

Obstetrical and neonatal factors and risk of autism

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Prevalence of Autism Spectrum Disorders

Prevalence in Canada is reported to be about 4-6 per 1000 children (about 1 in 165 children) and about 2 per 1000 for autism specifically

Numbers of diagnoses have been rising in recent decades

Various reasons are thought to contribute to this increase:

- Heightened awareness
- Changes in definitions of autism- broadening the definition
- Younger age at diagnosis
- Greater funding for services

Causes of Autism

- Causes likely multifactorial and include:
 - Genetics/heredity
 - Pre-natal factors/ obstetric/ neonatal factors
 - Possible exposure to environmental toxins
 - Viral infections
 - Immune system deficiencies

Causes of Autism

Genetics/heredity

- Autism runs in families- siblings have a 3-8% chance of being diagnosed with autism
- Monozygotic twins have only a 60% chance of being diagnosed with autism- supporting the role for other factors in autism etiology

Causes of Autism

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Embryology of Autism

Several in utero exposures are known to increase the risk of autism in the offspring

- Rubella
- Valproic acid

In 1994, Miller and Stromland (two pediatric ophthalmologists) made an interesting discovery: that thalidomide exposed children were at much higher risk of autism

Embryology of Autism

- They found that most of the thalidomide victims with autism had anomalies in the external part of their ears, but did not have malformations of the arms or legs.
- This pattern indicated that the children had been exposed in very early gestation- around 20 to 24 days after gestation
- At this time in gestation, the embryo's brain and nervous system are just beginning to develop- the first neurons are motor neurons of the cranial nerves- which operate the muscles of the eyes, ears, face, etc.
- They found that these thalidomide victims with autism also had abnormalities of eye movement or facial expression, supporting the involvement of cranial nerves

Etiology of Autism

These findings suggested that very early gestation is a critical time period in autism etiology

But, just as genetics do not account for all cases of autism, the early pregnancy teratogens do not account for all autism cases

Etiology of Autism

Other studies have investigated the role of other prenatal factors, labour and delivery factors and neonatal factors.

Prenatal factors:

PIH, diabetes, bleeding in pregnancy, parental age, smoking

Labour and Delivery factors:

C-section, 5-minute Apgar score < 7, fetal distress

Neonatal factors:

Male sex, SGA and LGA, anomalies

Objectives

- Identify prenatal, obstetrical and neonatal factors associated with the development of autism
 - Adjust for the influence of increased genetic susceptibility
 - Compare factors between those at increased genetic risk and those who are not
- Assess accuracy of administrative health data for autism diagnoses

Inclusion

- Children born between 1989 and 2002
- Resident of Nova Scotia
 - Identified from the Atlee Perinatal Database
 - Province-wide perinatal database that includes information on all hospital births (over 99%)
 - Includes extensive information on prenatal, labor and delivery and neonatal outcomes
- At least 2 years of follow-up data available

Administrative Databases

Administrative Databases (ICD coding for autism and other diagnoses):

- Hospital Discharge Abstract Database
- Physician Billing Database
- Mental Health Outpatient Database

All are
province-wide
databases

Other relevant databases:

- Family Benefits File
- Registration File

Files linked

- Atlee Database
- Hospital Discharge Abstract Database
- Physician Billing Database
- Mental Health Outpatient Database



Linked together based on 'scrambled' Health Card Number

Health Card Number assigned to each Nova Scotia resident at birth

Defining Autism

At least 1 autism code from any of these 3 databases between 1992-2005:

Hospitalization

Physician billing

Out-patient mental health

Autism Code: ICD-9 → 299

ICD-10 → F84

Definition of increased genetic susceptibility

Increased genetic susceptibility defined as:

Having a sibling with an autism diagnosis

or

A mother who had a psychiatric or neurologic condition

Analyses

Initially, univariate analysis for each factor

Multivariate model – variables tested for inclusion using likelihood ratio test

Cox proportional hazards models to estimate relative risks

- Appropriate for data where we have varied follow-up times (children born in the later years of the study have less follow-up time than children born in the earlier years)

