about an 80% concordance rate between identical twins, a 30% concordance rate between fraternal twins, and a 20% concordance rate between siblings of any type (Bohm, Stewart & Healy, 2013). However, despite the high concordance rates, over 700 different genes have been implicated as contributing to the disorder, and many are non-specific

exemplified by the fact that the same genes may appear in unaffected siblings or in those with other diagnoses such as schizophrenia. Remarkably, even within a single family, there is a mere 5% chance that two siblings having ASD will share the same genetic basis for it (Geschwind, 2011). Moreover, as interpregnancy intervals (IPI's) increase, the sibling concordance rate decreases (Bohm et al., 2013). If common genes cannot fully explain the high concordance rates between siblings, a look at environmental factors shared between siblings is warranted: namely, the maternal, or uterine, environment (Helt et al., in prep).

Hormones originating from the mother and supplied to the baby via the circulatory system directly aid with pregnancy and fetal brain development. Indeed, maternal and fetal hormone levels have been shown to possess moderate correlations with each other (Troisi, Roberts & Harger, 2003). Thus, the specific hormonal makeup of the in-utero environment constitutes an important, yet sparsely explored factor to consider when investigating the development of ASD (Helt et al., in prep). Previous research has conjectured that elevated maternal testosterone levels during pregnancy lead to an increased risk of ASD in children (Baron-Cohen, 1999). Baron-Cohen postulated that an extreme male brain develops in response to exposure to elevated fetal testosterone levels. He and his colleagues have hypothesized that an overly androgenized brain is one that possesses a strong ability to systemize, while also being unable to empathize. It is possible that because the androgen theory was the first research on a possible hormonal cause for autism, it has discouraged consideration of other hormones to which fetuses are exposed, such as estrogen.

Estrogen is a class of hormones, classically believed to solely function as part of the reproductive system (Shughrue & Merchenthaler, 2000). However,

recent research has exemplified it as a neuro-hormone: one which affects the daily functioning of the brain and possibly even its development (McCarthy, 2008). Hormones are synthesized in the endocrine system and function as signaling molecules for certain target cells. Intriguingly, gonadal steroid hormones possess a very unique chemical structure that has lipophilic qualities. This trait allows hormones such as estrogen to cross semi-permeable cellular membranes, by means of simple diffusion. Steroid hormones act upon the nucleus of their target cells and modulate gene transcription. Thus, large amounts of any steroid hormone could be expected to have an impact on many of the target tissues throughout a developing fetal Central Nervous System and may even have the ability to alter gene expression (Helt, et al., in prep). Ergo, hormones such as estrogen may exert powerful epigenetic effects upon a developing fetus (Saffarini, McDonnell, Amin, Huse, & Boekeldheide, 2015).

Estrogen most often enters the bloodstream endogenously; it is produced by the ovaries, the adrenal glands, and fat tissues. The hormone may also enter the blood exogenously, when it is directly administered by means of fertility treatments & oral contraceptives, when one is directly exposed to estrogen mimicking compounds in the environment such as bisphenol-A (BPA), or when one is simply consuming excessive amounts of dairy, red meat, or soy (Patisaul & Jefferson, 2010).

We are unaware of any research that has directly investigated a potential link between fetal estrogen exposure and ASD. Yet, a number of unrelated and isolated papers have reported findings that seem to be consistent with the idea that elevated maternal estrogen levels constitute a risk factor for the development of ASD. These include studies related to the reproductive system

(Cheslack-Postava, Liu, Bearman 2011; Lyall, Pauls, Santangelo, Spiegelman & Ascherio, 2011), studies with respect to general health indices (Lyall et al., 2011), and studies in regards to exposures to endocrine mimicking chemicals: oral contraceptives & ovulation inducing drugs, and environmental exposures to heavy metals, bisphenol-a (BPA), dichlorodiphenyltrichloroethane (DDT), phthalates, and mercury (Funderbunk, Carter, Tanguay, Freeman & Westlake, 1983; Lyall et al., 2011).

