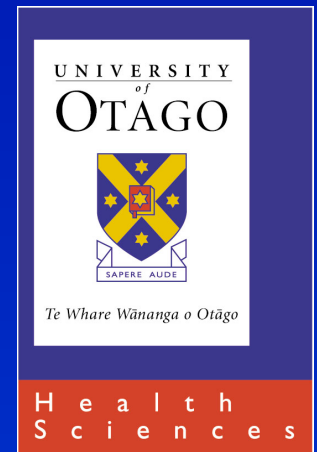
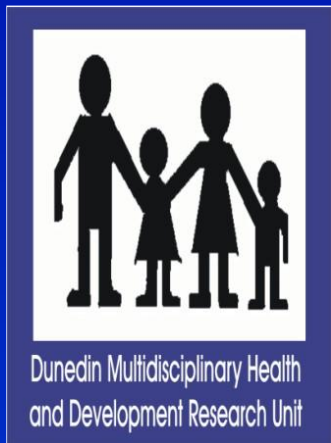


# Nature-nurture interplay and human behaviour

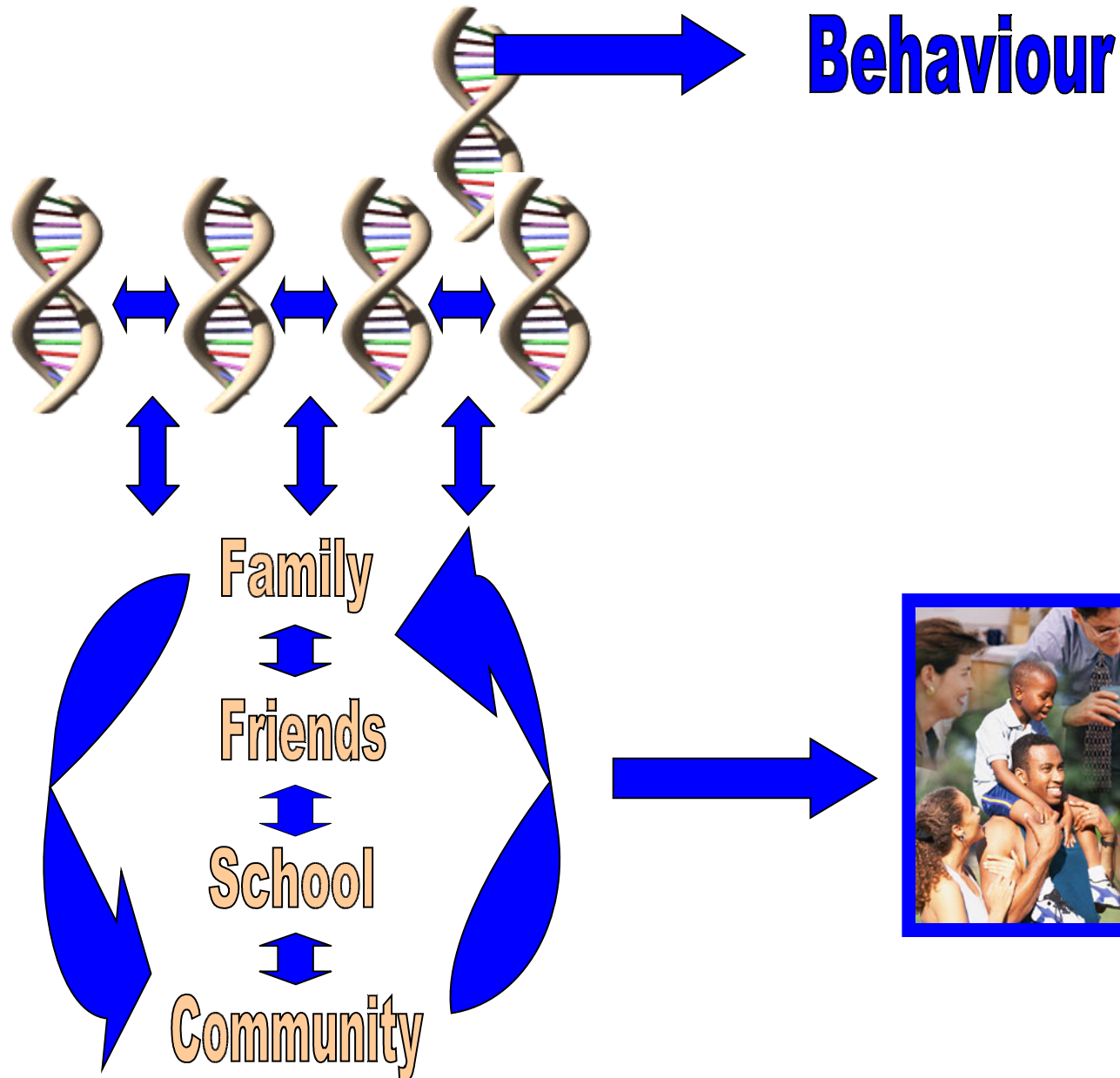
**Professor Richie Poulton**  
**Director, Dunedin Multidisciplinary Health  
and Development Research Unit;**  
**Co-Director, National Centre for Lifecourse  
Research**

