KIND KAROLINSKA INSTITUTET CENTER OF NEURODEVELOPMENTAL DISORDERS

Sektionen för Barnneuropsykiatri

Karolinska Institutet

Environmental Etiologies of Autism and Other Neurodevelopmental Conditions:

Twin Studies of the Cumulative Effect of Early Medical Events

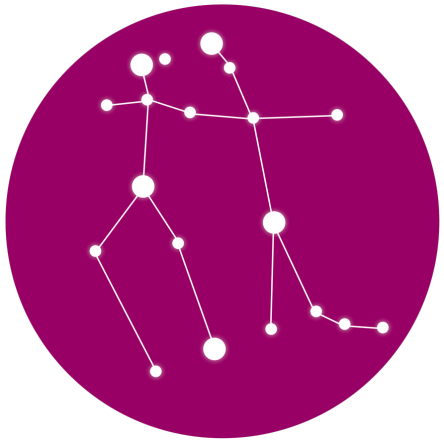
Torkel Carlsson

Med. dr.

Överläkare

BUP Konsultenhet

BUP FoUU



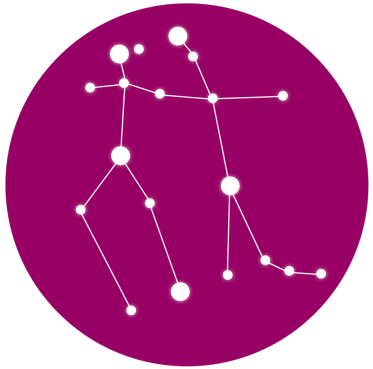
Orsaker till neuropsykiatriska tillstånd (NPF)

- Orsakerna är många och vi vet för lite
- Hög heritabilitet
  - → 93-98% för IF
  - → 64-95% för AST
  - → 77-92% för ADHD
  - → 70-85% för Tics

Detta lämnar utrymme för miljömässiga orsaker

Fyra modeller för NPF och underliggande etiologi

- The dimensional model
- The liability threshold model
- The cumulative stress hypothesis
- The three-hit concept

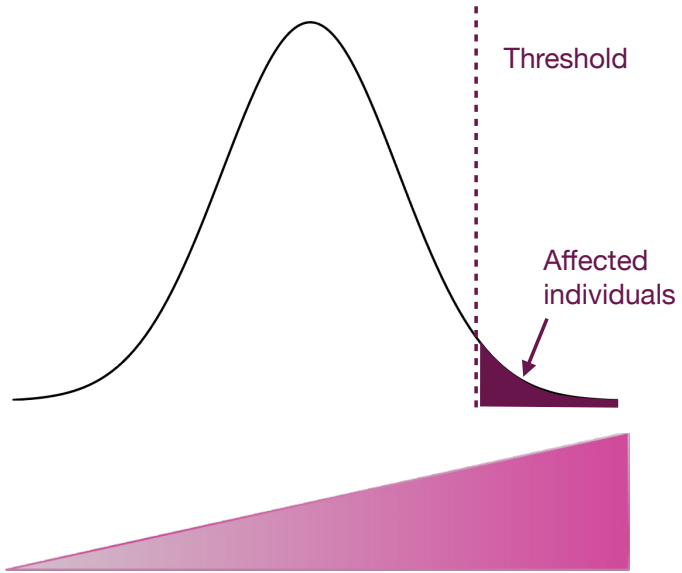


The dimensional model

- Ett *kontinuum* av drag i allmänbefolkning till symtom inom en diagnostisk population
  - med överlappande etiologier

The liability threshold model

- Den bakomliggande sårbarheten är normalfördelad
- En diagnos uppkommer när ett tröskelvärde uppnåtts



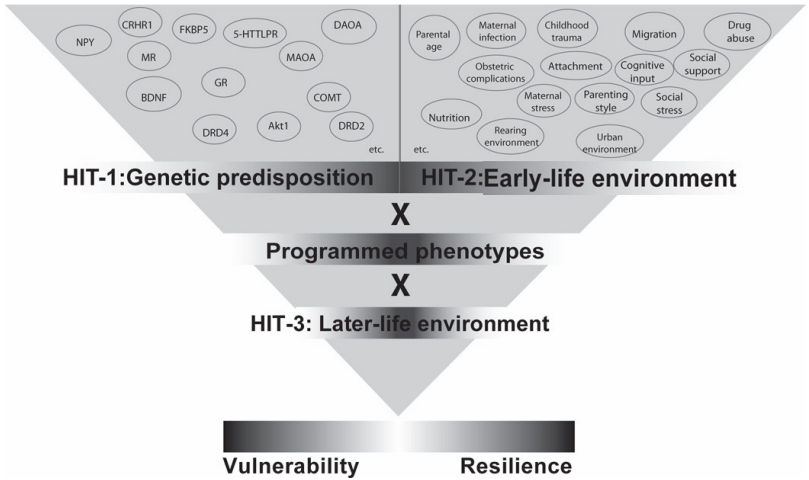
Mindre vanligt som modell för miljömässiga orsaker

The cumulative stress hypothesis

- Sårbarheten för ett givet tillstånd ökar om negativa händelser ansamlas under tidig barndom

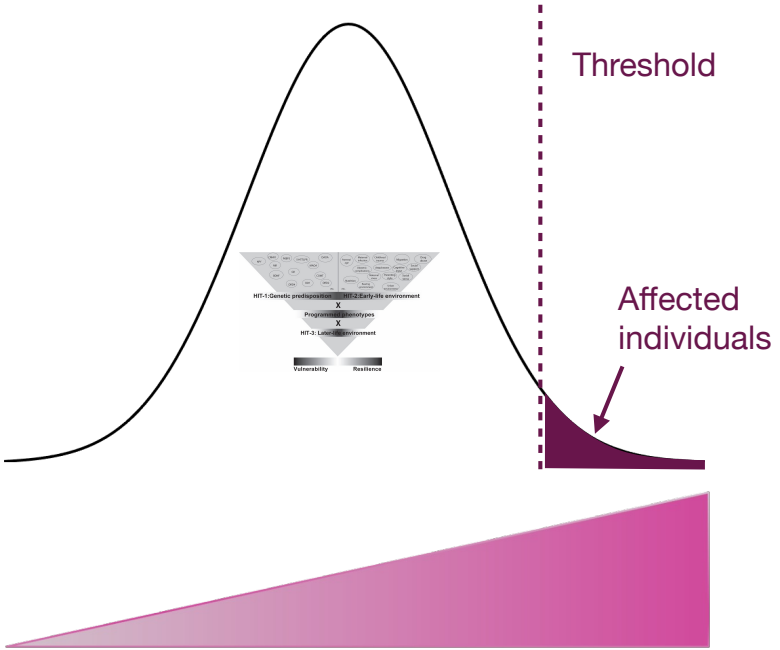
The three-hit concept

- The cumulative stress hypothesis är en andra ”träff”
- Evidens för AST har hittills setts i djurstudier