Lyall and colleagues (2011) examined the median maternal age of menarche and Body Mass Index (BMI) in connection with ASD; most of which are indicators of maternal estrogen dominance. It has been shown that women who begin to menstruate at a younger age are exposed to the hormone for a longer period of time than women who experience menarche at an older age. Data was gathered from over 61,000 mothers and analyzed by means of binomial regression analysis. The investigators found that early age at menarche was significantly and positively correlated with an increased risk of giving birth to a child with ASD. This is consistent with the hypothesis that women who have greater lifetime exposure to estrogen, and thus, greater circulating levels of the hormone, are at higher risk of having a child with ASD.

Another potential indicator for an increased risk of birthing a child with ASD is elevated BMI. In the same study, the researchers found that mothers with BMI scores greater than 30 by the age of 18 more than doubled the risk of having a child with ASD. Furthermore, in 2002, Wilkerson, Volpe, Dean, & Titus performed a similar study which yielded results that paralleled those findings. The investigators collected data via the maternal perinatal scale, which is a self-report about complications during pregnancy and general maternal health.

When contrasting 183 biological mothers of children with ASD to 209 healthy controls, the mothers of children with ASD had significantly higher BMI's (Wilkerson et al., 2002). Similar to early age at menarche, high BMI has been accepted as an index of high endogenous estrogen, as fat cells facilitate the storage of estrogen. Thus, these findings are also consistent with the hypothesis that high levels of estrogen may constitute a risk factor for the development of ASD.

If high estrogen levels constitute a risk factor for ASD, we may expect that mothers of children with ASD and their relatives would show an increased incidence of estrogen sensitive cancers; yet, extant research is contradictory about whether this is tru. Knickmeyer, Baron Cohen, Wheelwright and Hoestra (2007) administered a medical questionnaire to 54 women with ASD, 74 to mothers of children with ASD, and 183 to mothers of typically developing children. Mothers of children with ASD were much more likely to have a personal history of breast cancer and uterine cancer. Moreover, these same mothers reported having at least one relative who also possessed one of the aforementioned cancers. Although the authors discussed their findings in terms of the influence of testosterone on these cancers, there is a plethora of literature illustrating that estrogen exposure increases vulnerability to these cancers (Clemons & Goss, 2001). However, this potential link between cancers and ASD rates necessitates more exploration as a second study failed to replicate this finding. In 2009, the prevalence of estrogen-related female cancers in 111 mothers of ASD children and in 330 mothers of typically developing children was compared (Mouridsen, Rich, & Isager, 2009). There was no increased prevalence of estrogen sensitive cancers in the experimental group. Though, it is of note that the sample within

this study's experimental and control groups were much older than in Knickmeyer et al's (2007) study. Mother's ages in Mouridsen and Colleagues (2009) study averaged over 60 years old, which may have caused masking effects on the cancer findings, as the cancers women develop after menopause tend to not be as related to hormonal profiles, and thus the cancers women get at younger ages may be more relevant when conceptualizing possible ASD risk. These disparate discoveries in regards to cancer and ASD rates necessitate replication and clarification in order to further elucidate whether estrogen sensitive cancers and having a child with ASD share the common risk factor of elevated estrogen levels.

Other maternal risk factors, consistent with estrogen dominance, which may put children at risk for developing ASD, include having children after a relatively short IPI (Gunnes et al., 2013). Second born children conceived with an IPI of less than 12 months have a nearly four-fold increase in the risk of developing ASD, when compared with children born after at least a 36 month interval (Cheslack-Postava et al., 2011). Therefore, if a mother becomes pregnant within three months of giving birth, there is an increased risk of their child developing ASD. Because mother's estrogen levels increase during pregnancy, it is possible that the link between short IPI and ASD risk may be explained by the fact that estrogen levels following pregnancy may not yet have returned to baseline levels.