Results

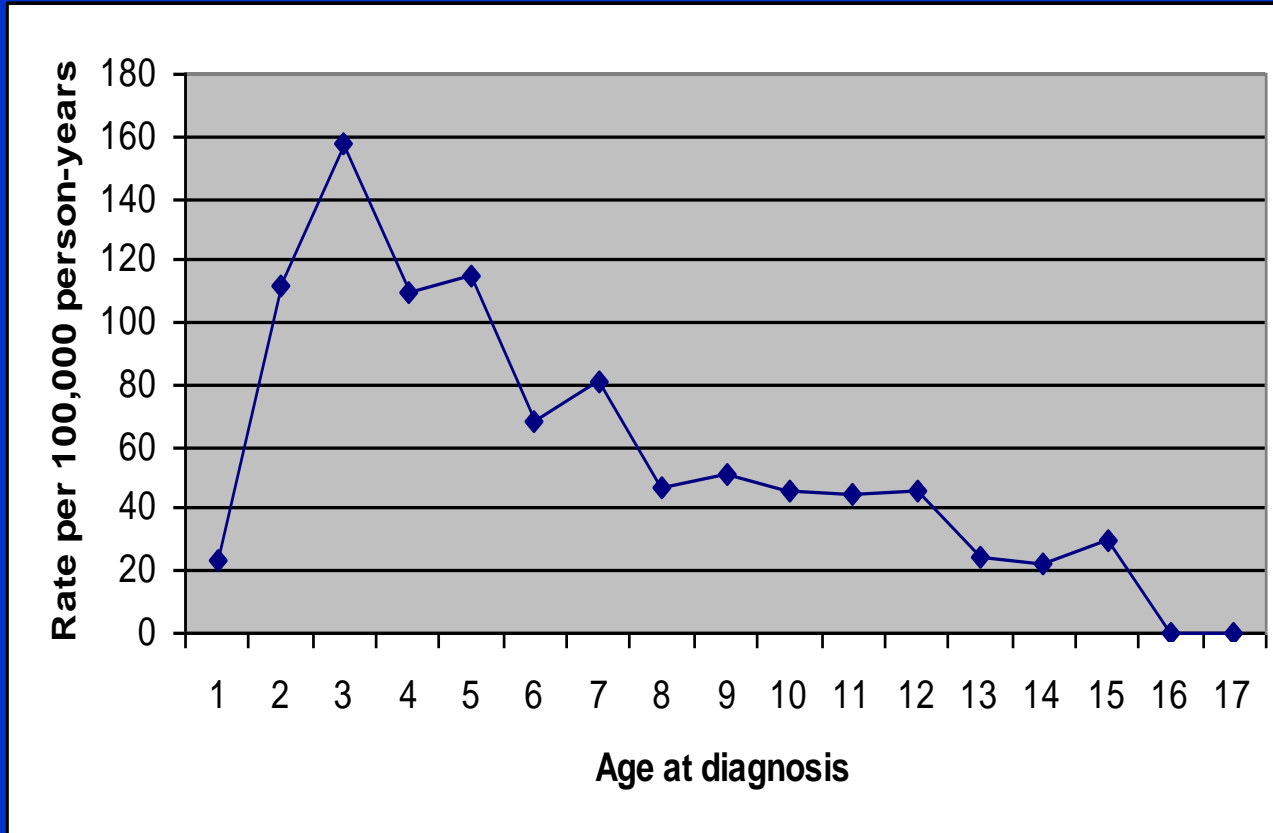
129,809 infants born between 1988 and 2002 and who linked to the administrative data and had ≥ 2 years of follow-up