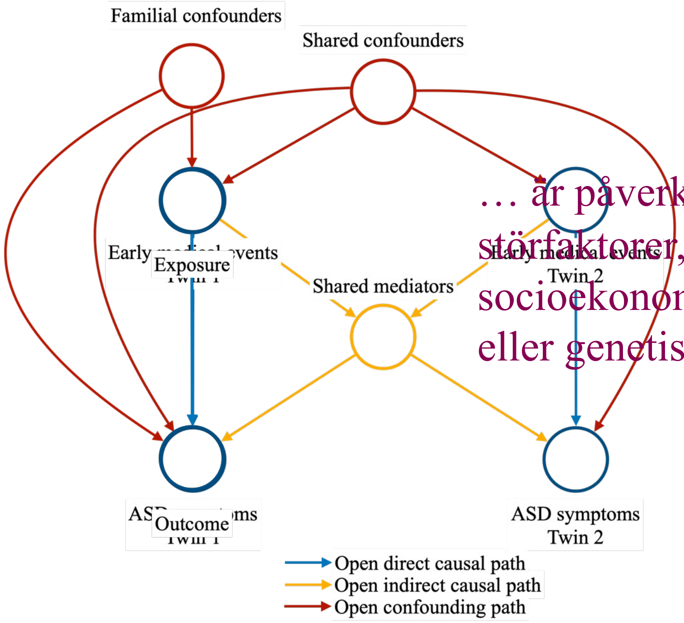
En sammanslagning av modellerna

Den kumulativa miljömässiga påverkan på NPF har inte tidigare studerats på människa



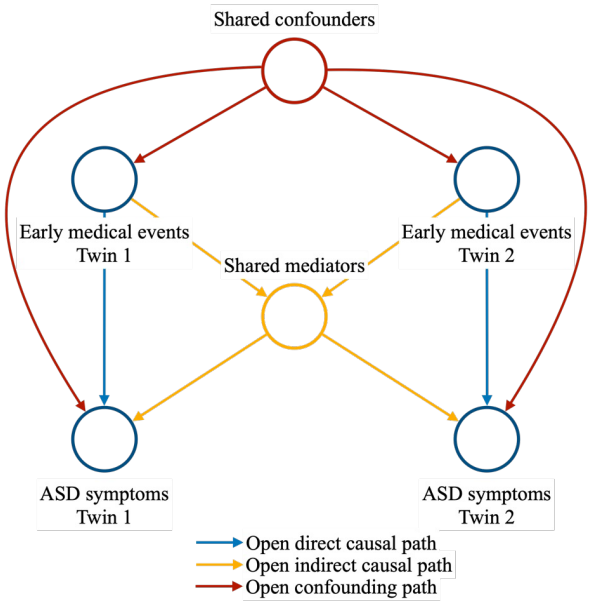
Familial confounding – ”familjekopplade störfaktorer”

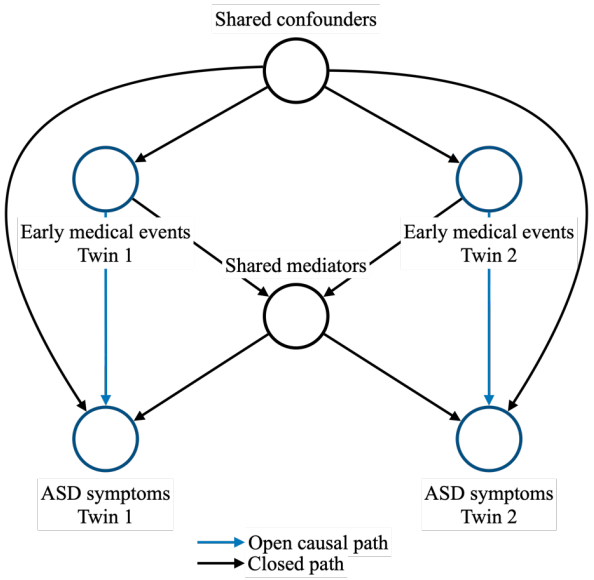
Med twin design kan dessa störfaktorer rensas bort



… är påverkat av störfaktorer, ex.vis socioekonomiska eller genetiska.

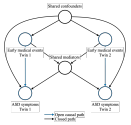
Familial confounding och co-twin designs



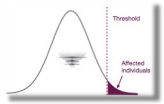


Mål

Studie IV:
- Testa om denna effekt är *specifik* för AST eller inte.
- Eller associerad med en *gemensam NPF-faktor*?

