All of Life Inventory: Autism
Getting at the Roots of the Epidemic

Introduction. Although broadened and more sensitive diagnostic criteria appear to be contributing to some of the increase in autism rates, most researchers acknowledge that there is a significance increase is going on too:

- "The autism caseload in California increased 600% between 1992 and 2006" Mazumdar, et al., 2012
- "Idiopathic autism, in particular, suspected to be caused by exposure of genetically susceptible individuals to unknown environmental triggers, has increased dramatically in the past 25 years" St-Hilaire, et al., 2012

As one author summarizes, "Researchers speak of 'epidemic outbreak' of the disease. Although the diagnostic framework has been expanded and thus more disorders now fall within the autistic spectrum, no one disputes the increased incidence of autism in modern societies, making it a major public health problem" Megremi, et al., 2013

Out of this concern, scientific activity has grown substantially, with "considerable research interest in determining factors which are etiopathogenetically, prognostically, preventively or/and therapeutically associated with the disorder" Megremi, et al., 2013

Despite abundant research (over 2000 studies pulled up in this lit review) , we continue talking as if we know very little about what's going on. One author, for instance, writes, "Despite the significant increase in autism spectrum disorer, there are few if any clues for its pathogenesis, hampering early detection or treatment" Angelidou, et al., 2012 Another states, "there is limited information regarding the susceptibility of specific autism candidate genes to dysregulation by environmental factors, and even less information on the types of environmental agents that may lead to increased risk for autism" Hu, et al., 2012

After 2000 studies, we believe the public deserves to hear more than declarations of "limited information" and "few if any clues" at what is going on. Indeed, this review alone confirms abundant information and *lots* of clues at what is (potentially) happening.

What usually happens is we get lost in debates regarding whether X or Y is "the cause" (or not) - insisting upon nearly insurmountable scientific standards that require tens of studies over many years - just to determine whether one particular factor could justifiably be called a "cause."

In the meanwhile, the general public is left in the dark of even the early hints- with little to no awareness of the range of possible contributors that have been identified. Rather than share possibilities science has uncovered, some insist that it remains "dangerous" to talk about risk factors until we know with complete certainty. For instance, Rutter, 2012 understandably cautions regarding the "avoidance of claims that go beyond the evidence" while Rossi, et al., 2013 goes even farther, noting that " much more risk information expected to follow from scientific studies currently underway":

> The availability of this risk information raises questions about whether and how it should be communicated to individuals, families, and the public at large. One ethical issue of particular concern with ASD risk communication is the possibility that it may cause inadvertent harm to risk message recipients.

While agreeing that great care should go into how and when information is communicated, it strikes me as unusual that the focus appears to be on the danger of saying 'too much' exclusively - rather than also saying *too little* (about an enormously powerful and insightful research literature that may be immediately helpful in understanding how to prevent and intervene in serious problems like autism).

In particular, a picture is emerging of compounding, cumulating "insults" to the body that can lead a child towards autism - "as a result of complex developmental interactions among brain networks" Elsabbagh, et al., 2011

When our focus is narrowly focused on one or two factors, however, this cumulative risk burden is missed. For instance, DeSoto, 2009 writes, "much professional awareness regarding environmental triggers for autism spectrum disorders has been narrowly focused on a single possible exposure pathway (vaccines). Meanwhile, empirical support for environmental toxins as a broad class has been quietly accumulating." Yudell, et al., 2013 adds, "the emerging picture of causation is in many cases complex, with multiple genes and gene-environment interactions being at play."

Interested in getting my own glimpse at the broad spectrum of potential contributors, I searched Pubmed for "risk factors" and "contributors" associated with autism. First in 2013, and with a follow-up two years later, I was astounded to find first 1400 studies, then another 1100 two years later. Although upwards of 2000 study summaries were reviewed, only a subset of those were identified as relevant. For instance, lots of studies look at autism as a risk factor itself for other things - such as obesity Egan, et al., 2013, bullying, self-injurious behaviors Duerden, et al., 2012, etc. Other studies consider risk factors for certain experiences within autism - like a family history of neuropsychiatric disorders and febrile seizures at risk for a subgroup of autistic regression Zhang, et al., 2012 or children born in spring-summer being less likely to have co-occurring schizophrenia spectrum traits (SST) Gadow, et al., 2012

Neither of these kinds of studies were relevant to this review - and were left to the side. Also left to the side were many of the molecular genetic and mouse studies looking at complex physiological patterns potentially involved with autism. While there are exciting findings emerging such as certain copy number variations (CNVs) Kirov, 2015 and the candidate genes MET, NRG3, and SLC6A4 Blair, et al., 2015 - my own skill-set and competence as a researcher is not sufficient to appreciate the nuance of these biological studies enough to identify their patterns. I leave that for others with that expertise.[1]

Of course, everything we do, we do in a body - so in a way, every item in the following survey is "biological" in some way. Furthermore, given the research on brain changeability and epigenetics (the 'fluid genome'), with other researchers I assume that a child's body will continue shaping over time to some degree with surrounding environmental factors in a complex developmental process. For this reason, I prioritize understanding of the surrounding, environmental factors - with a belief that through knowing them, we can help shape, heal and re-direct to some extent biological trajectories over time.

With the exception of in-depth brain and genetic science, then, the focus here was on any study - of any methodology - that shed light on a potential contributor to the development of autism. Rather than restrict to a particular kind of study, the assumption of methodological pluralism is that different kinds of studies offer different kinds of insights. By opening any review to a diversity of studies, the resulting picture likewise becomes diverse. This includes correlation and association studies that identify some kind of a connection between autism and another condition like acne. Even though acne is clearly not leading to autism - it comes up as connected with great

[1] In the biological area, then this review sticks with simple bio-markers and things that parents could recognize themselves or with a urine/blood test. As others review the genetic research and identify common patterns, they will be added to the survey.

regularity. For sake of discussion and exploration, we note these connections in our results as an interesting linkage that might offer a larger clue.