924 children had an autism diagnosis between 1992 and 2005

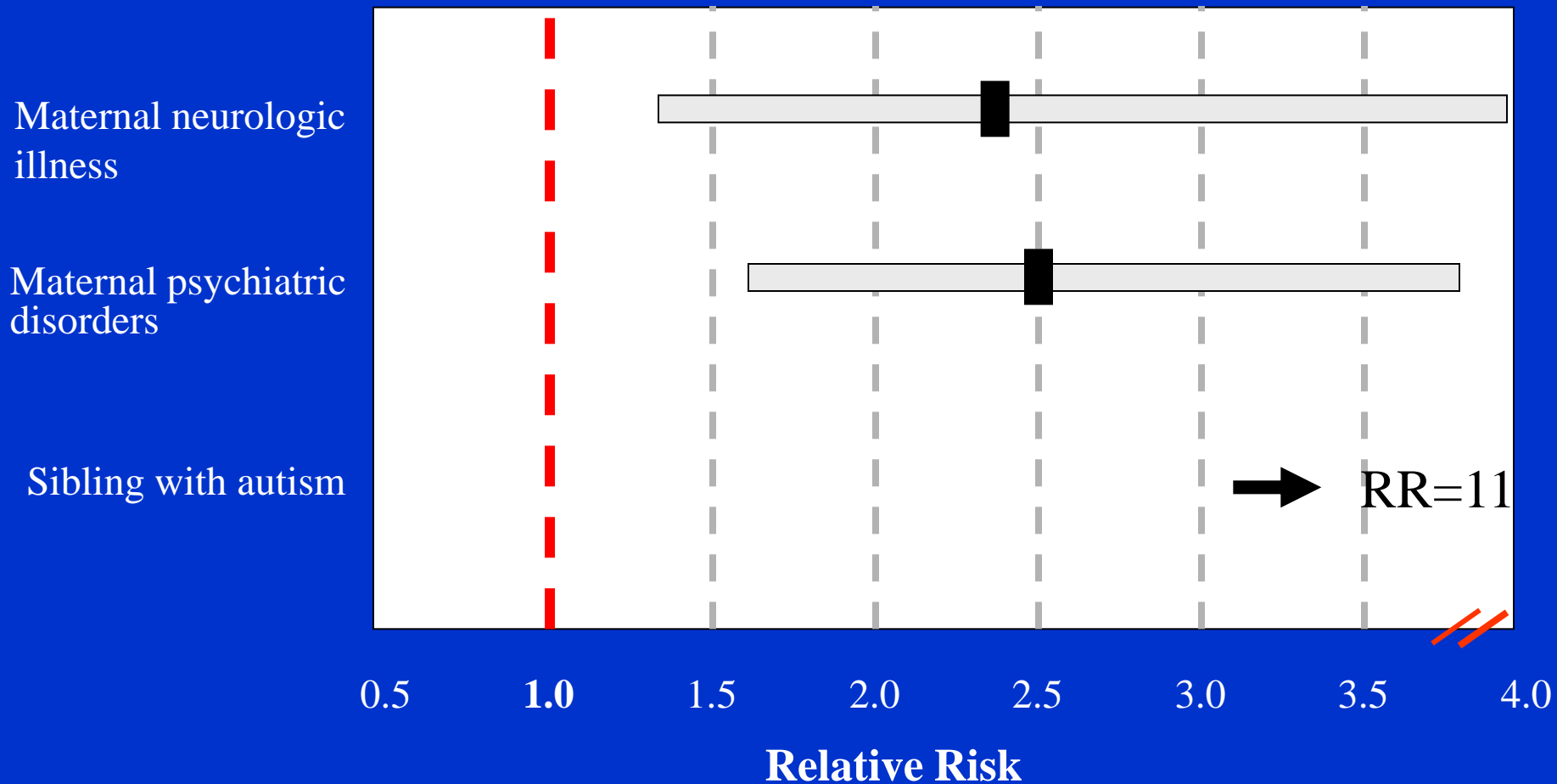
Average length of follow-up available: **10 years**

Approximately 2.4% of children had high ‘genetic susceptibility’