**Department of Preventive & Social Medicine**  
**Dunedin School of Medicine**  
**University of Otago**



# Background

- Human beings, their problems and their diseases are complex.
- Most research aims to identify genes that relate **directly** to specific disorders.
- Results have been disappointing and inconsistent.



# GxE and sexual behaviour

- There is a heritable component, as for most things, e.g. Martin et al (1977).
- Virtually all studies have been gene-phenotype or main effects studies, with the attendant problems.
- Halpern et al (2007) attempted to model GxE – mixed results.
- GxE predicting disease progression among those infected by HIV is perhaps the most impressive work to date (Fellay et al, 2007).

Martin et al (1977), *Journal of Biosocial Science*, 9: 91-97; Halpern et al (2007), *Archives of Sexual Behaviour*, 36:543-554; Fellay et al (2007), *Science*, 317:944-947.

# Five Steps

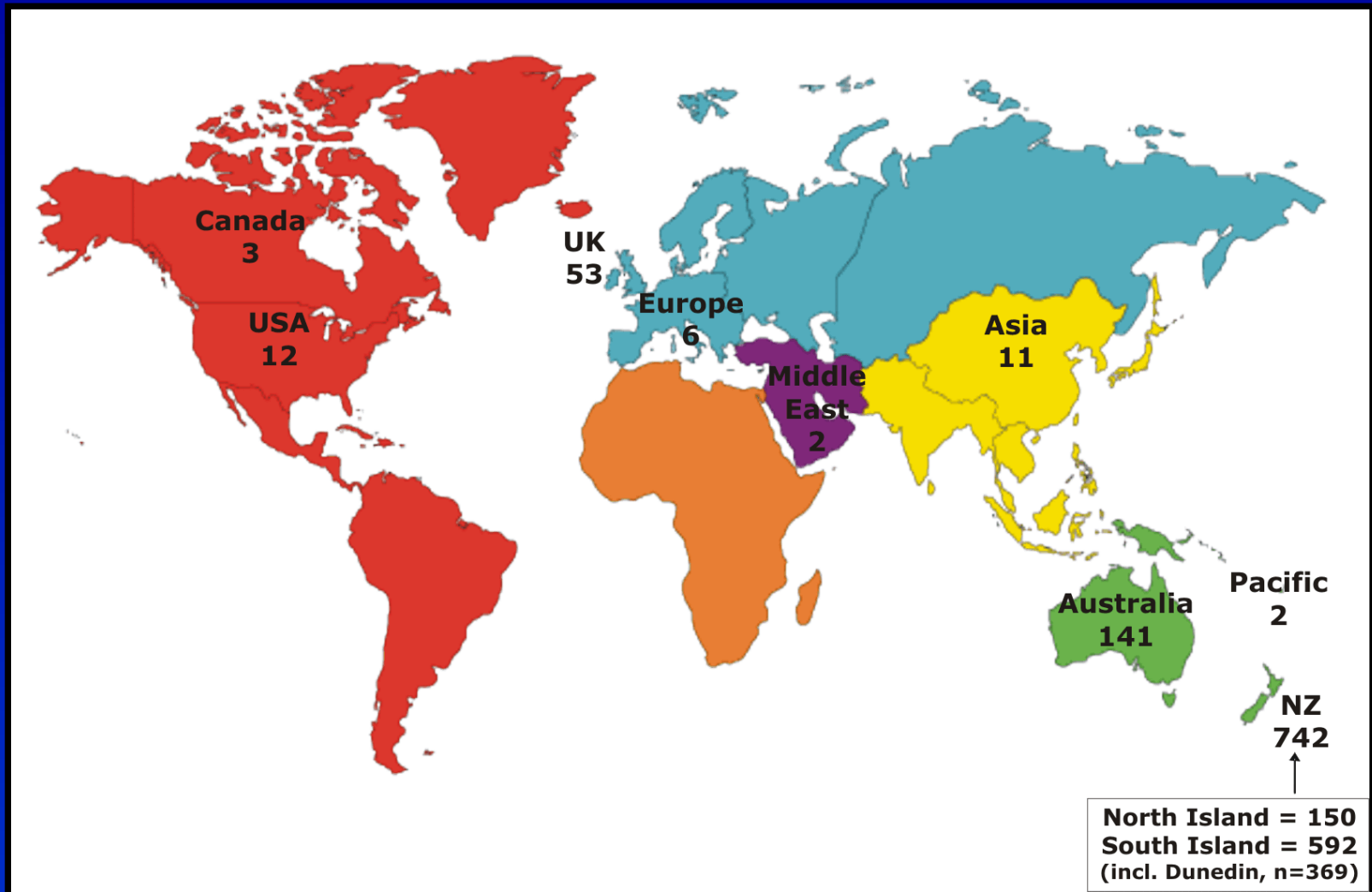
1. Identify a plausible combination of disorder, environmental risk factor and candidate gene to generate a hypothesis.
2. Test the interaction hypothesis between the gene, the environmental risk factor, and the disorder.
3. Replicate the findings with alternative measures of the disorder.
4. Check to see other genes are interacting with the gene being tested.
5. Test if the gene-environment interaction predicts other disorders.