Indeed, the point here is to note the range of potential contributors - *not* to try and explain how and why they are associated. For instance, "Mothers of infants residing in regional or remote areas," according to one study, experience less autism Leonard, et al., 2011. Although the authors theorize the connection as explained by a lack of services that would ascertain whether autism exists, other might suggest a protection in being far away from medical technology that has been implicated in other studies as potentially problematic. Studies of an urbanization-autism link have a similar contrast in explanations. In both (and all) cases, which explanation ultimately accounts for a connection is not the interest of this review. That is left for others to determine.[2]

I don't pretend to know which of these potential factors legitimately account for more or less of any influence - or how they might work together. Neither does this survey justify anyone suggesting one factor is more important than another - only painting the 'mural' of everything potentially at play. Once again, the goal here is simply to map potential contributors to help deepen and expand the public exploration and discussion.

Each question identified below is linked to at least one legitimate medical study (with hyperlinks inserted in the references immediately following each question to allow for cross-checking and review of the studies). In creating questions, I stuck as close as possible to the language of the actual studies - trying to not deviate from to boundaries of what a particular finding allowed. For this reason, the language in the survey can sometimes feel a bit complex.

Even with only one study associated with a finding, the choice here is to let people know about it - not as a cause or an established contributor, but simply as a *potential contributor*. It is left to parents and professionals to determine if and whether any of these factors are worth considering further in prevention or intervention plans.

If it's true that many things play a role in the development of autism, then it makes sense that our intervention efforts should likewise be considering a variety of potential targets of intervention. By having all the potential contributors at their fingertips, parents will, I believe, be better prepared to make decisions regarding their current or future children.

If you find this review beneficial to you in any way, I would appreciate hearing your experience. If you are a practitioner who would like to use this in any way, you can do so without my permission. If you are a researcher who would like to further develop this instrument - and find ways to study it, I would love to talk about potential collaborations! My e-mail is jzhess@gmail.com.

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[2] Although explanation of factors is not the purpose of this survey, it is worth pointing out that it seems clear from many studies that these factors most often work together in various complex ways. For instance, "Studies show increased autism risk among children born to mothers experiencing obstetrical complications. Although this is usually interpreted as suggesting that the obstetrical complications could be causing autism, it is possible that a single factor could be responsible for both complications and autism" Whitaker-Azmitia, et al., 2014 Another researcher similarly notes, "The common link between the majority of risk factors assessed in this review (including technological advancements, advanced parental age, socioeconomic status, and genetic predispositions towards ASDs in families of scientists and engineers) can be traced to a specific hormone, testosterone" Wen, et al., 2014

All of Life Inventory: Autism

As rates of autism continue to rise, the amount of research has also grown. It has become clear that autism is a complex medical disorder with an enormously varied set of potential contributors. The purpose of this inventory is to catalogue and map any possibilities identified in the larger medical literature in terms of correlations or contributions to autism risk. Each question is derived from research linking a specific factor to autism. As a whole, the inventory aims to illuminate particular configurations of vulnerabilities in a given family's situation - and, more broadly, to foster a deeper national conversation about the diverse array of vulnerabilities that appear to be shaping disease risk. To score the inventory, total up all "yes" answers in each section (combined with the total "no" answers of questions in boxes). [In other words, unless it's in a box - a YES answer indicates risk]. Section by section, this total number gives you an indication of how many "hits" or "insults" exist associated with autism. On both a preventive basis (raising awareness for future parents) and an intervention basis (empowering current parents with updated research) we hope this will be helpful.

Mother's Early Life

(1) Was the mother exposed to abuse as a child? Roberts, et al., 2013
(2) Did the mother experience menarche (first menstrual cycle of puberty) at a relatively early age? Lyall et al, 2010
(3) At age 18, did the mother have a high body mass index? Lyall et al, 2010

Parental Education, Work & Socio-Economic Status

(4) Does the family have a high median family income Bhasin, et al., 2007, a high socioeconomic class Izuwah, et al., 2015 or general socioeconomic advantage? Leonard, et al., 2011
(5) Do the parents have a high education level Jahan, et al, 2014 - with the mother, in particular, having a relatively high level of education? Croen, et al., 2002 Bhasin, et al., 2007
(6) Does the mother have a relatively *low* level of education? Burd, et al., 1999 Wang, et al., 2005 Jaspers, et al., 2013
(7) Has the family had economic problems Larsson et al, 2009 or low income Wang, et al., 2005 Rai, et al., 2012 in the time prior to or during the child's birth - potentially including an unemployed mother? Khaiman, et al., 2015
(8) Are one or both of the parents engaged in manual labor of some kind? Wang, et al., 2005 Rai, et al., 2012

Parent Birthplace & Ethnicity

(9) Are one or both of the child's parents born outside Europe Hultman, et al., 2002 Lauritsen, et al., 2005 Eriksson, et al., 2012 van der Ven, et al., 2013 Australia Williams, et al., 2008 or North America? Hultman, et al., 2002
(10) Are the parents migrants Magnusson, et al., 2012 Bolton, et al., 2014 - especially with a mother coming from south-east or north-east Asia Williams, et al., 2008 or poorer regions Lehti, et al., 2013 with a low human development index? Magnusson, et al., 2012 (with the exception of Hispanic children) Lehti, et al., 2015
(11) Does the child have a black Croen, et al., 2002 Dealberto, 2011 Afro-Caribbean Goodman, et al., 1995 or non-white parent? Gallagher, et al., 2010

Family Health

(12) Do medical or developmental illnesses run in the family generally? Brimacombe, et al., 2007
(13) Is there a family history of ovarian, uterine, and prostate cancers, tumors, or growths? Ingudomnukul, et al., 2007
(14) Are there family members currently or in the past with autoimmune disorders Wu, et al., 2015, including type 1 diabetes Comi, et al., 1999 Atladottir et al, 2009 Wu, et al., 2015 adult rheumatoid arthritis Comi, et al., 1999 Atladottir et al, 2009 Wu, et al., 2015 hypothyroidism Comi, et al., 1999 Anderson, et al, 2014 Wu, et al., 2015

coeliac/celiac disease Ludvigsson, et al., 2013 Atladottir et al, 2009 psoriasis Wu, et al., 2015 and systemic lupus erythematosus? Comi, et al., 1999
(15) Is there a family history of Pink disease (infantile acrodynia), related to mercury poisoning? Shandley, et al., 2011