Autism rates by age at first hospitalization or out-patient claim

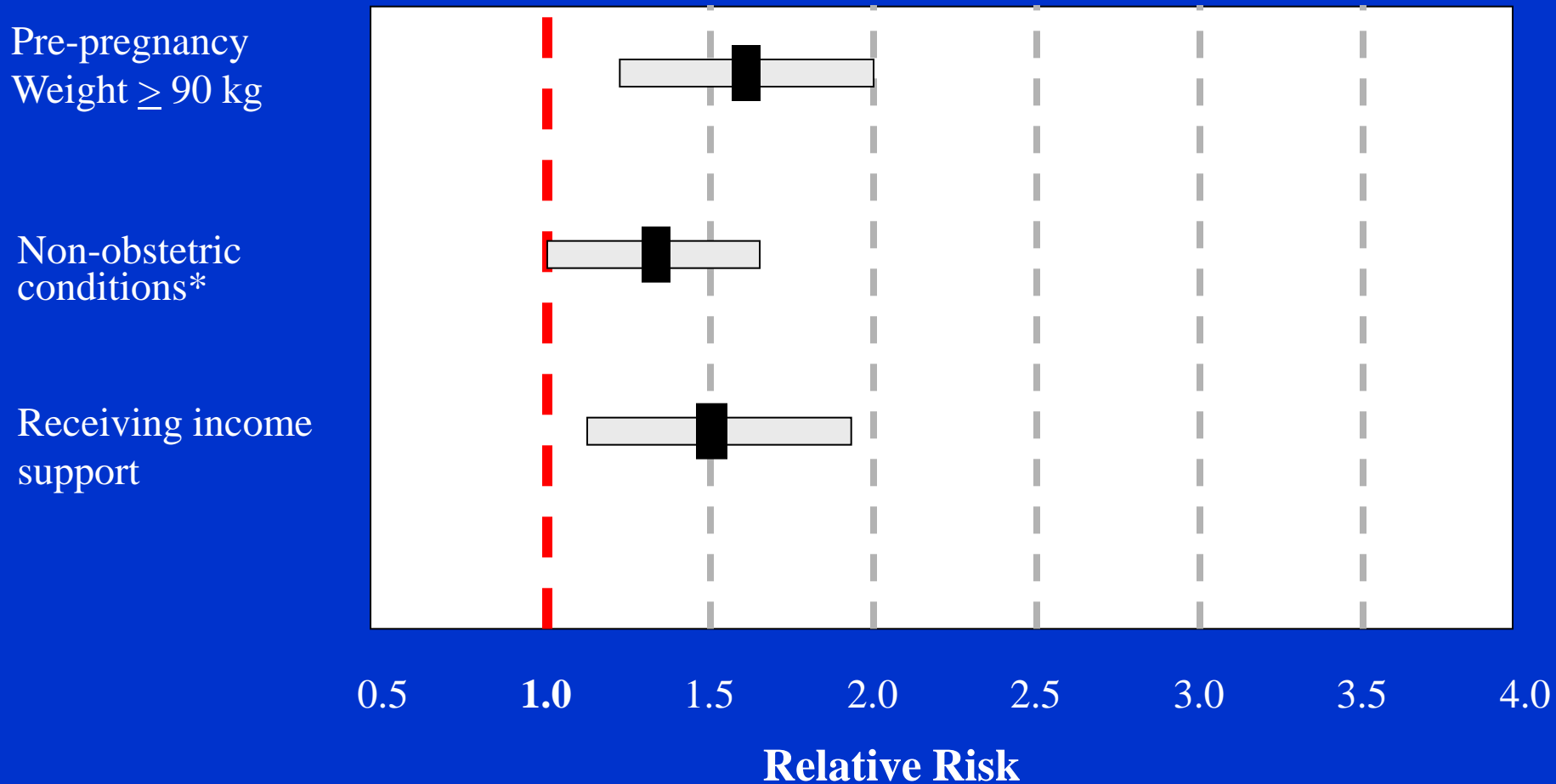


Autism and genetic susceptibility factors:



