with ASD show genetic, neurologic or metabolic differences that may be causally linked to this disorder; the origins of the remaining majority of cases remain etiologically obscure. Neuro-structural differences in the developing brain in children with ASD have been identified. In this context, inflammation has been cited as a contributing factor responsible for these neuro-structural differences. Additional epidemiolog

Epidemiological data on pediatric illnesses show not only an elevated incidence of ASD over the past several decades, but also in the incidence of childhood infections, asthma and other autoimmune disorders, whose rate of increase has occurred in parallel to that of ASD [5-7]. The link between infectious disease and brain development can be found in research that has shown that immune system cytokines whose levels may be affected by infectious disease play an important role in normal brain development as well as contributing to pathological injury to the developing brain.

In support of the posited risk factor/ASD incidence rate association, clinical data suggest that the incidence rates of early childhood infections have increased significantly over the past several decades. Clinical research studies on the patterns of childhood infections have shown that rates of infant and early childhood infectious disease have been affected by changes in early childhood care practices over the past half century that have been associated with an increased incidence of pediatric infections despite the widespread availability of antibiotics and vaccines.

The cause may be related to changes in infant care practices that result in increased risk of exposure to infectious disease early in life. According to Monthly Labor Review, one of the most dramatic changes in the US society in the past 75 years has been the increasing percentage of women, including mothers of infants that work outside the home, resulting in a substantial increase in the number of infants in daycare [8]. In 2014 the percentage of US children of working mothers in daycare under a year old was 57.1%. Research has shown that incidence rates for infections in infancy are higher for babies cared for in multiple settings, particularly daycare. A study by Bell et al. in 1989 of 843 children under 36 months of age showed that children cared for at home had 2.03 infections on average during the six month study period [9]. Adjusted rates of excess infection rates were 0.09 in relatives' homes, 0.1 in daycare homes, 0.79 in day care centers and 0.66 in multiple settings. Interestingly, the strongest predictor of early childhood illness was the number of children in a single room in a caregiving facility: the greater the number of children, the greater the infection rate. Moreover, children in daycare centers were 4.5 times more likely to be hospitalized for infections than children in other care settings.

An additional study by Hurwitz et al. showed a statistically significant increase in respiratory illness rates in infants from 6 weeks to 17 months who attended group daycare [10]. Yet another clinical study by Shay et al. showed that between 1980 and 1996 rates for hospitalization of infants suffering from bronchiolitis increased significantly, particularly among children younger than 6 months, in which the increase was 239% [11]. Moreover, the rate of hospitalization for children with bronchiolitis increased for all age groups during this time period. These infectious disease rate increases correlated with increased rates of early childhood daycare enrollment during this period. Among children of working mothers aged between 1 and 2 years, the enrollment percentage increased from 12% in 1982 to 25% in 1993. For children 0–12 months, this percentage rose from 5% to 20% during this time frame. The authors concluded that the trend of increasing childcare enrollment in group daycare may be associated with increased rates of respiratory syncytial virus (RSV) associated bronchiolitis in very young children. According to a study by Hagerhed-Engman et al., children who attended day care had an increased risk of airways infections, eczema and food allergies [12]. A total of 10,851 children, 1–6 years were assessed in this study. This increased risk was mainly seen in younger children 1–4 years.

To the extent that immune system responses to early childhood infectious disease may, in some (genetically predisposed?) children, affect critical windows of brain development, the incidence and severity of early childhood infectious disease rates from any cause may represent a risk for ASD.

Modern caregiving trends increasingly have involved shorter duration of exclusive breastfeeding as the primary source of infant nutrition as well as the introduction of a variety of solid foods early in life. Earlier childrearing practices into the 20th century in the US and most parts of the developed world involved breastfeeding (often exclusively) for most of the 0–3 years critical IS/CNS developmental window associated with ASD risk.

Several important research studies have shown that specific infant feeding patterns such as early introduction of bottle feeding or solid food in place of longer periods of exclusive breastfeeding may lead to reduced lung and airway growth and increased risk of autoimmune disorders [13]. The link between breast- feeding duration and immune system function may involve components of breast milk that affect immune system stability and function. These stabilizing effects of breast milk on the immune system may also have a protective effect against ASD. The correlation between infant feeding pattern and ASD risk is particularly compelling given the documented association between gastrointestinal dysfunction in infancy and ASD [14].

Maternal (and possibly paternal) obesity comprises another important risk factor for altered brain development and ASD. Currently, approximately 34% of women of childbearing age in the US are obese; these numbers have increased appreciably over the past several decades. A US study of 1311 mothers and children between 2005 and 2012 showed that severely obese mothers (BMI>35) were three times more likely to have a child who develops ASD [15]. The increased risk of ASD in children of obese mothers was independent of other risk factors, including pregnancy weight gain, gestational diabetes, duration of breastfeeding, postnatal depression or infant birth weight.

Maternal gestational diabetes (GDM) is often associated with obesity and represents yet another (separate from obesity) risk factor for ASD. A study by Feig et al. conducted in Ontario, Canada showed that the incidence of GDM and pre-GDM in pregnancy doubled between 1996 and 2010 [16].

In utero exposure to drugs that interact with neural pathways has been implicated as an important risk factor for ASD. Cannabis/ tetrahydrocannabinol (THC) is the most widely used psychotropic drug; its use has increased substantially over the past 20 years; moreover, more recent formulations of the drug display enhanced potency due to changes in preparation methods [17]. Currently, cannabis use during pregnancy is estimated at 10%. Recent studies by

can result from in utero cannabis exposure. Moreover, Siniscalco et al. [20] have suggested that the endocannabinoid (EC) system may play an important role in the integrated IS/CNS developmental pathway that is dysregulated in autism. Their research has shown that the cannabinoid receptor type 2(CBR2) signal pathway is upregulated in peripheral blood mononuclear cells (PBMCs) from children with ASD. This finding raises the possibility that the endocannabinoid (EC) system may be associated with ASD. In addition, the authors found reduced levels of bone marrow differentiated macrophages (BMDCs) in children with ASD that may be linked to altered CBR-2 levels.

Endogenous cannabinoids bind to type-1 cannabinoid receptors in the central nervous system (CNS) to guide neural pattern formation and network connectivity in the developing brain. Research by Cutando et al. provides evidence that THC binding of EC-1 receptors as a consequence of subchronic cannabis exposure may affect these signal pathways, at least in part, by activating microglial cells

T e Quantitative Exposure T reshold hypothesis for ASD is consistent with our current understanding of the epidemiological risk factors and etiological mechanisms connecting immune system dysfunction with abnormal brain development seen in ASD. T e model has important predictive value, as it suggests that, rather than attempting to identify a specifc causative agent linked to ASD, the combined risk factor profle should be evaluated in population studies in order to specify more accurately the limits of pre-threshold exposure.

While the QTE hypothesis proposes that the sum total exposure to

data suggesting that vaccines per se are linked to any increase in ASD