Family Mental Health
(16) Do mental or emotional challenges (sometimes called "psychiatric illnesses") run in the family generally Brimacombe, et al., 2007 Zhang, et al., 2012 and on the paternal side specifically Khaiman, et al., 2015 - including affective disorders such as major depressive disorder? Bolton, et al., 1998
(17) Does the mother struggle with psychiatric disorders Lauritsen, et al., 2005 Eriksson, et al., 2012 Rai, et al., 2013, including anxiety disorder Piven, et al., 1991 Jokiranta, et al., 2013, ADHD van Steijn, et al., 2012, depression Wilkerson, et al., 2002 Eriksson, et al., 2012 Rai, et al., 2013 Gao, et al., 2015 bipolar disorder Morgan, et al., 2012 or a schizophrenia spectrum disorder Larsson, et al., 2005 Sullivan, et al., 2012 Jokiranta, et al., 2013 including schizo-affective disorder? Gillberg, et al., 1992
(18) Does the father struggle with anxiety disorder Piven, et al., 1991 Jokiranta, et al., 2013, symptoms of obsessive-compulsive disorder (OCD) Kano, eta l., 2004, ADHD van Steijn, et al., 2012, depression Bolton, et al., 1998 Jokiranta, et al., 2013, bipolar disorder Sullivan, et al., 2012 Jokiranta, et al., 2013 or a schizophrenia spectrum disorder? Larsson, et al., 2005 Sullivan, et al., 2012 Jokiranta, et al., 2013
(19) Do any of the child's siblings struggle with affective disorder (e.g., depression or anxiety) Piven, et al., 1990 bipolar disorder Sullivan, et al., 2012 or schizophrenia? Sullivan, et al., 2012
(20) Is substance abuse common among parents and/or siblings in the immediate family? Gutierrez, et al., 1998

Family Social Characteristics
(21) Are there any notable social challenges and deficits in families Goussé, et al., 2011, including social phobia Gutierrez, et al., 1998 and general impairments in social functioning, such as a family pattern of being aloof, shy, over-sensitive, 'withdrawn' or 'difficult'? Murphy, et al., 2000
(22) Is there a pattern in this family's history of an underlying tendency to be anxious and 'tense'? Murphy, et al., 2000
(23) Is there a trend of family relatives having impulsive, irritable or eccentric traits Murphy, et al., 2000 or experiencing motor tics? Bolton, et al., 1998

Family Autism History
(24) Does the child have siblings with (even mild) autistic patterns Bolton et al 1994 Lauritsen, et al., 2005, especially a brother Eriksson, et al., 2012, an older sibling Schwichtenberg, et al., 2010 Ozonoff, et al., 2011 Werling, et al., 2015 or more than one sibling affected? Schwichtenberg, et al., 2010 Ozonoff, et al., 2011
(25) Are there any first-degree relatives Gillberg, et al., 1992, including siblings Lauritsen, et al., 2005 with Asperger's syndrome or other pervasive developmental disorders (PDDs)? Lauritsen, et al., 2005
(26) Do any first-degree family members experience an abnormally large head (macrocephaly) Fidler, et al., 2000 and/or ridge counts on the fingers and palms? Milićić, et al., 2003
(27) Does the mother Kröger, et al., 2011 or father Eriksson, et al., 2012 have autistic traits or a full diagnosis on the autism spectrum? van Steijn, et al., 2012

Parental Age Trends
(28) Is the mother older Idring, et al., 2014 than at least 25 Quinlan, et al., 2015 - but especially 35 or older? Tsai, et al., 1983 Williams, et al., 2008 Reichenberg et al, 2010 Leonard, et al., 2011 Sandin, et al., 2012 Mamidala, et al., 2013 Maramara, et al., 2014

(29) Is the father older? Burd, et al., 1999 Lauritsen, et al., 2005 Reichenberg, et al., 2006 Gabis et al, 2010 Ben Itzchak et al, 2011 Idring, et al., 2014 Khaiman, et al., 2015 - with a higher risk starting at age 30 Zhang et al, 2010 van Balkom, et al., 2012 or 35 Quinlan, et al., 2015 and increasing significantly past age 40 Buizer-Voskamp, et al., 2011 and age 45? D'Onofrio, et al., 2014
(30) Were the child's grandparents on either side older at the time his/her parent was being born? Frans, et al., 2013

Circumstances Surrounding Conception
(31) Did the mother have a previous termination of pregnancy (abortion)? Burd, et al., 1999
(32) Were the parents related in consanguineous manner (sharing an ancestor)? Morrow, et al., 2008
(33) Did the pregnancy depend upon the use of assisted conception/assisted reproductive technology (ART) Zachor, et al., 2011 - including artificial insemination Lyall, et al., 2012/ ovulation induction/intrauterine insemination (IUI) Bay, et al., 2013/intracytoplasmic sperm injection (ICSI) Kissin, et al., 2015 or various infertility treatments involving hormonal interventions? Mamidala, et al., 2013
(34) Was the child born after a short interbirth (IBI) or interpregnancy interval (IPI) Coo, et al., 2015 - especially less than 1 year between the birth of one child and pregnancy with another? Cheslack-Postava, et al., 2011 Gunnes, et al., 2013
(35) Was the child first-born Tsai, et al., 1983 Lord, et al., 1991 Gillberg, et al., 1992 Piven, et al., 1993 Glasson, et al., 2004 Leonard, et al., 2011 Schrieken, et al., 2013 Visser, et al., 2013 or the only child in the family? Gillberg, et al., 1992 Plubrukarn, et al., 2005
(36) Was the child a fourth Piven, et al., 1993 or later-born child? Tsai, et al., 1983 Lord, et al., 1991
(37) Was the child a twin Hallmayer, et al., 2002 or one of multiple, simultaneous births? Croen, et al., 2002 Ho, et al., 2005 Williams, et al., 2008 Turner, et al., 2011 Gardener, et al., 2011 Maramara, et al., 2014