Adjusted for other factors in model

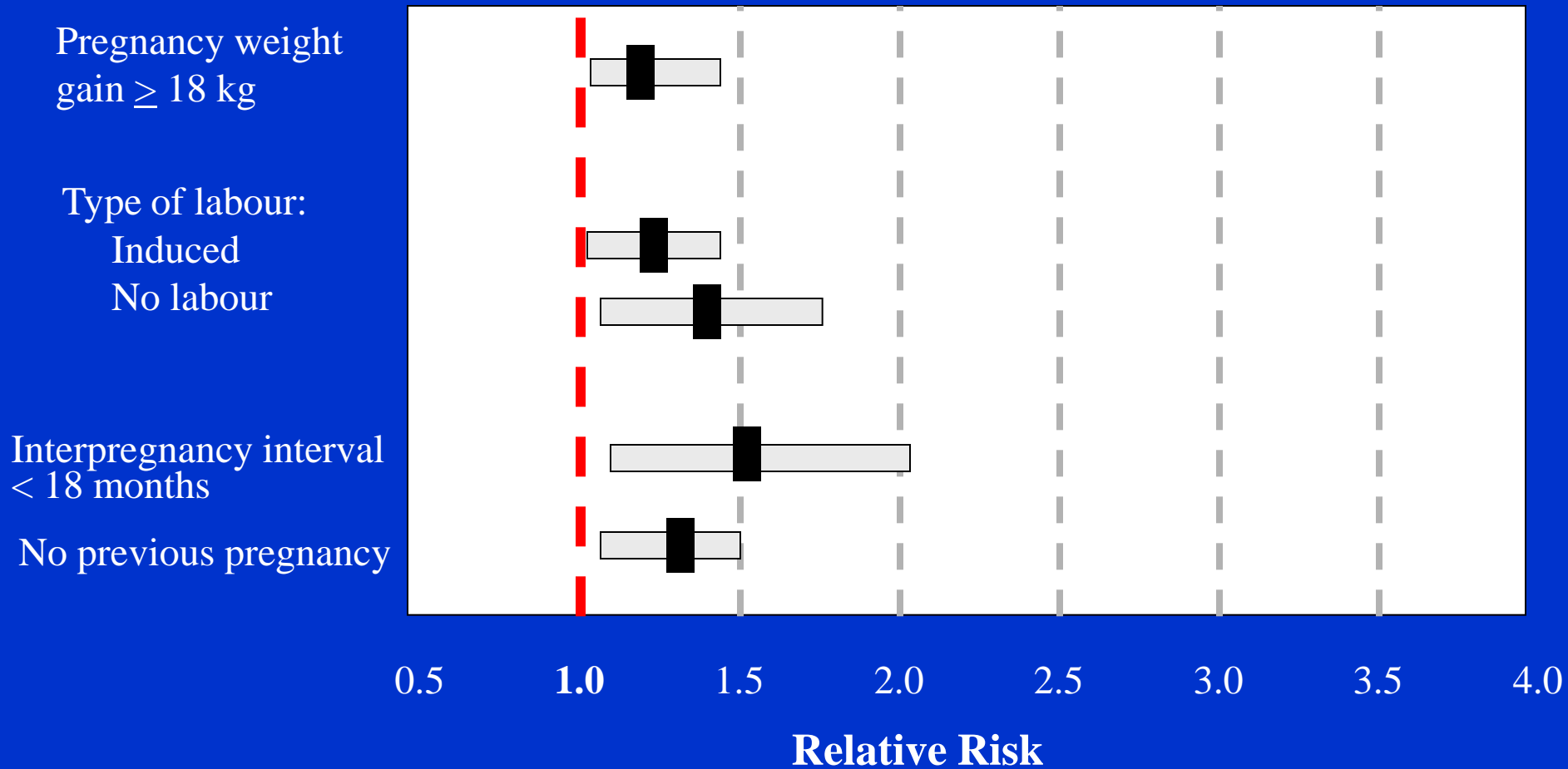
Autism and maternal factors



*Includes: pulmonary disease, heart disease, renal disease or anemia

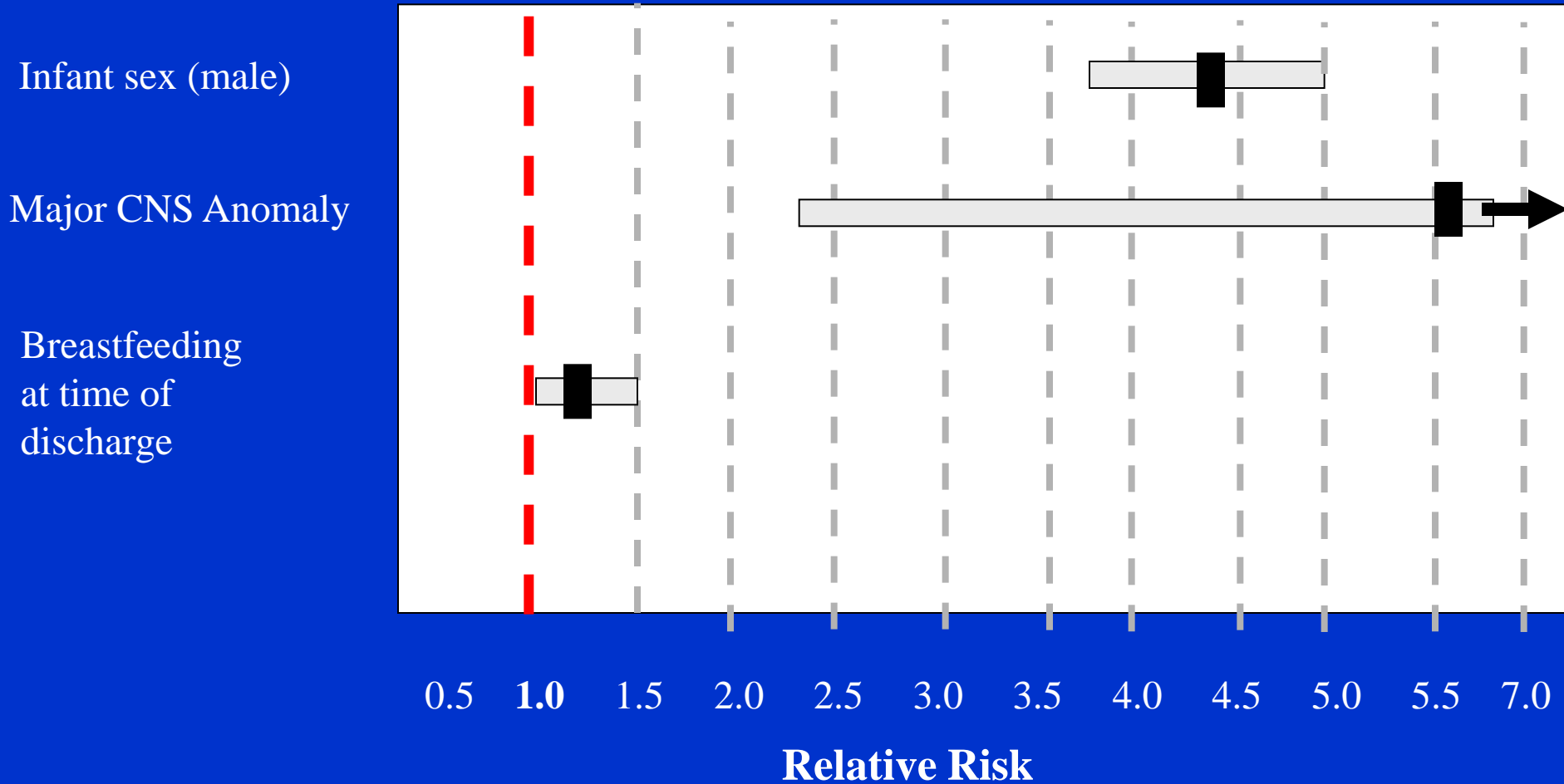
Adjusted for other factors in model (including genetic susceptibility factors)

Autism and obstetric factors



Adjusted for other factors in model (including genetic susceptibility factors)

Autism and newborn factors



Adjusted for other factors in model (including genetic susceptibility factors)

Comparison of Factors among Children with High and Low Genetic Susceptibility

High Genetic Susceptibility:

Male
Birth weight > 4000g
Maternal non-obstetric conditions

Low Genetic Susceptibility:

Income support
High pre-pregnancy weight
High weight gain in pregnancy
Short inter-pregnancy interval
or no previous pregnancy
Male sex
Type of labour
CNS anomaly
Breastfeeding