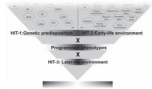


Studie III:
- Testa den kumulativa effekten på ett *stort befolkningsmaterial*



Studie I:
- Systematisk översikt *av alla tvilling och syskonstudier*
- Tidiga miljöfaktorer och NPF

Studie II:
- Identifiera *tidiga medicinska händelser*
- Testa hypotesen om en *kumulativ effekt* på AST



Studie I

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Regular Article

Early environmental risk factors for neurodevelopmental disorders – a systematic review of twin and sibling studies

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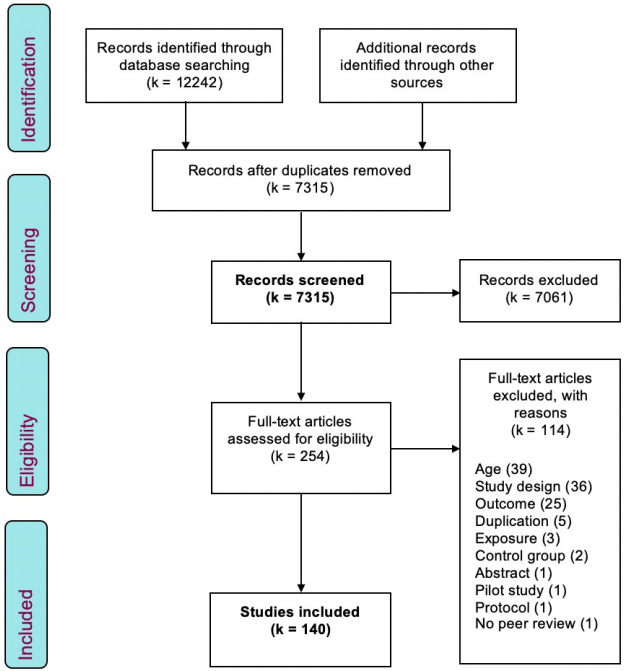
- PECOS:
  - → Fall-kontrol and kohort studier
  - → Tvilling- eller syskonjämförelse
  - → Specificerad miljöfaktor med exponering före 5 års ålder
  - → En eller flera NPF enligt DSM-5
  - → Utfall: Inomparsjämförelsen



Studie I – Resultat, AST

Table 2. Environmental factors, prenatal—autism spectrum disorder (ASD)

Environmental factor		Author (year)	*N*	HR (95% CI)	*OR* (95% CI)	RR (95%CI)	Other	NOS
Prenatal								
Maternal medication	Any	Mason-Brothers et al. (1990)	233				χ^2: ns	7
	Antidepressant	Brown et al. (2017)	620	1.60 (0.69 to 3.74)				8
		Sørensen et al. (2013)	96	1.1 (0.5 to 2.3)				7
		Sujan et al. (2017)	10,975	0.83 (0.62 to 1.13)[a]				7
		Rai et al. (2017)	175		**1.69 (1.06 to 2.72)**			7
		Hagberg et al. (2018)	531			1.53 (0.89 to 2.62)		7
	Antibiotics	Isaksson et al. (2017)	206		5.93 (0.27 to 128.82)[b]			3
	Systemic β2-agonists only	Gong et al. (2019)	1,133		0.80 (0.45 to 1.43)[c]			7
	Inhaled β2-agonists	Gong et al. (2019)	1,133		0.94 (0.61 to 1.47)[c]			7
	Other asthma medications	Gong et al. (2019)	1,133		0.74 (0.42 to 1.31)[c]			7
Paternal medication	SSRI before conception	Yang et al. (2017)	2,687	0.74 (0.34 to 1.59)				7
Antenatal nutritional supplementation[d]		DeVilbiss et al. (2017)	–[e]	0.77 (0.52 to 1.15)				8
Prenatal viral exposure	Infection	Oerlemans et al. (2016)	152		2.72		*p* = .114	7
		Isaksson et al. (2017)	206		0.98 (0.17 to 5.45)[b]			3
		Mason-Brothers et al. (1990)	233				χ^2: ns	7
	Measles	Deykin and MacMahon (1979)	163			**5.5**	***p* = .0412**	5
	Mumps	Deykin and MacMahon (1979)	163			**5.5**	***p* = .0474**	5
	Rubella	Chien et al. (2018)	323		0.75 (0.07 to 8.32)			6
		Deykin and MacMahon (1979)	163			**3.3**	***p* = .0044**	5
	Chickenpox	Deykin and MacMahon (1979)	163			1.7	*p* = .1677	5
Toxic exposure	Mercury	Williams et al. (2008)	15				*p* = .62	5
	PCB	Otake et al. (2006)	5				*p* > 0.05	5
	Solvents/paints	Grossi et al. (2018)	35		2.56 (0.76 to 8.72)			6
	PVC	Grossi et al. (2018)	35		1.47 (0.50 to 4.3)			6
	Tap water (cupper)	Grossi et al. (2018)	35		2.19 (0.6 to 7.4)			6
Metal uptake in uterus	Manganese	Arora et al. (2017)	32				***r* = −.25 (−.40 to −.10)**	8
	Lead	Arora et al. (2017)	32				***r* = .40 (.20 to .60)**	8

Studie I – Resultat, AST

Composite score of neonatal complications		Deykin and MacMahon (1980)	143		2.0 (1.3 to 3.0)		6
		Bryson et al. (1988)	17			**F (3,74) = 4.02, p < .01**	7
		Finegan and Quarrington (1979)	23			**χ^2(1df) = 14.73 (1df) p < .001**	4
		Piven et al. (1993)	39			F (1,38) = 2.8, p = ns	6
		Ronald et al. (2010)	5,796			r = .00 SE: −.07	7
Composite score of pre-, peri- and neonatal complications		Bryson et al. (1988)	17			**F (3,74) = 2.98, p < .04**	7
		Chien et al. (2018)	323			**F = 7.41, p = .007**	6
		Finegan and Quarrington (1979)	23			**χ^2(1df) = 17.02, p < .001**	4
		Lord et al. (1991)	46			**F (7, 91) = 2.43, p < .05**	7
		Rutt et al., (1971)	33			**p < .01**	6
		Steffenburg et al., (1989)	22			**χ^2: p = .02**	8
		Zwaigenbaum et al. (2002)	78			**F (1,104) = 8.1, p = .005**	7
		Deb et al. (1997)	30			ns	6
		Piven et al. (1993)	39			F (1,38) = 0.8, p = ns	6
Infancy and childhood							
Nursing	Not breastfed	Burd et al. (1988)	50			χ^2(1df) = 0.22, p > .05	4
	Early introduction of top feeds	Manohar et al. (2018)	30		**6 (1.33 to 55.19)**		5
	Fatty acid deficiency symptoms	Brown et al. (2014)	19		**2.77 (1.28 to 5.99)**		3
	Not breastfed 1st hour	Brown et al. (2014)	19		**3.84 (1.12 to 14.28)**		3
	Place of birth	Brown et al. (2014)	19			χ^2(1df) = 0.40, p = .620	3
	Maternal fish consumption	Brown et al. (2014)	19			χ^2(2df) = 2.13, p = .343	3
	Exclusively breastfed	Brown et al. (2014)	19			χ^2(2df) = 0.85, P = .653	3
	Virus infection during nursing	Isaksson et al. (2017)	206		6.75 (0.96 to 47.63)[d]		3
	Maternal antibiotics d. nursing	Isaksson et al. (2017)	206		0.52 (0.09 to 3.08)[d]		3
Maternal infection or antibiotics during pregnancy and nursing		Isaksson et al. (2017)	206		7.61 (0.96 to 60.46)[d]		3
Medication during childhood	Early antibiotic exposure	Hamad et al. (2018)	57,063	1.03 (0.86 to 1.23)			7
		Grossi et al. (2018)	35		2.03 (0.40 to 9.1)		6
Dysregulation 1st year		Willfors et al. (2017)	100			**β = 31.75, p = .03**	8
Medical events first 5 years		Willfors et al. (2017)	100			**β = 78.18, p = .002**	8
Childhood recurrent infections[e]		Mason-Brothers et al. (1993)	233		**2.03 (1.10 to 3.73)**		6