Pregnancy Timing and Location
(38) Did conception happen sometime in the North American winter season - between November Mazumdar, et al., 2012 and March? Zerbo, et al, 2011
(39) Was the child born between March and October? [spikes documented in March Gillberg, 1990 Mouridsen, et al., 1994 Barak, et al., 1995 Stevens,et al., 2000 Lee, et al., 2008, April Lee, et al., 2008, May Lee, et al., 2008, June Lee, et al., 2008 Gardener, et al., 2011, July Gardener, et al., 2011 August Barak, et al., 1995 Gardener, et al., 2011 September Lee, et al., 2008 October, Lee, et al., 2008].
(40) Was the child born in certain historical periods - including periods from 1970 to 1976 in Israel Barak, et al., 1995 1980 to 1989 in Denmark Atladóttir, et al., 2015 or since 2002 in the U.S.? Keyes, et al., 2012

General Maternal Health
(41) Did the woman's blood serum reflect Rh-negativity Geier, et al., 2007 Geier, et al., 2008 low plasma serotonin Connors, et al., 2006 or increased concentrations of interferon-gamma, interleukins IL-4 and IL-5? Goines et al, 2011
(42) Did the woman experience hormone abnormalities Ingudomnukul, et al., 2007 including low levels of progesterone Whitaker-Azmitia, et al., 2014 or high levels of testosterone? Zettergren, et al., 2013
(43) Did the woman have severe acne Ingudomnukul, et al., 2007 or excessive hair on her body (hirsutism)? Ingudomnukul, et al., 2007
(44) Did the woman have an irregular menstrual cycle Ingudomnukul, et al., 2007 dysmenorrhea Ingudomnukul, et al., 2007 or polycystic ovary syndrome? Ingudomnukul, et al., 2007

(45) Did the woman identify with bisexuality, asexuality Ingudomnukul, et al., 2007 or tomboyism? Ingudomnukul, et al, 2007
(46) Does the woman categorize as overweight Gardner, et al., 2015 or generally obese before pregnancy Dodds et al, 2010 Krakowiak et al, 2012 Gardner, et al., 2015 - especially in the obese class II or III? Jo, et al., 2015
(47) Did the woman have breast or uterine cancers, tumors, or growths? Ingudomnukul, et al., 2007

General Paternal Health
(48) Was the father underweight? Gardner, et al., 2015

Illness During Pregnancy
(49) Did the mother experienced serious infections during the pregnancy Visser, et al., 2013 - including, but not limited to the following: gestational respiratory infections Mamidala, et al., 2013 urinary infections Wilkerson, et al., 2002 or viral infections Wilkerson, et al., 2002 such as influenza Atladóttir, et al., 2012 and symptomatic congenital cytomegalovirus (CMV) infection? Yamashita, et al., 2003
(50) Were there any other signs of inflammation in the womb El-Ansary, et al., 2012, such as fever during pregnancy Zerbo et al, 2012 - especially a prolonged episode of fever? Atladóttir, et al., 2012
(51) Did the woman have epilepsy? Ingudomnukul, et al., 2007
(52) Did the mother have autoimmune diseases Chen, et al., 2015 developed during pregnancy, such as thyroid disease Chen, et al., 2015 systemic lupus erythematosus (SLE) Vinet, et al., 2015 asthma, allergies Croen, et al., 2005 or psoriasis? Croen, et al., 2005
(53) Did the mother show signs of metabolic disease, including diabetes and hypertension Krakowiak et al, 2012 Rivera, et al., 2015 or gestational diabetes mellitus (GDM) diagnosed at 26 weeks or earlier (high blood sugar that starts or is first diagnosed during pregnancy)? Lyall, et al., 2012 Krakowiak et al, 2012 Xiang, et al., 2015
(54) Did the mother experienced any other chronic or acute medical conditions during pregnancy Zhang et al, 2010) that might involve gestational complications Zhang et al, 2010 such as edema (swelling is the enlargement of organs, skin, or other body parts)? Zhang et al, 2010

Medical Treatments During Pregnancy
(55) Did the woman take prescription medications of some kind during pregnancy? Wilkerson, et al., 2002 Guinchat, et al., 2012
(56) Is there any signs that the mother has especially adverse reactions to drugs (high sensitivity/intolerance to chemicals)? Heilbrun, et al., 2015
(57) During the pregnancy, did the mother take SSRI antidepressants? Croehn et al, 2011 Eriksson, et al., 2012 Rai, et al., 2013, valproate/valproic acid for bipolar disorder Alsdorf, et al., 2005 Ornoy, 2009 Dufour-Rainfray et al, 2011 or other psychoactive medications? Eriksson, et al., 2012
(58) Was the fetus exposed to antiepileptic/anticonvulsant meds or migraine medication Rasalam et al, 2005- especially sodium valproate acid (VPA)? Alsdorf, et al., 2005 Rasalam, et al., 2005Ornoy, 2009 Bromley, et al., 2013
(59) Was the fetus exposed to terbutaline (Brethine, Bricanyl, Brethaire, or Terbulin) - used to treat asthma, bronchitis, and other lung disorders? Croen, et al., 2011
(60) Was the fetus exposed to thalidomide - used to treat certain skin diseases and cancers? Stromland et al, 1994 Rodier, 2002 Miller, et al., 2004 Miller, et al., 2005 Dufour-Rainfray, et al., 2011
(61) Was the fetus exposed to the antipyretic drug, Paracetamol/Acetaminophen (Tylenol) Bauer, et al., 2013 or various antibiotics during pregnancy? Atladóttir, et al., 2012
(62) Was the fetus exposed to misoprostol (Cytotec) - used for ulcers or to attempt termination of a pregnancy? Bandim, et al., 2003 Miller, et al., 2005

Potential Toxic Exposures During Pregnancy

(63) Did the mother smoke during pregnancy? Hultman, et al., 2002 Indredavik, et al., 2007 Larsson et al, 2009 Nijmeijer et al, 2010

(64) Was the mother exposed to second-hand smoke during pregnancy? Zhang et al, 2010