Indeed, elevated estrogen levels may constitute a risk of giving birth to a child with ASD, even when they result from exogenous exposures. Funderbunk and colleagues (1983), showed a positive correlation between women exposed to synthetic estrogen close to their time of conception and giving birth to a child

with ASD. The incidence of infertility and two or more spontaneous abortions among parents with ASD was significantly elevated when compared to the normal population due to the use of OID's (Ovulation Inducing Drugs), which contain estrogen mimicking chemicals. In Funderburk's survey of 61 patients, it was found that about 18% of the mothers had gestational exposure to estrogen compounds. Intriguingly, this frequency of gestational hormone exposure among the children with ASD was significantly higher than that of the general population.

Lyall and co-investigators (2011), compiled data from 2985 cohort participants in the Nurses study. Each had their child between 1993 and 2003. The women self reported their history of infertility and OID use in multiple questionnaires and were asked if their child had ASD. Exposure to OID's only before the first pregnancy was considered, which ensured that the exposure occurred before any child was born. Within the sample, 111 had ASD, and adjusted odds ratios demonstrated that a history of infertility combined with the use of OID's resulted in a two fold increase of giving birth to a child with ASD. Although the power to study the cumulative effect of OID's was very limited, there was a definitive trend: there existed a greater risk for giving birth to a child with ASD if the mother reported OID use on two or more questionnaires vs. if the woman reported no OID use at all. Clomid blocks estrogen receptors in the brain, thus tricking the brain into synthesizing more luteinizing hormone and follicle stimulating hormone due to lower "sensed" estrogen levels. The overproduction of these two hormones may result in higher estrogen levels (Helt, et al., in prep). These findings support our estrogen hypothesis of ASD.

The current study seeks to explore the idea that elevated maternal estrogen levels, due to either endogenous or exogenous causes, may increase the chance of giving birth to a child with ASD. The research involves the collection of survey data from parents of children with and without ASD in order to explore whether these previous findings will occur in the same group, and seem to be best explained under the theoretical umbrella of maternal estrogen levels. If maternal estrogen levels are indeed associated with risk for a child with ASD, we expect to see that the mothers of children with ASD would have higher rates of health problems associated with high levels of estrogen (for example, breast cancer and severe premenstrual syndrome) and lower rates of health problems associated with lower levels of estrogen (e.g. hypertension and hyperthyroidism); moreover, we would expect to see health profiles indicative of greater lifetime exposure to estrogen (for example, BMI and early menarche). This research is novel and very much exploratory.

Materials & Methods

Participants

The mothers of children with ASD and the mothers of typically developing children were recruited to participate in an online survey. Fathers and non-biological mothers were excluded from the study, as the variable of interest was in-utero exposure to estrogen. Also, mothers with children who had genetically or medically known causes of ASD (e.g., Fragile X Syndrome, tuberous sclerosis, Rett syndrome) were also excluded. 253 mothers of children with ASD and 221 mothers of typically developing children completed and

submitted the survey. The majority of the sample was recruited by means of CT-Listservs and aimed at parents of children with ASD or special needs. Each mother was then asked to recruit a friend or neighbor, to serve as her own control in order to decrease the variance in SES and age between the two groups. There were no significant differences in socio-economic status (SES) between the two groups, as measured by the Hollingshead Index (Cirino, Chin, Sevcik, Wolf, Lovett and Morris, 2002), $t(461) = 1.027$, $p = .98$. Moreover, there were no significant differences in the average age of the mothers ($M = 41.2$, $M = 42.5$), $t(461) = 1.33$, $p = 1.03$, or the average age of the children ($M = 9.8$, $M = 10.5$), $t(461) = .975$, $p = .245$, in both categories.