Studie I – Resultat, AST

	Chien et al. (2018)	323	2.43 (0.74 to 7.89)		6
General anesthesia during labor	Glasson et al. (2004)	465	1.09 (0.54 to 2.20)		6
	Creagh et al. (2015)	262		χ^2: $p = .7659$	3
	Mason-Brothers et al. (1990)	233		χ^2: ns	7
Breech presentation	Glasson et al. (2004)	465	1.40 (0.82 to 2.39)		6
	Mason-Brothers et al. (1990)	233		χ^2: ns	7
	Piven et al. (1993)	39		χ^2: ns	6
Umbilical cord around neck	Glasson et al. (2004)	465	1.19 (0.71 to 1.97)		6
	Mason-Brothers et al. (1990)	233		χ^2: ns	7
Low Apgar	Glasson et al. (2004)	465	**1.64 (1.02 to 2.65)**		6
	Mason-Brothers et al. (1990)	233		χ^2: ns	7
	Piven et al. (1993)	39		χ^2: ns	6
Respiratory distress	Hadjkacem et al. (2016)	50	**5.2 (1.2 to 21.6)**		6
	Froehlich-Santino et al. (2014)	137	**2.11 (1.27 to 3.51)**[c]		8
	Glasson et al. (2004)	465	**1.64 (1.15 to 2.34)**		6
	Piven et al. (1993)	39		χ^2: ns	6
Hypoxia	Glasson et al. (2004)	465	**1.81 (1.21 to 2.69)**		6
	Froehlich-Santino et al. (2014)	137	**1.71 (1.08 to 2.71)**[c]		8
Resuscitation	Chien et al. (2018)	323	1.65 (0.75 to 3.61)		6
	Glasson et al. (2004)	465	1.22 (0.93 to 1.59)		6
Composite score of perinatal complications	Oerlemans et al. (2016)	152	**1.70 (1.04 to 2.79)**		7
	Grossi et al. (2018)	35	1.94 (0.7 to 5.5)		6
	Abd Elhameed et al. (2011)	14		**χ^2: $p = .0001$**	5
	Hadjkacem et al. (2016)	50		**$p = .003$**	6
	Rutt and Offord (1971)	33		**$p < .01$**	6
	Bryson et al. (1988)	17		$F(3,74) = 0.71$, $p > .05$	7
	Finegan and Quarrington (1979)	23		χ^2: ns	4
	Piven et al. (1993)	39		$F(1,38) = 0.45$, $p =$ ns	6
Incubation	Chien et al. (2018)	323	**2.21 (1.23 to 3.95)**		6

Studie I – Resultat, ADHD

Table 6. Environmental factors—categorical attention-deficit/hyperactivity disorder (ADHD)-diagnosis

Environmental factor		Author (year)	N	HR (95% CI)	*OR* (95% CI)	Other	NOS
Prenatal							
Maternal medication	Antidepressant	Sujan et al. (2017)	10,975	0.99 (0.79 to 1.25)[a]			7
		Laugesen et al. (2013)	348	0.7 (0.4 to 1.4)			7
		Man et al. (2017)	–[b]	0.54 (0.17 to 1.74)			7
	Glucocorticoids	Laugesen et al. (2017)	–[c]	1.03 (0.87 to 1.20)			7
Smoking during pregnancy		Altink et al. (2008)	539			$\chi^2 = 6.91$, $p = .009$[d]	5
		Obel et al. (2011)	–[e]	1.20 (0.97 to 1.49)			7
		Obel et al. (2016)	–[f]	1.07 (0.94 to 1.22)			7
	1–9 cig/day	Skoglund et al. (2014)	317,836	0.88 (0.73 to 1.06)			7
	≤10 cig/day	Skoglund et al. (2014)	317,836	0.84 (0.65 to 1.06)			7
		Oerlemans et al. (2016)	301		1.18	$p > 0.05$	7
Alcohol use during pregnancy		Eilertsen et al. (2017)	–[g]	0.97 (0.93 to 1.01)			6
Parental age	Advanced, both parents	Oerlemans et al. (2016)	301		1.20	$p > 0.05$	7
	Paternal age >45	D'Onofrio et al. (2014b)	–[h]	**13.13 (6.85 to 25.16)**			8
	Advanced maternal age	Mimouni-Bloch et al. (2013)	56		**1.10 (1.02 to 1.20)**		3
	Age <20 y	Chang et al. (2014)	–[i]	**0.81 (0.71 to 0.94)**			8
		Hvolgaard Mikkelsen, Olsen, Bech, and Obel (2017)	6,436	1.28 (0.94 to 1.73)			8
Birth order	First born	Oerlemans et al. (2016)	301		1.16 (0.99 to 1.35)		7
		Pearsall-Jones et al. (2008)	16			χ^2 = ns	4
Interpregnancy interval	0–5 months	Class et al. (2018)	346,739	0.83 (0.64 to 1.07)			8