# Retention in the Dunedin Study

Age	Year	Number	Percent*
<b>Birth</b>	<b>1972-73</b>		
<b>3</b>	<b>1975-76</b>	<b>1037</b>	<b>100%</b>
<b>5</b>	<b>1977-78</b>	<b>991</b>	<b>96%</b>
<b>7</b>	<b>1979-80</b>	<b>954</b>	<b>92%</b>
<b>9</b>	<b>1981-82</b>	<b>955</b>	<b>92%</b>
<b>11</b>	<b>1983-84</b>	<b>925</b>	<b>90%</b>
<b>13</b>	<b>1985-86</b>	<b>850</b>	<b>82%</b>
<b>15</b>	<b>1987-88</b>	<b>976</b>	<b>95%</b>
<b>18</b>	<b>1990-91</b>	<b>993</b>	<b>97%</b>
<b>21</b>	<b>1993-94</b>	<b>992</b>	<b>97%</b>
<b>26</b>	<b>1998-99</b>	<b>980</b>	<b>96%</b>
<b>32</b>	<b>2004-05</b>	<b>972</b>	<b>96%</b>

\* Percentage seen of those who were eligible (i.e. alive) at each age

# Location of Study Members at age 32



# Current research activities include studies of:

- **SES inequalities - selection v causation**
- **Employment**
- **Personality continuities across the life-course**
- **Antisocial behaviour and criminality**
- **Long-term consequences of child abuse**
- **Intergenerational relations (Study members & their parents)**
- **Maori health/cultural identity**
- **Mental health (including substance abuse)**
- **Self-harm/coping**
- **Intimate relationships and domestic violence**
- **Dental health**
- **Sexual & reproductive health**
- **Cardiovascular risk factors**
- **Cardiovascular reactivity**
- **Respiratory functioning**



# Current research activities (contd)

- **Blood based studies**

- HPV (wart virus)
- Herpes immunity
- Cardiovascular disease risk factors
- IgE, alpha 1 antitrypsin

- **Genetic studies**

- Mental health
- Asthma/allergy
- Cardiovascular risk factors

- **Methodological studies**

- Comparison of Dunedin sample with national data
- Attrition analyses

# The cycle of violence

- **Childhood maltreatment is a universal risk factor for antisocial behaviour increasing later criminality by about 50%.**
- **But the majority of maltreated males do not become delinquents or criminals?**