Measures

The online survey required participants to check boxes or type brief responses. As the study was focused on both the child and the mother, it required important demographical information. Some examples included: age of mother and child, number of children, gender, educational background, employment status, and diagnosis and developmental outcomes of their child or children. The main body of the survey was aimed at discerning indicators of maternal estrogen dominance and the mother's hormonal and general health profile; specifically, questions targeted towards topics such as menstrual cycles, contraceptive use, history of hormone related conditions, and body mass index. In addition, the survey asked about exogenous exposures during each specific pregnancy that would hypothetically contribute to maternal estrogen dominance. These included drug use, exposures to endocrine mimicking chemicals, and diet during pregnancy. Mothers accessed a link with a statement about the purpose and length of the study. Their consent was implied by their

continuation of the survey. The study was approved by the Institutional Review Board at Trinity College and was conducted by means of the Neuroscience Program and Professor Helt's Developmental laboratory.

Data Analysis

All of the categorical data from the online questionnaire was coded and analyzed using the Statistical Package for the Social Sciences (SPSS) software with Chi-Square analysis to investigate specific occurrences within each group. The variance and trends of the non-categorical data was examined by means of T-tests to look at differences between the two groups.

Results

After chi-square analysis, the group of mothers of children with ASD when compared with controls showed higher incidences of breast cancer, $\chi(1) = 5.067, p = 0.024$, a condition associated with high levels of endogenous estrogen (see figure 1). Specifically, the ASD group had more than double the chance of developing breast cancer and the mothers in the non-ASD group had breast cancer rates that did not significantly differ from the national average (Center for Disease Control, 2013).

Estrogen is protective against hyperthyroidism and as expected with our hypothesis, lower incidences of hyperthyroidism were seen when comparing mothers of children with ASD to those of typically developing children: $\chi(1) = 4.674, p = 0.031$ (see figure 2). As mentioned before, hyperthyroidism is a condition associated with lower levels of endogenous estrogen.

After performing paired T-tests, similar results were seen and were consistent with our estrogen hypothesis. In addition to the previous data, mothers of children with ASD reported both a higher body mass index by age 18, *t(461) = -2.89, p = 0.04* (see figure 3), and a younger age at menarche, *t(468) = 4.175, p < .0001* (see figure 4), both of which are consistent with greater lifetime exposure to estrogen compared with mothers of typically developing children. Fat is a storage venue for hormones, and the onset of menarche also means the beginning of the production of estrogen within the female body.

Results from chi square analysis that were not significant included: incidences of hypothyroidism, *χ(1) = 1.097, p = 0.295,* and rates of generalized female cancer, *χ(1) = 1.247, p = 0.264*, as well as all types of cancer *χ(1) = 1.02, p = 0.764*.

Discussion

The overall pattern of results were consistent with our hypothesis that elevated levels of maternal estrogen may constitute a risk factor for giving birth to a child with ASD. Mothers of children with ASD had earlier age of menarche, higher body mass index by age 18, lower rates of hyperthyroidism, and higher rates of breast cancer. All of those conditions are associated with higher than normal circulating estrogen levels (Lyall et al., 2011; Olivo, Gordon, Rafii & Southren, 1975; Knickmeyer et al., 2007).

Breast cancer is correlated with higher levels of estrogen (American Cancer Society, 2016; Clemons, 2011). Consistent with our hypothesis of a correlation between high levels of maternal estrogen and ASD, mothers of

children with ASD showed higher rates of health problems associated with high levels of estrogen such as breast cancer (see figure 1). Rates of all types of estrogen-related female cancers were not significantly different between groups. This may be due to the fact that some cancers have older ages of onset than the average age in our study cohort. Additionally, it may be because other types of estrogen sensitive cancers have very low base rates: it could have been that this study did not possess the necessary statistical power to find differences between the groups even if they exist.

Supporting our hypothesis, lower rates of health problems associated with lower levels of estrogen, such as hyperthyroidism (see figure 2), were seen in mothers of children with ASD. This can be explained by the fact that estrogen is protective against hyperthyroidism (Olivo et al., 1975).