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Studie I – Resultat, ADHD

		(2017)			*inattentiveness*	
Meningitis		Berg et al. (2002)	304	Yes	The post-meningitic children had significantly more symptoms of *inattention*, *hyperactivity* and *impulsiveness* than their siblings	6
		Bergman et al. (1987)	31	No	All paired, multivariate, and repeated measures analysis of covariance with repeated covariate differences are nonsignificant	7
General anesthesia		Sun et al. (2016)	105	No	No statistically significant differences in mean scores were found between sibling pairs in *attention*, *executive function* and *behavior*	8
Surgery	d-Transposition of the great arteries	[illegible] et al. (1998)	35	No	No difference between siblings regarding *externalizing behaviors*	7
	Congenital heart disease surgery <6m	Schultz et al. (2017)	14	No	No differences between sibling pairs on parent reported *inattentiveness* or *hyperactivity/impulsiveness*	6
Parental depression		Gjerde et al. (2017)	–[i]	Possibly	After sibling comparison, only concurrent maternal depression 1.5 to 5 years postpartum was significantly associated with *externalizing problems*, but not 6 months postpartum	5
Parenting	Harsh parental discipline	Asbury et al. (2003)	2,353	Yes	Significant correlation between harsh parental discipline parent rated *hyperactivity* at age 4	7
		Asbury et al. (2006)	2,581	No	No significant correlation between harsh parental discipline at age 4 and teacher rated *hyperactivity* at age 7 in discordant MZ twins	7
	Negative parental feelings	Asbury et al. (2003)	2,353	Yes	Significant correlation between negative parental feelings parent rated *hyperactivity* at age 4	7
		Asbury et al. (2006)	2,581	No	No significant correlation between negative parental feelings at age 4 and teacher rated *hyperactivity* at age 7 in discordant MZ twins	7
	Instructive parent-child communication	Asbury et al. (2006)	2,581	Yes	Significant correlation between instructive parent–child communication at age 4 and teacher rated *hyperactivity* at age 7 in MZ discordant twins	7
	Informal parent-child communication	Asbury et al. (2006)	2,581	No	No significant correlation between Informal parent-child communication at age 4 and teacher rated *hyperactivity* at age 7 in MZ discordant twins	7
Time in childcare		Zachrisson et al. (2013)	–[j]	No	No relation between hours of homogenously high-quality child care and *externalizing behavior* problems was evident in sibling analyses	5
Parental education		Mascheretti et al. (2017)	–[b]	No	On both *hyperactivity* and *inattentiveness*	4
Transient income decline		Ramanathan et al. (2017)	2,069	Yes	Exposed children had significantly more *externalizing behavioral* problems than the non-exposed matched siblings	7

Studie I – Resultat, IF/Språkstörning/DCD/Tics

Environmental factor		Author (year)	*N*	HR (95%CI)	*OR* (95% CI)	Other	NOS
INTELLECTUAL DISABILITY							
Prenatal							
Suicide attempt with Tardyl during pregnancy		Petik et al. (2012)	27			**χ^2(1df) = 79.3, *p* < .0001**	7
Fetal growth rate		Monset-Couchard et al. (2004)	36			χ^2: $p = .90$	9
		Steingass et al. (2013)	88		6.00 (0.96 to 37.53)		8
		Chatterji et al. (2014)	732			$\beta = -0.19$, $p < .05$)	5
Gestational age[a]	21–31 weeks	Heuvelman et al. (2018)	3,296		**7.84 (4.55 to 13.50)**		7
	32–36 weeks	Heuvelman et al. (2018)	3,296		**1.79 (1.42 to 2.24)**		7
	42 weeks	Heuvelman et al. (2018)	3,296		1.21 (0.99 to 1.48)		7
	43–45 weeks	Heuvelman et al. (2018)	3,296		**2.07 (1.28 to 3.36)**		7
Malformations	Orofacial clefts	Tillman et al. (2018)	6,884	**2.73 (2.15 to 3.46)**			8
Perinatal and neonatal							
Breastfed on discharge		Sussmann et al. (2009)	49		**0.17 (0.05 to 0.66)**		6
Being second born		Steingass et al. (2013)	88		2.25 (0.45 to 11.15)		8
Abnormal ultrasound		Steingass et al. (2013)	88		2.85 (0.82 to 9.89)		8
Sepsis/NEC		Steingass et al. (2013)	88		1.64 (0.57 to 4.77)		8
COMMUNICATION DISORDER							
Prenatal							
Malformations	Orofacial clefts	Tillman et al. (2018)	6,884		**3.61 (2.57 to 5.07)**		8
DEVELOPMENTAL COORDINATION DISORDER							
Being first born		Pearsall-Jones et al. (2008)	16			ns	4