*Are we correctly classifying kids
with autism and those without??*

Gold Standard Data

Children referred to and assessed by Autism Team at IWK Health Centre in Halifax, Nova Scotia

A diagnosis of autism is made based on :

- The Autism Diagnostic Interview-Revised
- The Autism Diagnostic Observation Schedule
- Clinical judgment using DSM

Gold Standard Diagnostic Criteria

Gold Standard Data

264 children assessed by Autism Team at the IWK
(this diagnosis was considered the Gold Standard)

The diagnoses from these 264 children were compared to
the diagnoses from the administrative data

The Autism Team Database is independent from the
administrative databases

Gold Standard Diagnosis

Autism Dx based
on Administrative
Data

	Autism	
	Yes	No
Yes	122	20
No	54	68

Overall Accuracy: 72%

Sensitivity: 69%

Gold Standard Diagnosis

Autism Dx based
on Administrative
Data

Autism

Yes

No

Yes

122

20

No

54

68

Of the 54 False Negative results, 46 children had at least one MSI billing claim for mental disorder of personality disorder

Conclusions from Validation Study

Administrative data does reasonable well at capturing autism diagnoses (sensitivity ~ 70%)

Risk factor analysis repeated using 'true cases': Results similar to results using administrative data for autism diagnoses

Summary of risk factors

Sibling with autism

Maternal history of neurologic disorders

Maternal history of psychiatric disorders

} Genetic
Susceptibility

Income support

Male sex

Inter-pregnancy interval < 18 months
or no previous pregnancy

Pre-pregnancy weight $\geq 90\text{kg}$

Pregnancy weight gain $\geq 18\text{ kg}$

} Prenatal Factors

CNS anomaly (? prenatal factor)

Breastfeeding

} Neonatal Factors

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→ CNS anomaly (? prenatal factor)

→ Breastfeeding

} Neonatal Factors

Breastfeeding:

Why would it be associated with a higher risk of autism?

It is not explained by its association with income and other factors, because the analysis adjusted for these factors

Clearly, not the message we want to give!

Pregnancy interval < 18 months and no prior pregnancy

Being first born (i.e., no prior pregnancy) has been reported as a risk factor in previous studies

Short pregnancy interval between index pregnancy and previous pregnancy: Two possible explanations

1. That the effect of short interval is somehow causally linked to development of autism- with a similar mechanism that short interval has been linked to obstetric problems
2. Families who have an affected child may choose not to have another child. Since children with autism are not usually diagnosed until after 18 months, families with intervals of over 18 months will be more likely to have an affected child- which places the index child at much higher risk of developing autism

High pre-pregnancy weight and autism in offspring

It is interesting to note the parallel in rising rates of obesity and rising rates of autism

Is there a biologic reason to explain an association between high pre-pregnancy weight and autism?

Could this be a causal relationship?

A leptin hypothesis...

Leptin facts

Leptin is a hormone secreted by adipocytes

Leptin correlates with the percentage of body fat, and obese subjects have higher leptin levels than normal weight subjects- it is thought that obese people may become 'leptin resistant'

Plasma leptin levels have been found to be increased in children with autism

Children with autism have not been found to be more obese or overweight than other children

Leptin can cross the blood-brain barrier

Leptin Hypothesis

Possible hypotheses...

Leptin level (either prenatal exposure, or exposure soon after delivery) is a determinant in the neuropathology in autism,

OR

Leptin level is related through an accompanying phenomena (e.g., leptin is involved in immune modulation and there is mounting evidence of immunological dysfunction in children with autism)

Leptin Hypothesis

Future Studies:

It would be interesting to measure leptin level from cord blood or early neonatal blood to determine if leptin level is associated with autism risk

Measure maternal leptin level in early pregnancy, and see if this is associated with neonatal leptin level, and autism risk

Conclusions

Among genetically susceptible children, obstetric factors do **not** seem to have a role

Among children with low genetic susceptibility, some prenatal factors are independent risk factors for development of autism

Association with pre-pregnancy weight and weight gain in pregnancy has not been reported previously is an important topic for future study

Thanks...

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