Consistent with our hypothesis and previous research (Lyall et al. 2011), the experimental group showed higher rates of conditions associated with greater lifetime exposure to estrogen as illustrated by figures 3 and 4: the mothers of children with ASD had an earlier age at menarche (see figure 3). On average, the mothers of children with ASD received their period almost a year before the mothers of typically developing children. The average age of onset for menarche is decreasing, and it is possible that high levels of exogenous estrogen in meat and dairy products may be causing this circumstance (Segovia-Siapco et al., 2015); and as rates of ASD are also on the rise, it is possible that increased lifetime exposure to estrogen experienced by younger women directly impacts their chances of birthing a child with ASD (Helt et al., in prep) and that this could be a contributing factor to the skyrocketing rates in diagnosis.

Furthermore, our findings indicate that mothers of children with ASD had a higher BMI by age 18 (see figure 4) compared with the control group. Their BMI on average was about one point higher than the BMI of mothers of typically developing children. In previous studies where BMI was compared between the two groups in a similar fashion (Lyall et al., 2011), it was still seen to be significant when controlling for factors that have been previously been shown to affect ASD risk, such as infertility and ovulation inducing drugs (OID's). This finding supported our estrogen theory hypothesis as well.

If there is indeed a link between maternal estrogen levels and ASD risk, there are indirect and direct potential mechanisms of action that can explain this phenomenon (Helt et al., in prep). One possibility is that as estrogen levels rise, the immune system of a mother is lowered (Robinson & Klein 2015). This would put the fetus at risk for greater exposure to viruses, as prenatal exposure to viruses has been correlated with ASD risk (Grabrucker, 2013). Furthermore, it puts the developing baby at an increased vulnerability to toxins and teratogens, prenatal exposure to which has also been correlated with ASD risk (e.g., Dufour-Rainfray et al., 2011).

A second possibility is that the effects that estrogen exerts on neurotransmitters, particularly serotonin, increases the likelihood of ASD (Barth, Villringer & Sacher, 2015). Scientific literature has shown that Selective Serotonin Re-uptake Inhibitor (SSRI) use during pregnancy is correlated with higher rates of ASD (Boukhris, Sheehy, Mottron, Berard, 2016), and that a significant number of children with ASD show abnormal levels of serotonin (Ritvo, Yuwiler, Geller, Ornitz, Saeger & Plotkin, 1970).

A third, and more direct, possibility is that estrogen exerts strong epigenetic effects on the brain and can possibly change gene expression within the fetus for the worse, as it is responsible for turning many genes on and off early in development (Saffarini et al., 2015). Indeed, there appears to be a molecular dysregulation of estrogen receptors ERβ, CYP19A1, and ER-coactivators located within the middle frontal gyrus in children with ASD (Crider, Thakkar, Ahmed & Pillai, 2014). Thus, further study into a neurobiological basis for ASD at the cellular and molecular level is also warranted.

Finally, it is even possible that the notion of high maternal estrogen levels constituting a risk factor for ASD is compatible with the androgen or extreme male brain theory of ASD (Baron-Cohen, 1999). There is a potential that during human pregnancy, as during rat pregnancy, there is an aromatization of estrogens (estradiol, estrone, estriol) into fetal testosterone (Elbaum & Keyes, 1976). Thus, estrogen may potentially have defeminizing effects on the brain.

The link between maternal estrogen levels and ASD, should it be replicated in future studies, may be of greater concern and impact now than it would have been in previous decades given the abundant environmental exposures to xenoestrogens in the current environment (Helt et al., in prep). If so, it may be that the relationship between elevated maternal estrogen and ASD risk is much more sensitive for the milder phenotypes of ASD, which are now diagnosed after the change in diagnostic criteria to a spectrum (Helt et al., in prep).