Caspi et al (2002), *Science*, 297; 851-854

# **Genetic factors may act to increase (or decrease) environmental risk exposure**

- **Passive gene-environment correlations**
- **Evocative gene-environment correlations**

# **Genetic factors may act to modify the influence of environmental risks on psychiatric outcomes**

- **Genotypes may exacerbate reactions to environmental adversities**
- **Genotypes may have a protective function**

# **In this study...**

**We characterised genetic susceptibility to childhood maltreatment in terms of individual differences in a functional polymorphism in the promoter of the monoamine oxidase (MAOA) gene.**

# Why the MAOA gene?

- **The MAOA gene is located on the X chromosome (Xp11.23-11.4).**
- **It encodes the MAOA enzyme, which metabolizes neurotransmitters such as norepinephrine (NE), serotonin (5-HT) and dopamine (DA), rendering them inactive.**
- **Genetic deficiencies in MAOA activity have been linked with aggression in mouse and man.**
- **Deficient (i.e. “knockout” or low) MAOA activity may dispose the organism toward neural hyper-reactivity to threat.**

# The gene-maltreatment link

- **Animal studies show that maltreatment stress in early life alters NE 5-HT, and DA neurotransmitter systems leading to an increase in aggression in “adulthood”.**
- **In humans, altered NE and 5-HT activity is linked to aggressive behaviour and childhood maltreatment has lasting neurochemical correlates.**

**Step 1**

# Testing Gene x Environment Interaction in a Cohort Design

- DNA samples obtained via blood (93%) and saliva (7%)
- Study members were grouped as “High” MAOA activity (carrying the 3.5 or 4 repeat variants) and “Low” MAOA activity (carrying the 2, 3 or 5 repeat variants).
- Ethnic stratification?