Studie I – Resultat, IF/Språkstörning/DCD/Tics

		Oerbeck et al. (2003)	49	Possibly	Significant sibling difference on one of three measures, but all show small absolute differences	8
	Meningitis	Bergman et al. (1987)	31	No	No significant differences	7
Exposure to general anesthesia		Sun et al. (2016)	105	No	No significant differences	8
DEVELOPMENTAL COORDINATION DISORDER, *motor skills*						
Prenatal						
Fetal growth	Birth weight	Ylitalo et al. (1988)	22	Possibly	Significant twin differences for fine motor skills and visuo-motor [illegible]	9
	> 801-gram Preterm	Kilbride et al. (2004)	25	Yes	Peabody Developmental Motor Scales mean sibling difference: 12.6 (95%CI 4.3–20.9), $p = .004$	8
	SGA	Monset-Couchard et al. (2004)	36	Possibly	Former SGA twins tended to have motor deficiencies, $p = .10$	8
Maternal medication	Paracetamol	Brandlistuen et al. (2013)	1,561	Yes	Siblings exposed more than 28 days: β = 0.24, (95% CI 0.12–0.51); and less than 28 days: β = 0.10, (95% CI 0.02–0.19)	6
	Ibuprofen	Brandlistuen et al. (2013)	1,561	No	Ibuprofen exposure was not associated with neurodevelopmental	6
Perinatal and neonatal						
Perinatal hypoxic risk		Raz et al. (1998)	25	No	No significant difference between twins	8
		Raz et al. (1996)	28	No	No significant difference between twins	8
Infancy and childhood						
Congenital heart disease surgery <6 m		Schultz et al. (2017)	14	Yes	Significant twin differences for fine motor skills, but not visual motor integration ($p = .06$)	6
Medical conditions	Congenital hypothyroidism	Rovet (1986)	101	Yes	Significant findings on several measures	5
		Oerbeck et al. (2003)	49	Yes	Mean sibling differences of motor coordination, dominant hand: 11.06 (95%CI 14.6–8.5), p=<.001; and global motor proficiency: 12.10 (95% CI 9.3–15.0), p=<.001	8
	Meningitis	Bergman et al. (1987)	31	No	No significant sibling differences	7
Exposure to general anesthesia		Sun et al. (2016)	105	No	No significant sibling differences	8
Severely malnourished		Lloyd-Still et al. (1974)	41	No	Lincoln–Oseretsky (mean ± SD): Exposed sibling (16.5 ± 18.7) and unexposed (18.6 ± 15.6), p = ns	7
TIC DISORDER, *tic symptom severity*						
Perinatal and neonatal						
Fetal growth	Birth weight	Hyde et al. (1992)	16	Yes	Significant tic score difference between lighter and heavier twin	7

Studie I –Konklusioner

AST

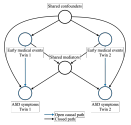
- Hög ålder hos fader, låg födelsevikt, medfödda missbildningar, och perinatal respiratorisk stress
- *Inte* blödning under graviditet, preeklampsi, gestationsdiabetes, BMI och elektiv och akut kejsarsnitt
- Motstridigt: Antidepressiv medicin, moderns ålder, för tidig födsel, värkinduktion, och gulsot

ADHD

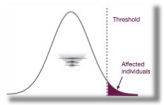
- Låg födelsevikt, för tidig födsel, och låg familjeinkomst/inkomstbortfall
- *Inte* antidepressiv medicin, infection hos modern, BMI och rökning under graviditet
- Motstridigt: alcohol under graviditet, och föräldraålder

Mål

Studie IV:
- Testa om denna effekt är *specifik* för AST eller inte.
- Eller associerad med en *gemensam NPF-faktor*?



Studie III:
- Testa den kumulativa effekten på ett *stort befolkningsmaterial*



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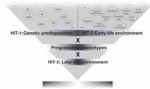


Studie II – Metoder

- Steg 1
  - → 13 AST diskordanta MZ par från RATSS
  - → *Detaljläsning av alla journaler*
- Steg 2
  - → 126 par
  - → Diskordant i autistiska drag

Early-life environment

Studie II – Resultat, steg 1 AST diskordans

Categories	Wilcoxon sign rank test	Variables	McNemar's/ Wilcoxon sign rank test
Delivery related factors	Z= -1.34 p= .180	Apgar 5 min	-
		Fetal distress	-
		Breech birth	*p*= .625
Minor medical neonatal factors	Z= -1.51 p= .131	Hypoglycemia	-
		Hyperbilirubinemia	*p*= 1.00
		Oxygen treatment	-
		Iron depletion	-
		Thrombocytopenia	-
Growth at birth	-	**Birth weight**	**Z= -2.20 p= .028***
Microcephaly	-	Head circumference relative to length	*p*= .219
Minor and frequent infections	Z= -.58 p= .564	Frequent ear infections	*p*= 1.00
		Infections asthma before 5y	*p*= 1.00
		Gastroenteritis <2y	-
Serious infections <2y	Z= .00 p= 1.00	Pyelonephritis <2y	-
		Septicemia <2y	*p*= 1.00
Total allergy	-	Eczema <5y	*p*= 1.00
		Allergy <5y	-

Categories	Wilcoxon sign rank test	Variables	McNemar's/ Wilcoxon sign rank test
Total epilepsy <5y	Z= -1.41 p= .157	Epilepsy <5y	-
		Seizures 1st y	*p*= .50
Serious medical conditions 1st y	Z= -1.00 p= .317	Cerebral hemorrhage	*p*= 1.00
		Cerebral paresis	-
		Hydrocephalus	-
Congenital heart and vessel malformations	-	Heart and large vessels malformation, Cerebral AVM	-
Brain atrophy	-	Brain atrophy	-
Head contusion	-	Head contusion <3y	-
Visual impairments	-	Glasses	*p*= 1.00
Dysregulation <1 y	**Z= -2.56**	Poor sleep	*p*= .063
		Feeding disabilities	*p*= .125
		Frequent vomiting	-
		Crying a lot	*p*= .250
		Worried <1 y	-
The cumulative load of early medical events	**Z= -2.85 p= .004****	Including all above listed variables	

Early-life environment

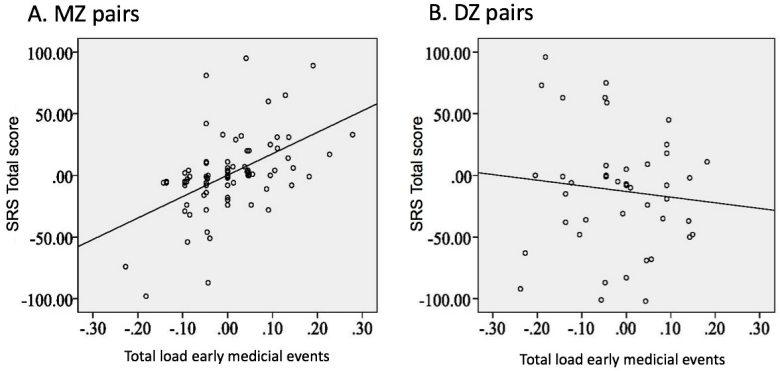
Studie II – Resultat, steg 2

Citation: Transl Psychiatry (2017) 7, e1014; doi:10.1038/tp.2016.269
www.nature.com/tp