(65) Is there a parental history of excessive alcohol consumption Sundquist, et al., 2014 - and is there evidence the fetus was exposed to alcohol/ethanol? Harris, et al., 1995 Dufour-Rainfray et al, 2011 Ortega, et al., 2011 (see FAS case Nanson, 1992)

(66) Is there any potential exposure to organochlorine pesticide applications including dicofol and endosulfan Roberts et al, 2007 or DDT (dichlorodiphenyltriichloroethene)? Audouze, et al. 2011

(67) Did the mother have amalgam fillings (a source of mercury exposure) Holmes, et al., 2003 thimerosal-containing Rho D immunoglobulin injections Holmes, et al., 2003 or a TCR vaccine during her pregnancy? Geier, et al., 2007 Geier, et al., 2008

(68) Is the mother living near enough of a freeway to be exposed to traffic pollution? Volk et al, 2010 Weisskopf, et al., 2015 fine particulate matter (PM2.5) Talbott , et al., 2015

(69) Is the mother living close to industry Hamadé, et al., 2013 - including power plants Palmer et al, 2009, coal-fired power plants and cement plants with coal-fired kilns Blanchard, et al., 2011 enough to be exposed to emissions?

(70) Is the mother living or attending school within a 20-mile radius of toxic waste sites, including U.S. government Superfund sites earmarked for pollution clean-up? DeSoto, 2009

(71) Are there heavy metal concentrations in ambient air around the birth residence - including the following: cadmium, trichloroethylene, vinyl chloride Windham, et al., 2006 styrene and chromium Talbott, et al., 2015 mercury Windham, et al., 2006 Roberts, et al., 2013 nickel Windham, et al., 2006 Lewandowski et al, 2009 diesel, lead, manganese, or an overall measure of metals? Roberts, et al., 2013

(72) Are there chlorinated solvents Windham, et al., 2006 in ambient air around the birth residence[e.g., used in degreasers, cleaning solutions, paint thinners, pesticides, resins, glues, and other mixing and thinning solutions]. - including methylene chloride? Roberts, et al., 2013

(73) Is there a potential prenatal exposure to lacquer, varnish, or xylene? McCanlies et al, 2012

(74) Is there any evidence of prenatal Polycyclic Aromatic Hydrocarbon (PAH) exposure - e.g., in oil, coal, and tar deposits, and produced as a byproduct of fuel burning and food grilling? Perera et al, 2012

(75) Is there any potential exposure to phthalates Testa, et al., 2012 - e.g., PVC flooring, especially in a parents' bedroom? Larsson et al, 2009

(76) Is there any potential exposure to bisphenol A (BPA) in plastic ware and canned food? Kaur, et al., 2014

(77) Is there condensation on the windows of the home- reflecting a low ventilation rate? Larsson et al, 2009

(78) Is the pregnant mother living in an urban residence Wang, et al., 2005 Lauritsen, et al., 2014 or a location with an increasing degree of urbanization? Lauritsen, et al., 2005

(79) Is the mother residing in a remote area - more removed from city life? Leonard, et al., 2011

Nutrition During Pregnancy

(80) Did the mother consume sufficient polyunsaturated fats during pregnancy - including ω-3 fatty acid and Linoleic acid (LA) (a polyunsaturated omega-6 fatty acid)? Lyall, et al., 2013

(81) Did the mother eat a diet rich in omega-6 PUFAs during gestation and lactation (found in cooking oils, shortening, margarine and animal products)? Jones, et al., 2013

(82) Did the woman experience excessive pregnancy weight gain Bilder, et al., 2013 Dodds et al, 2010 *or* significant weight loss during the pregnancy? Ortega, et al., 2011

(83) Did the woman experience a deficiency of Vitamin D during the pregnancy? Grant and Soles, 2009

(84) Did the mother take prenatal vitamins during the 3 months before pregnancy or the first month of pregnancy Schmidt et al, 2011 - including folic acid in the first month? Schmidt, et al., 2012
(85) Did the mother show any deficiency of B-complex vitamins - especially Thiamine (vitamin B1)? Ortega, et al., 2011
(86) Overall, did the mother have an unhealthy diet? Rivera, et al., 2015

Emotional Atmosphere of Pregnancy
(87) Did the mother experience significant stress during the pregnancy? Ward, 1990 Visser, et al., 2013 Say, et al., 2015
(88) Did the mother experience specific stressors during pregnancy including, but not limited to: family discord Ward, 1990 or family migration? Magnusson, et al., 2012
(89) Did the pregnancy face a threatened abortion before 20 weeks gestation? Glasson, et al., 2004 Langridge, et al., 2013
(90) Did the mother report an unhappy emotional state during pregnancy Zhang et al, 2010 Hamadé, et al., 2013 or depressive mood? Say, et al., 2015

The Pregnant Body
(91) Were there trophoblast inclusions (TIs) in the placenta? Walker, et al., 2013
(92) Was there uterine or vaginal bleeding Juul-Dam, et al., 2001 Brimacombe, et al., 2007 Gardener, et al., 2011 Maramara, et al., 2014 maternal hemorrhaging Gardener, et al., 2011 or acute intrapartum hemorrhage? Limperopoulos, et al., 2008
(93) Was there any signs of intrauterine stress Wilkerson, et al., 2002 or fetal distress? Glasson, et al., 2004 Gardener, et al., 2011 Mamidala, et al., 2013 Polo-Kantola, et al., 2014
(94) Before birth, was there any evidence of a lack of oxygen to the fetus (fetal hypoxia)? Burstyn, et al., 2011 Maramara, et al., 2014 - or any other evidence of first trimester brain-stem damage? Johansson, et al., 2001
(95) Did the mother experience high blood pressure during pregnancy? (see gestational diabetes) Polo-Kantola, et al., 2014
(96) Is there evidence of chorioamnionitis (an inflammation of the fetal membranes due to a bacterial infection - often associated vaginal examinations or prolonged labor)? Limperopoulos, et al., 2008
(97) Was there evidence of poor fetal growth Langridge, et al., 2013 Abel, et al., 2013 or growth restriction? Haglund, et al., 2010
(98) Was there evidence of excessive fetal/ intrauterine growth Leonard, et al., 2008 Abel, et al., 2013 or macrosomia (large birth size - 8 pounds, 13 ounces or more)? Haglund, et al., 2010