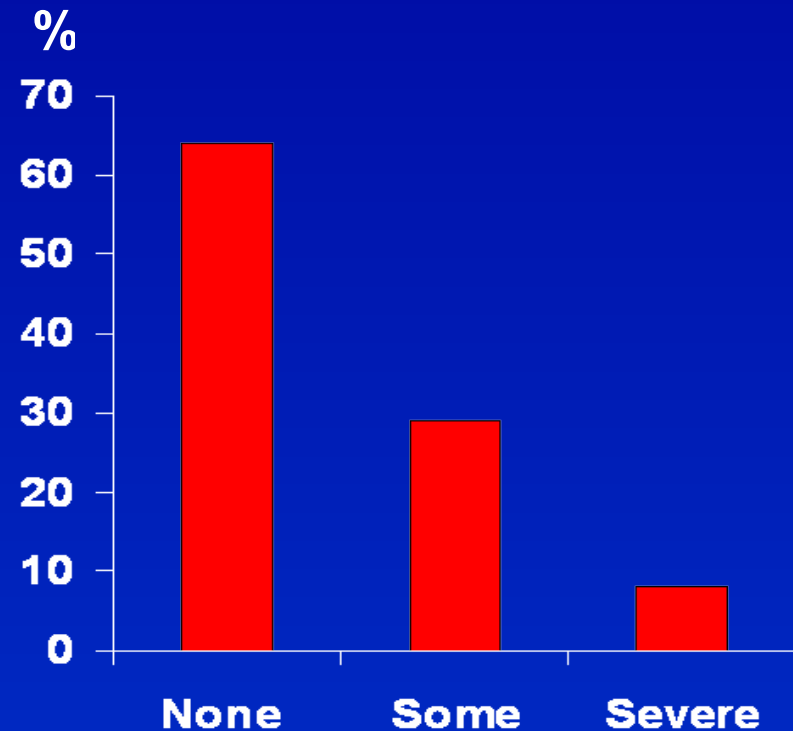


# **Childhood maltreatment ages 3-11 years**

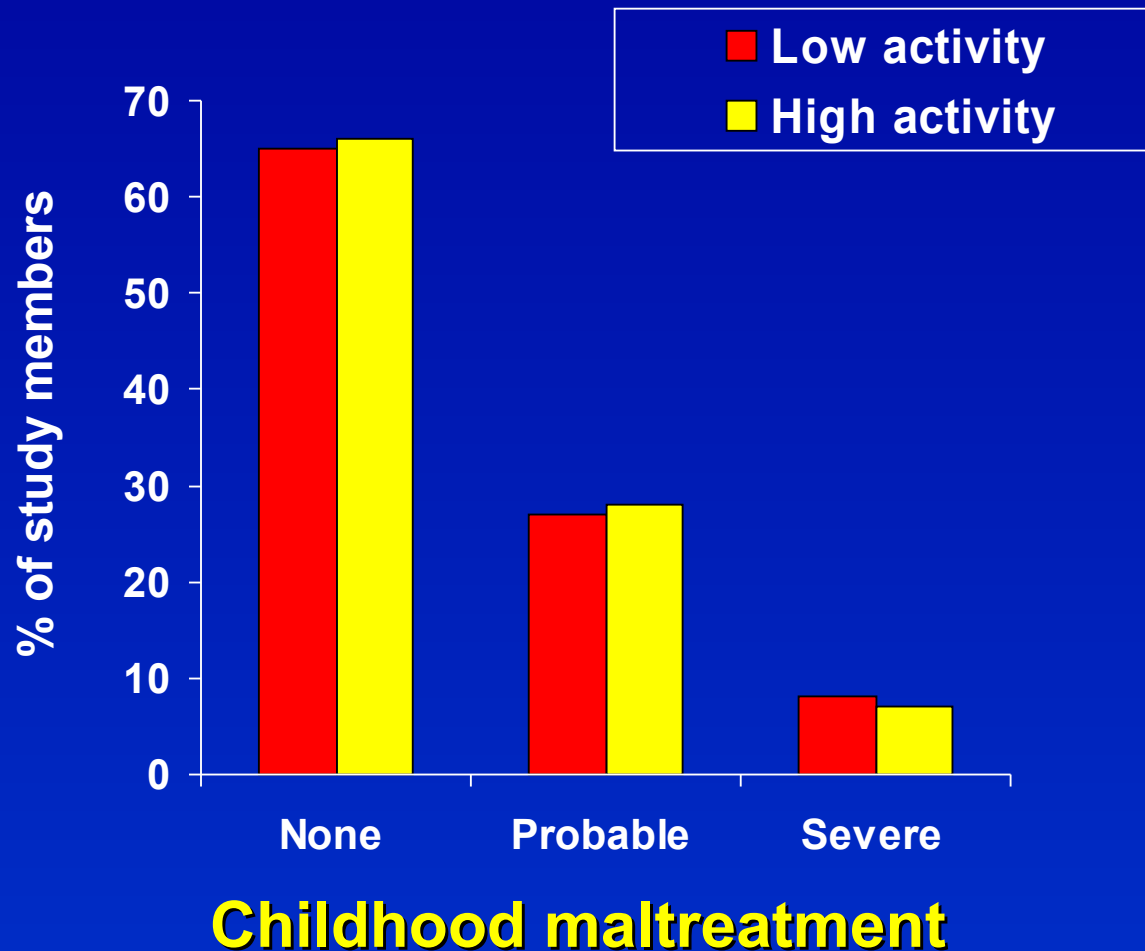
- **Observations of mother's behaviour (age 3)**
- **Parental reports of harsh discipline (ages 7-9)**
- **Multiple caregiver changes (through age 11)**
- **Physical harm (retrospective report)**
- **Unwanted sexual contact (retrospective report)**

# Childhood maltreatment (ages 3 -11 years)

For each Study child, we derived a cumulative exposure index by summing the number of maltreatment experiences reported during the first decade of life.