ORIGINAL ARTICLE

Medical history of discordant twins and environmental etiologies of autism

C Willfors[1,2,9], T Carlsson[1,3,9], B-M Anderlid[4,5], A Nordgren[4,5], E Kostrzewa[1,2], S Berggren[1,2,6], A Ronald[7], R Kuja-Halkola[8], K Tammimies[1,2] and S Bölte[1,2,6]



- Den kummulativa bördan av tidiga medicinska händelser och autistiska drag (β=78.18, p=.002)

Early-life environment

Mål

Studie IV:
- Testa om denna effekt är *specifik* för AST eller inte.
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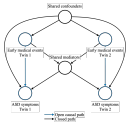

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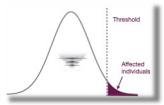

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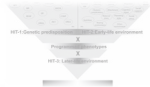


Studie III – Metoder

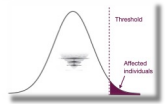
- Bygger på Studie I och II
  - → Exponering: Den kumulativa bördan
    - Låg födelsevikt, medfödda missbildningar, och perinatal respiratorisk stress
- Utfall: AST-diagnos och AST-symptompercentiler
- CATSS – The Child and Adolescent Twin Study in Sweden
  - → Svenska tvillingregistret
  - → En kohort på 15,701 MZ och DZ tvillingpar
  - → Länkad till:
    - Det medicinska födelseregistret (MBR)
    - Det nationella patientregistret (NPR)

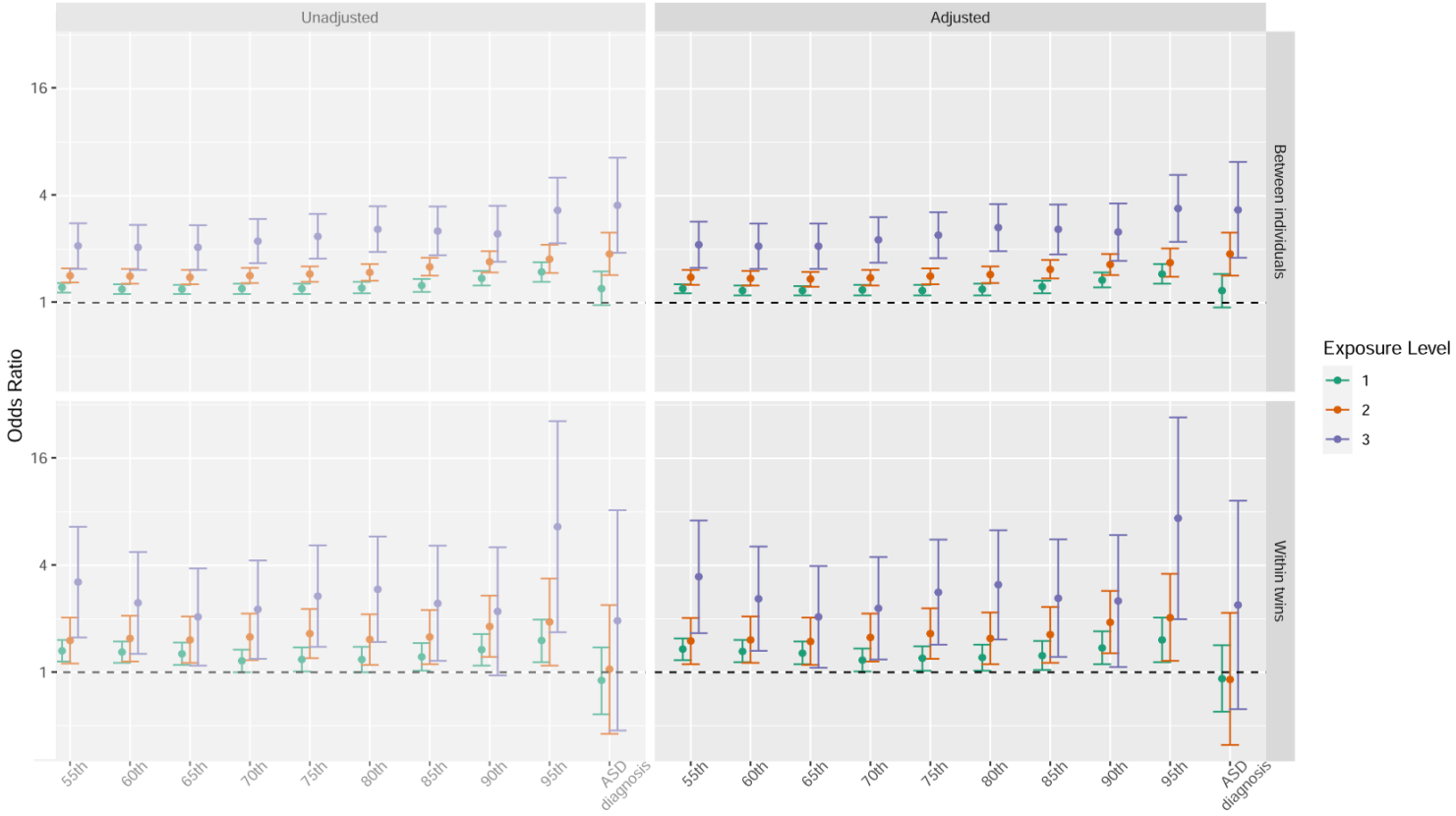
Translational Psychiatry www.nature.com/tp

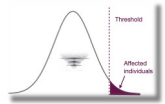
ARTICLE OPEN Check for updates

Association of cumulative early medical factors with autism and autistic symptoms in a population-based twin sample

Torkel Carlsson[1,2,3✉], Mina Rosenqvist[4], Agnieszka Butwicka[4,5,6], Henrik Larsson[4,7], Sebastian Lundström[8,9], Pei-Yin Pan[1,2], Karl Lundin Remnélius[1,2], Mark J. Taylor[4] and Sven Bölte[1,2,10]

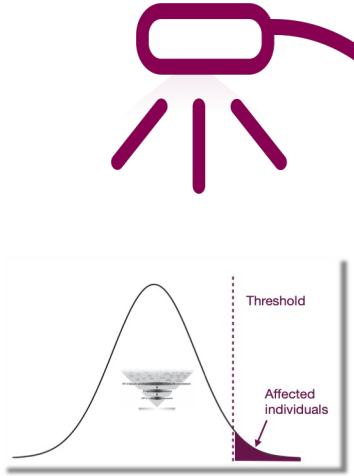



Unadjusted
Adjusted
Between individuals
Within twins
Odds Ratio
16
4
1
55th
60th
65th
70th
75th
80th
85th
90th
95th
ASD diagnosis
Exposure Level
1
2
3


Threshold
Affected individuals

Studie III – Diskussion

- Stöd för:
  - → The cumulative stress hypothesis för AST
  - → The dimensional model
  - → Liability threshold model
- Har vi letat under gatlyktan?