The Birth Experience
(99) When the mother was admitted to a hospital for delivery, did she experience severe illness Limperopoulos, et al., 2008 or abnormal MRI studies? Limperopoulos, et al., 2008
(100) Did labor or obstetrical complications arise during labor? Lyall, et al., 2012 Mamidala, et al., 2013
(101) Did the woman experience a prolonged labor? Wilkerson, et al., 2002 Brimacombe, et al., 2007 Maramara, et al., 2014
(102) Was the woman's pregnancy augmented Gregory, et al., 2013 induced Glasson, et al., 2004 Gregory, et al., 2013 or did she otherwise experience a labor less than 1 hour? Glasson, et al., 2004
(103) Did the woman receive (caudal/sacral) anesthesia via an epidural? Glasson, et al., 2004
(104) Did the baby come in an abnormal, breech presentation? Wilkerson, et al., 2002 Larsson, et al., 2005 Bilder et al, 2009 Gardener, et al., 2011

(105) Was the baby delivered by an emergency or elective/scheduled cesarean section? Hultman, et al., 2002 Glasson, et al., 2004 Eriksson, et al., 2012
(106) Were there any umbilical-cord complications at the birth Gardener, et al., 2011, including a nuchal cord? Zhang et al, 2010
(107) During birth, was there any evidence of birth injury or trauma Gardener, et al., 2011 including birth asphyxia? Mamidala, et al., 2013
(108) Was there a delayed birth cry? Mamidala, et al., 2013
(109) Did the newborn breathe a mixture of meconium and amniotic fluid into the lungs around the time of delivery (meconium aspiration syndrome)? Matsuishi, et al., 1999 Gardener, et al., 2011

Newborn Health & Characteristics
(110) Was the child male? Croen, et al., 2002 Limperopoulos, et al., 2008 Williams, et al., 2008 Zahn-Wexler et al, 2008 Larsson et al, 2009 Leonard, et al., 2011 Hamadé, et al., 2013 Werling, et al., 2013 Zahorodny, et al., 2014
(111) Was the child born premature or preterm Brimacombe, et al., 2007 Williams, et al., 2008 Pinto-Martin, et al., 2011 Hwang, et al., 2013 Abel, eta l., 2013 Mamidala, et al., 2013 Schrieken, et al., 2013 Maramara, et al., 2014 Goldin, et al., 2015-Say, et al., 2015 especially very preterm (gestational age at birth <32 weeks) Eryigit-Madzwamuse, et al., 2015 Treyvaud, et al., 2013 or extremely preterm (23-27 weeks of gestation)? D'Onofrio, et al., 2013
(112) Did the child have a shorter or lower gestational age at birth Pinto-Martin, et al., 2011 Moore, et al., 2012 Leavey, et al., 2013 Atladóttir, et al., 2015- especially a very low gestational age from less than 32 weeks Lampi, et al., 2012 to 35 weeks? Larsson, et al., 2005 Zhang et al, 2010
(113) Did the child have a very high gestational age of 42 weeks or more? Lord, et al., 1991 Zhang et al, 2010
(114) Did the child have decreased or low birth weight (LBW) Burd, et al., 1999 Wilkerson, et al., 2002 Limperopoulos, et al., 2008 Losh, et al., 2012 Schrieken, et al., 2013 Maramara, et al., 2014 - whether moderately low (<2500 g) Lampi, et al., 2012 or very low (<1500 g)? Lampi, et al., 2012 Eryigit-Madzwamuse, et al., 2015
(115) Was the child small for gestational age (SGA)? Wilkerson, et al., 2002 Hultman, et al., 2002 Lampi, et al., 2012
(116) Was the child in suboptimal condition after birth Lyall, et al., 2012 Visser, et al., 2013 - as reflected in a low Apgar score - less than 6 at 1 minute Glasson, et al., 2004 or less than 7 Hultman, et al., 2002 Polo-Kantola, et al., 2014 at 5 minutes? Larsson, et al., 2005 Gardener, et al., 2011
(117) Did the child have neonatal jaundice(hyperbilirubinemia), assessed by total serum bilirubin (TSB)? Maimburg et al, 2010 Gardener, et al., 2011 Amin, et al., 2011 Guinchat, et al., 2012 Mamidala, et al., 2013
(118) Did blood tests show neonatal anemia Gardener, et al., 2011 or ABO or Rh incompatibility? Gardener, et al., 2011
(119) Was there evidence of cerebellar hemorrhagic injury (common in infants who survive premature birth) Limperopoulos, et al., 2007 or cranial ultrasound evidence of ventricular enlargement? Movsas, et al., 2013
(120) Did the baby's condition require neonatal treatment with monitoring? Polo-Kantola, et al., 2014

Newborn Dysfunction
(121) Was there any evidence of a birth defect/congenital malformation? Dawson et al, 2009 Gardener, et al., 2011 Hultman, et al., 2002
(122) Did the child have an abnormally large head (macrocephaly) Fidler, et al., 2000 *or* a proportionally smaller head circumference compared to his/her height? Schrieken, et al., 2013
(123) Did the child have congenital muscular torticollis (chin pointing to one shoulder, while the head tilts toward the opposite shoulder)? Schertz, et al., 2013