The strength of this study is rooted in its novel and exploratory nature. However, the present study does possess limitations. The sample size was too small for definitive conclusions to be drawn, and the population used (mothers who were part of CT listservs aimed at parents of special needs and children with ASD specifically) may not be representative of all mothers. Also, the respondents relied on their memories for their health history, as opposed to checking their medical records. Future studies can mitigate these factors by using a larger sample size and possibly even conducting the study prospectively and longitudinally with currently pregnant women (at risk for birthing an ASD child). In this circumstance, more direct tests could be performed on mothers' current hormonal profiles. All of the aforementioned could be beneficial in terms of future exploration of the link between ASD risk and maternal estrogen levels.

In sum, there is a potential that brain development may be negatively affected by gestational exposure to high levels of estrogen in a manner that increases risk for ASD (Helt et al., in prep). If so, the implications could be tremendous. For example, it is possible that mothers could actually change their risk of having a child with ASD by proactively altering their behavior. For instance, they could change their diet and limit their exposure to xeno-estrogens and other endocrine mimickers (e.g. plastics, beauty products, highways, pesticide rich environments, mercury coal producing plants). This is crucial, as the average woman in America puts 6 endocrine mimicking compounds in her body every day.

Given the expansion of endocrine mimicking chemicals in the environment in recent decades, could changing maternal hormone profiles be part of the reason for the diagnosis of ASD being on the rise? This study

necessitates replication using a significantly larger sample size before definitive conclusions may be drawn, though our hypothesis was supported: the mothers of children with ASD had higher rates of health problems associated with high levels of estrogen and lower rates of health problems associated with lower levels of estrogen, suggesting a link between estrogen exposure and ASD. This warrants further investigation into our hypothesis and other potential mechanisms of action that can explain this phenomenon if future research parallels our findings.

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Figure 1. Incidence of breast cancer in mothers of ASD children vs. in mothers of typically developing children. $\chi(1) = 5.067, p = 0.024$
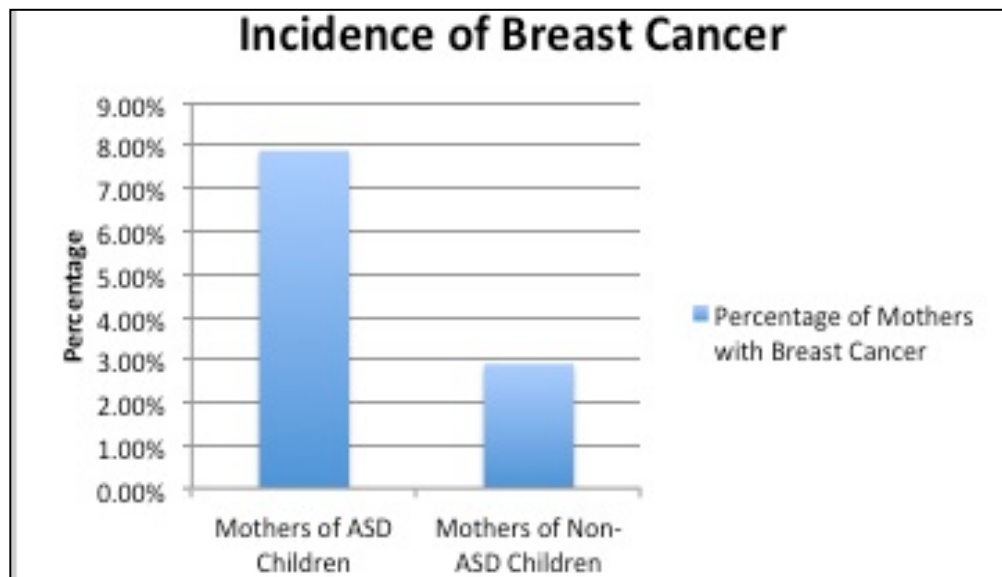