# Exposure to childhood maltreatment as a function of MAOA activity



# Testing Gene x Environment Interaction in a Cohort Design

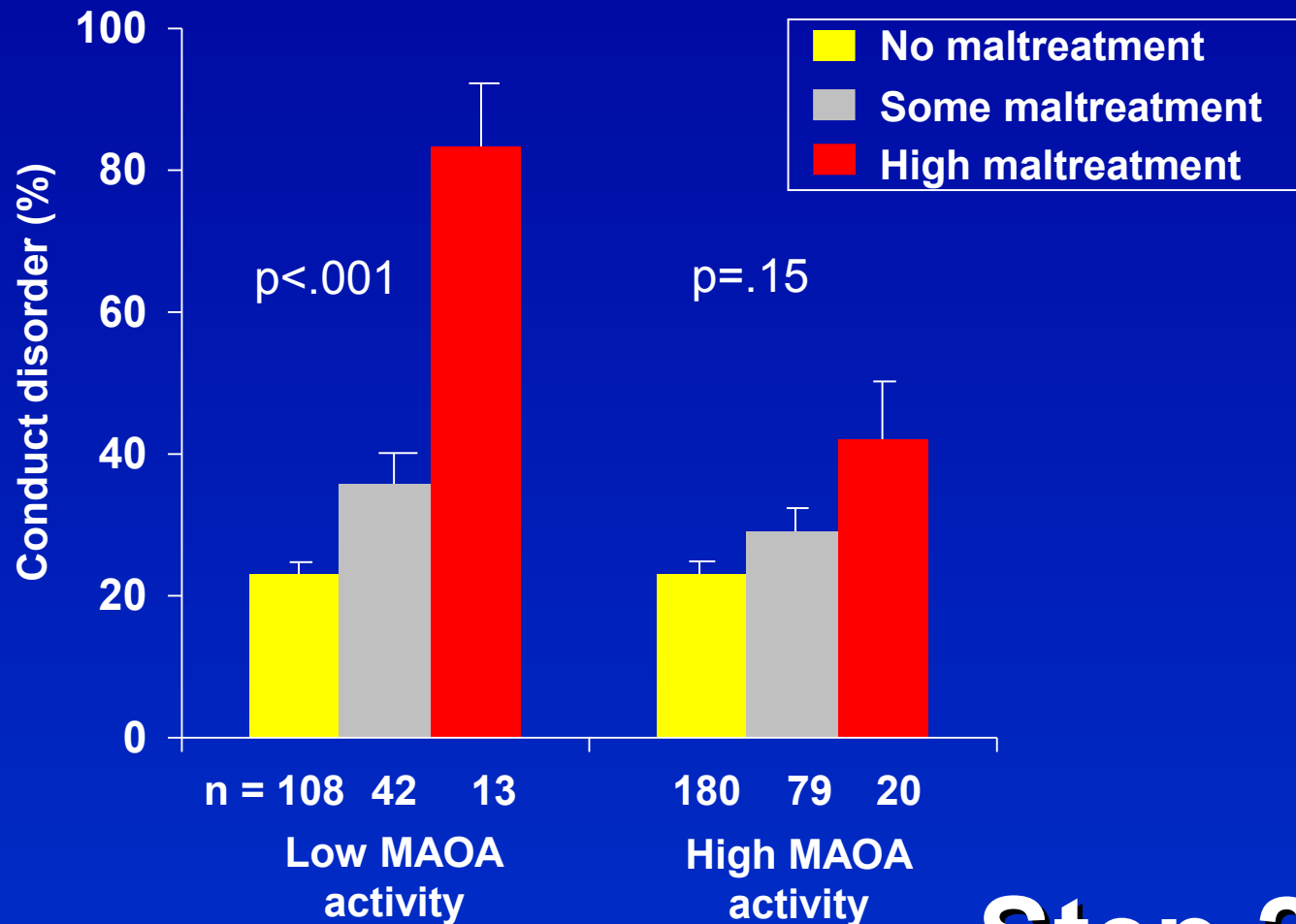
- **Genetic status: High vs low MAOA activity**
- **Severity of childhood maltreatment, between ages 3-11 years**

**Evidence for gene x environment interaction would be found if the MAOA gene modified the influence of maltreatment on children's development of severe antisocial behaviour.**

# Diagnosis of conduct disorder in adolescence

- **According to criteria of DSM-IV**
- **Based on diagnostic interviews with Study members (at ages 11, 13, 15, 18) and checklists completed by their parents and teachers**
- **At each assessment age, symptom information was gathered with reference to the "past 12 months"**
- **28% of the Study males were diagnosed with CD at one or more assessment ages**