(124) Were there any unusual aspects to the child's hands, including abnormal ridge counts on the fingers and palms Milicić, et al., 2003 or an unusually lower Masuya, et al., 2015 or higher right-hand ratio between the second and fourth digits of the finger (2D:4D - a biomarker of the prenatal ratio of testosterone to estrogen) Hönekopp, 2012 Masuya, et al., 2015
(125) Did the child have profound or severe visual impairment Mukaddes, et al., 2007 Parr, et al., 2010 or some kind of unfavorable visual status - including threshold retinopathy of prematurity (ROP) Msall, et al., 2004 optic nerve hypoplasia (ONH) and septo-optic dysplasia (SOD)? Parr, et al., 2010
(126) Did the child have Prader-Willi syndrome (PWS) Descheemaeker, et al., 2006 CHARGE association (CA) Strömland, et al., 2005 Klinefelter syndrome Cederlöf, et al., 2014 Möbius sequenceJohansson, et al., 2001 Bandim, et al., 2003 or low-level aneuploidy? Yuro, et al., 2007
(127) Did the child have hydrocephalus (a build-up of fluid on the brain that leads to swelling) Lindquist, et al., 2006 or newborn encephalopathy (NE)? Badawi, et al., 2006
(128) Did the baby have a low melatonin level (produced in the dark by the pineal gland and is a key regulator of circadian and seasonal rhythms)? Melke, et al., 2008
(129) Did the baby have phenylketonuria (PKU) (without the ability to properly break down an amino acid called phenylalanine)? Baieli, et al., 2003
(130) Did the baby have temporal lobe tubers Besag, 2004 or tuberous sclerosis complex (TSC) - a genetic disorder causing non-malignant brain tumors? Smalley, 1998 Gutierrez, et al., 1998 Bolton, et al., 2002 Kothur, et al., 2008 Numis et al, 2011
(131) Did the baby have some degree of cerebral dysfunction Hwang, et al., 2013 or significant neurological impairment (as suggested by the presence of lower intellectual level and/or cerebral palsy)? Mukaddes, et al., 2007

Child's Health Condition

(133) Does the baby have childhood epilepsy Clarke, et al., 2005 Tuchman and Cuccaro, 2011 Maski, et al., 2011 Lo-Castro, et al., 2014 or syndromes associated with epilepsy - including Dravet syndrome, Landau-Kleffner syndrome, Aicardi, 1999 Lennox-Gastaut syndrome or benign partial seizures? Besag, 2004
(134) Does the child have early-onset seizures, particularly infantile spasms (West Syndrome) Smalley, 1998 Gutierrez, et al., 1998 Zaroff, et al., 2004 Berg, et al., 2011 or febrile seizures (brought on by a fever)? Zhang, et al., 2012
(135) Does the child show any airway symptoms of wheezing or asthma Larsson et al, 2009 or atopic dermatitis (AD) - an allergic disorder Billeci, et al., 2015
(136) Does the child have hyperandrogenism, or androgen excess - a medical condition characterized by excessive levels of androgens in the body and associated physical effects? Xu, et al., 2015
(137) Does the child have any gastrointestinal/GI dysfunction problems Casanova, 2008 Wang et al, 2011 Hsiao, 2014, including intestinal permeability D'Eufemie at al, 1996 or celiac disease? Ludvigsson, et al., 2013
(138) Does the child have gender dysphoria (GD)? VanderLaan, et al., 2015
(139) Does the child have any psychiatric problems Ward, 1990 - including depression Magnuson, et al., 2011 anxiety Rzepecka, et al., 2011 obsessive-compulsive symptoms Bolton, et al., 1998 hyperactive/attention problems Kröger, et al., 2011 Jo, et al., 2015 or anorexia nervosa? Berkman, et al., 2007

Newborn Feeding & Sleeping

(140) Was the child breastfed immediately following birth? Brown, et al., 2014
(141) Did the baby experience feeding difficulties (e.g., vomiting, reflux, colic and failure to feed) Whitely, 2004 Gardener, et al., 2011
(142) Did the child experience sleep problems or dysfunction, such as insomnia? Sounders, et al., 2009 Rzepecka, et al., 2011 Maski, et al., 2011

Newborn Movement

(143) Did the child show non-right-handedness (left- and mixed-handedness)? Gilberg, 1983 Soper, et al., 1986
(144) Did the child show motor impairments? Maski, et al., 2011
(145) Did the child have a tic disorder, such as Tourette disorder (TD) or chronic motor tics? Canitano, et al., 2007

Medical Procedures as a Child

(146) Did the newborn child receive the antipyretic drug, paracetamol/acetaminophen (Tylenol) - often used in circumcision, during fevers, or after vaccinations? Shultz, et al., 2008 Bauer, et al., 2013
(147) Did the child receive a Hepatitis B vaccination? Gallagher, et al., 2010
(148) Did the child receive several courses of antibiotics such as amoxicillin/clavulanate (Augmentin), especially before he or she was one year old? Fallon, 2005
(149) Did the child receive one or more surgeries involving anesthesia before he or she was 2 Ko, et al., 2015 or 3 years old? DiMaggio, et al., 2011
circumcised boys Frisch, et al., 2015
(150) At some point, did the child receive a vaccine with organic mercury (Thimerosal) Geier, et al., 2004 Young et al, 2008 - including Diphtheria-Tetanus-acellular-Pertussis (DTaP) vaccines administered from 1997 through 2001? Geier, et al., 2005

Childhood Infections & Viruses

(151) Was there evidence of previous childhood infections Hamadé, et al., 2013 - especially elevated rates of infection in the first 30 days? Rosen, et al., 2007
(152) Did the child experience several bouts of otitis media? Fallon, 2005
(153) Was there other evidence of inflammation in infancy El-Ansary, et al., 2012 - including in the small intestine? Ludvigsson, et al., 2013
(154) Did bacteroidetes species exist at high levels - including Actinobacterium, Desulfovibrio species and Bacteroidesvulgatus Finegold et al, 2010 or strains of Clostridium species and enterococci, as well as sometimes lactobacilli? Ekiel et al, 2010
(155) Were genitourinary infections more frequently diagnosed in first two years? Rosen, et al., 2007
(156) Did the child experience Borrelia burgdorferi or tick-borne diseases? Bransfield et al, 2008
(157) Was there a higher prior frequency of the bacterial skin infection impetigo (caused by Staphylococcus aureus, and less frequently by Streptococcus pyogenes)? Whitely, 2004
(158) Was there evidence of the polyomavirus (in the brain)? Lintas et al, 2010
(159) Was there a congenital cytomegalovirus infection? Yamashita et al, 2003 Kawatani et al, 2010
(160) Was there increased mycoplasma, Chlamydia Pneumoniae and Herpes virus HHV-6 infections? Nicolson et al, 2007