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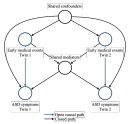

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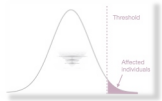

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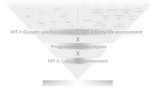
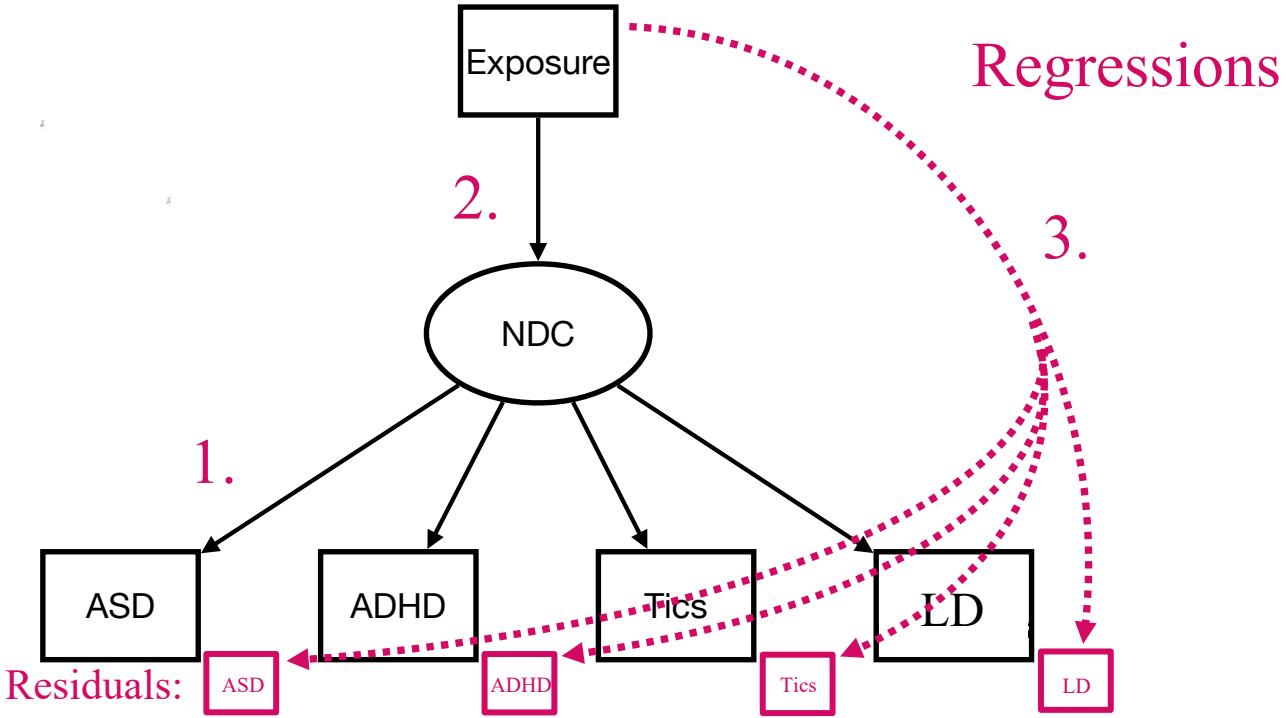
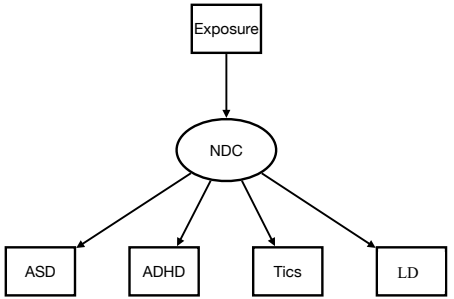


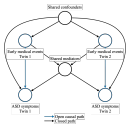
Studie IV – Metoder



Studie IV – Diskussion

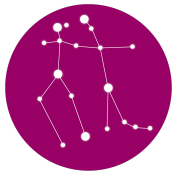
- Ger stöd för:
  - → Ett kausalsamband mellan den kumulativa bördan av tidiga medicinska händelser och NPF
  - → Att det finns en gemensam bakomliggande NPF-faktor
    - (Tidigare forskning har föreslagit detta för genetiska orsaker)





Konklusioner från avhandlingen

1. Behovet av syskon- och tvillingstudier är stort – på grund av familial confounding
2. Tidiga medicinska händelser kan betraktas som miljöfaktorer bakom autism och de passar in i “the dimensional model” för autism och “the liability threshold model”
3. Den bekräftar “the cumulative stress hypothesis” för AST för första gången hos människa
4. Den föreslår att denna kumulativa miljömässiga effekt påverkar en gemensam NPF-faktor



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- All **twins** and **parents of twins** participating and contributing in RATSS and CATSS
- Supervisors and co-authors
- Funders

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- Research school for clinicians in epidemiology (KI-SLL)
- Sällskapet Barnavårdd
- The HM Queen Silvia's Jubilee Fund
- Professor Bror Gadelius Minnesfond

Environmental Etiologies of Autism and Other Neurodevelopmental Conditions:

Twin Studies of the Cumulative Effect of Early Medical Events

Torkel Carlsson
Med. dr.
Överläkare
BUP Konsultenhet
BUP FoUU