Incidence of Breast Cancer

Figure 2. Incidence of hyperthyroidism in mothers of ASD children vs. in mothers of typically developing children. $\chi(1) = 4.674, p = 0.031$
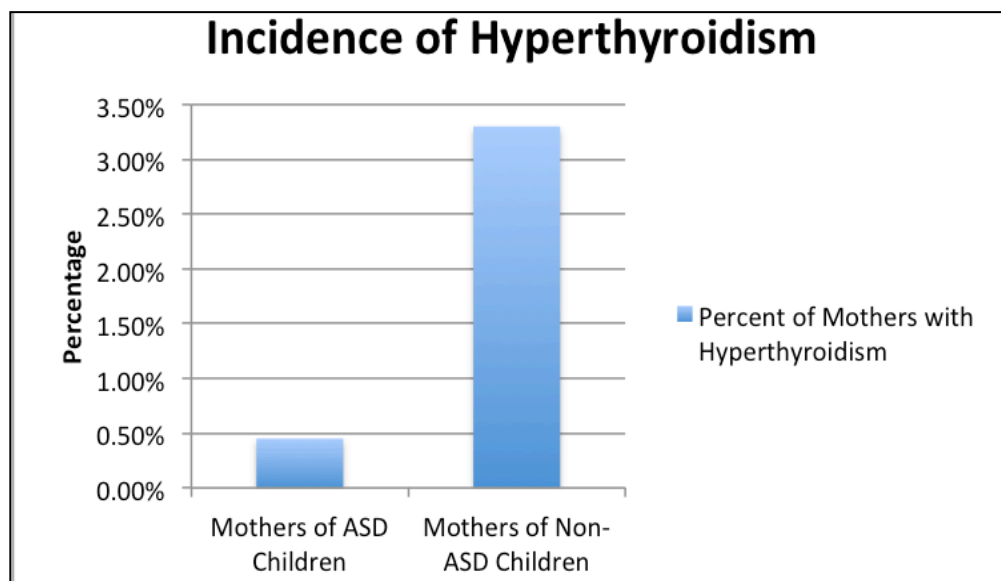
Figure 3. Average age of menarche in mothers of ASD children vs. in mothers of typically developing children. ***t(461)= -2.89, p = 0.04***
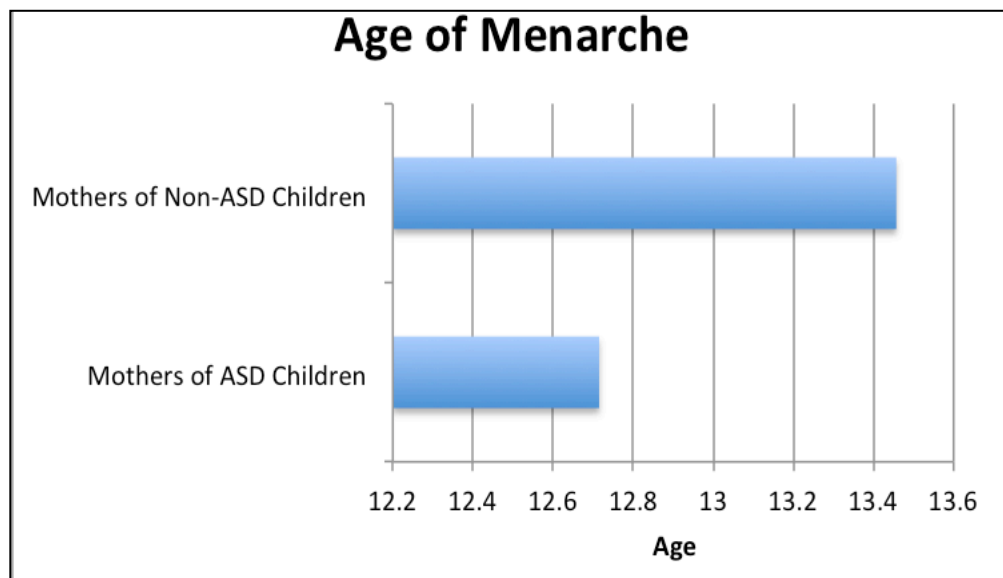
Figure 4. Average BMI by age 18 in mothers of ASD children vs. in mothers of typically developing children. *t(468) = 4.175, p < .0001*