Immune System Abnormalities

(161) Was there evidence of autoimmunity in the child - including an altered toll receptor responses Jyonouchi et al, 2008 or a humoral immunity profile? Wasilewska et al, 2012.
(162) Was there evidence of autoimmunity to the central nervous system (CNS), especially to myelin basic protein (MBP)? Singh, et al., 2002
(163) Were there measles antibodies in the blood Singh, et al., 2003 or a heightened level of antibodies associated with the measles virus and the measles-mumps-rubella (MMR) vaccine? Singh, et al., 2002 Singh, 2009
(164) Were there antibodies found for any of the following: a 45 kDa cerebellar protein and other cerebellar proteins raised maternally? Goines et al, 2011 to gliadin, a component of gluten, and to cerebellar peptides? Vojdani et al, 2004 to casein, lactalbumin and beta-lactoglobulin Lucarelli, et al., 1995 Kawashti et al., 2006 to brain elements, related to herpes viral infection, particularly Herpes virus HSV-2 Mora et

al, 2009 anti-amygdala, anti-caudate nucleus, anti-cerebellum anti-brain stem, anti-hippocampus, anti-corpus callosum and anti-cortex antibodies Mora et al, 2009 and anti-nuclear antibodies? Mostafa, et al., 2009
(165) Were there autoantibodies found for any of the following: to neuron-axon filament protein (NAFP) and glial fibrillary acidic protein (GFAP) (Singh et al., 1997) to GABAergic Golgi neurons of the cerebellum Rossi et al, 2011 to the voltage-dependent anion channel (VDAC) and hexokinase-I Gonzalez-Gronow et al, 2010 Metallothionein autoantibodies Russo, 2008 to myelin basic protein? Singh, 2009

Blood and Urine Levels

(166) Were there high levels of homocysteine Ali et al, 2011 Hodgson, et al., 2014 or S-adenosylhomocysteine Hodgson, et al., 2014 (indicative of oxidative stress and decreased methionine synthase activity - as well as decreased antioxidant resources overall) Hodgson, et al., 2014 - as perhaps reflected in a low level of antioxidant Glutathione (GSH)? Gu, et al., 2015
(167) Were there high blood levels of any of the following: cytokines IL1B, IL1RA, IL5, IL8, IL12, IL13, IL17 and GRO-alpha Suzuki et al, 2011 Apolipoprotein B-100, Complement Factor H Related Protein (FHR1) , Complement C1q and Fibronectin 1 (FN1) levels Corbett et al, 2007 thioredoxin, thioredoxin reductase and peroxiredoxins (PRDX1 and PRDX3) Al-Yafee et al, 2011 androstenedione Ruta et al, 2011 copro- , hexacarboxyl- and pentacarboxyl- porphyrin Woods et al, 2010 MCP-1, RANTES and eotaxin Ashwood et al, 2011 or oxalate? Konstantynowicz et al, 2011
(168) Were there low blood levels of any of the following: cysteine methionine and cystathionine Geier, et al., 2006 follicle-stimulating hormone Geier, et al., 2006 homocysteine Geier, et al., 2006 tryptophan Kaluzna-Czaplinska et al, 2010 or chemokines involved in the T-helper cell immune system and hematopoiesis? Manzardo et al, 2011
(169) Were there low glutathione levels in the blood James, et al, 2009 Geier, et al., 2006 Hodgson, et al., 2014 or the brain? Chauhan et al, 2012
(170) Were urinary levels of any of the following unusually high: oxalate Konstantynowicz et al, 2011 homocysteine Kaluzna-Czaplinska et al, 2011 N-methyl-2-pyridone-5-carboxamide, N-methyl nicotinic acid, and N-methyl nicotinamide Yap et al, 2010 or taurine? Yap et al, 2010
(171) Were there lower urinary levels of any of the following: glutamate Yap et al, 2010
(172) Was there evidence for any of the following: changes in mammalian-microbial cometabolites including dimethylamine, hippurate, and phenyacetylglutamine Yap et al, 2010 thyroid hormone perturbations - including very low thyroxine (T4) levels Hoshiko, et al., 2011 a reduction in plasmaglutathione s transferase activity Al-Yafee et al, 2011

Childhood Nutrition

(173) Was there fatty acid deficiency symptoms Brown, et al., 2014 or lower blood fatty acid levels Ooi, et al., 2015 reflecting a lower level of total short chain fatty acids including lower levels of acetate, proprionate, and valerate Adams et al, 2011 - or evidence of problems with fatty acid metabolism (e.g., plasma fatty acid profiles showing docosahexaenoic acid (DHA, 22:6n-3) as significantly decreased in phosphatidylethanolamine - or Dimethyl acetals significantly decreased in phosphatidylethanolamine and phosphatidylcholine) Wiest et al, 2009
(174) Did the child have low cholesterol levels Tierney et al, 2006 or dyslipidaemia (high plasma triglyceride low HDL-C)? Kim et al, 2010
(175) Was there a deficiency of any of the following vitamins in the early postnatal and early childhood periods: vitamin D Gong, et al., 2014 vitamins A, vitamin E, and lycopene Krajcovicova-Kudlackova, et al, 2009 Xia et al, 2010 vitamin C Xia et al, 2010 folic acid/folate and vitamins B6 and B12? Xia et al, 2010 Kaluzna-Czaplinska et al, 2011 Ali et al, 2011
(176) Was there any evidence of any of the following: calcium deficiency Xia et al, 2010 zinc deficiency Xia et al, 2010 Grabrucker, et al., 2014, or iron deficiency/iron deficiency anaemia? Chen, et al., 2013 Sidrak, et al., 2013

(177) Did the child consume products with a lot of high fructose corn syrup? Dufault et al, 2012

Childhood Environmental Exposures

(178) Was there any evidence of a toxic metal burden Adams et al, 2009 - especially reflected in elevated lead Yassa, 2014 or mercury levels Holmes, et al., 2003 Geier et al, 2010 Yassa, 2014 perhaps in hair samples? Hodgson, et al., 2014

(179) Did the child live in an urban residence during childhood Lauritsen, et al., 2014 or did the child move to a higher level of urbanicity after birth? Lauritsen, et al., 2014