# Conduct Disorder (ages 10-18) by MAOA gene activity and childhood maltreatment

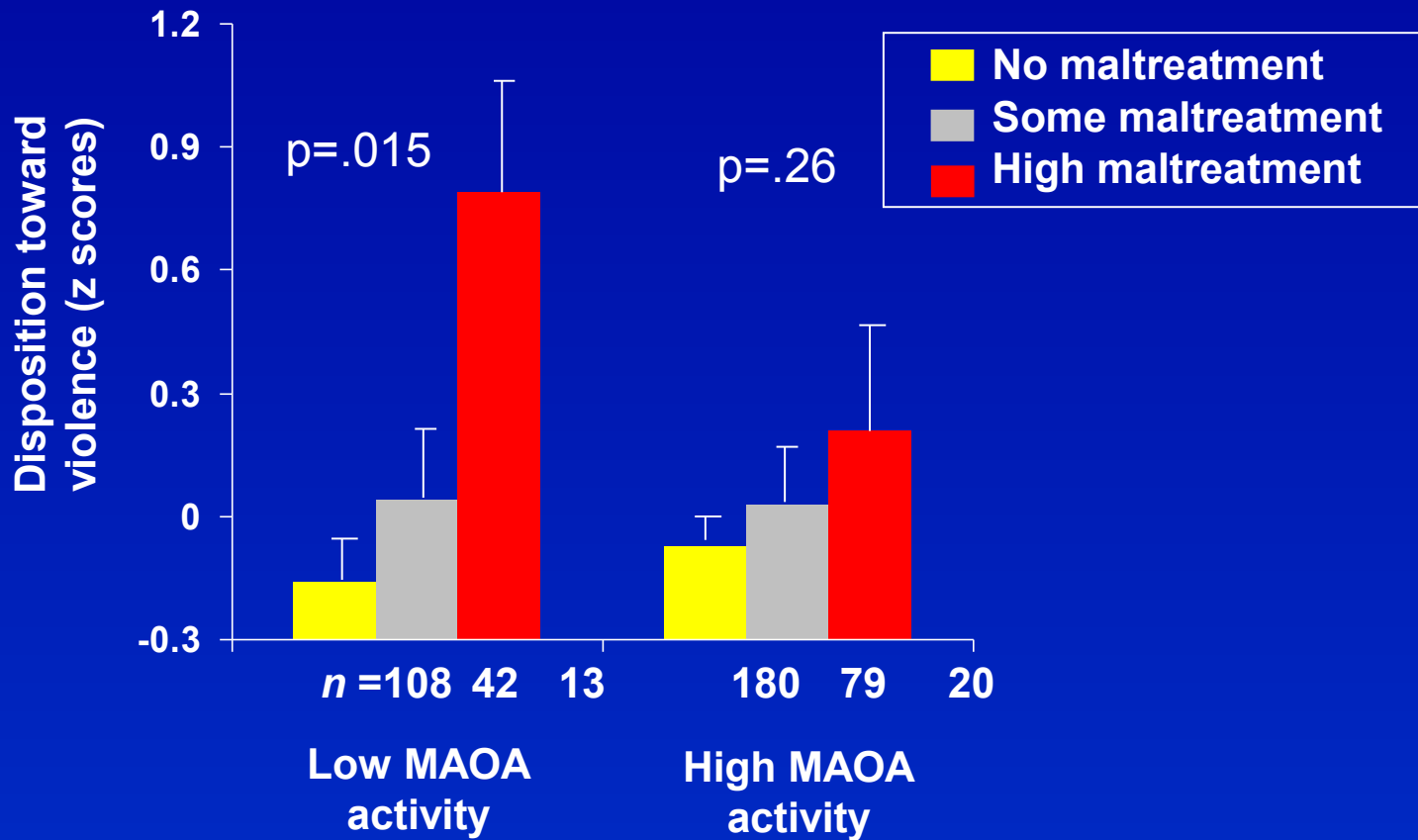


**Step 2**

# Personality disposition toward violence (self-report at age 26 years)

- Sometimes I daydream about injuring or hurting someone
- My temper is quick and hot
- When I get angry, I fly off the handle before I know it
- When I get angry I am ready to hit someone
- I admit that I sometimes enjoy hurting someone physically
- I enjoy a good brawl
- Sometimes I hit people who have done something to deserve it

# Aggressive personality (age 26) by MAOA gene activity and childhood maltreatment

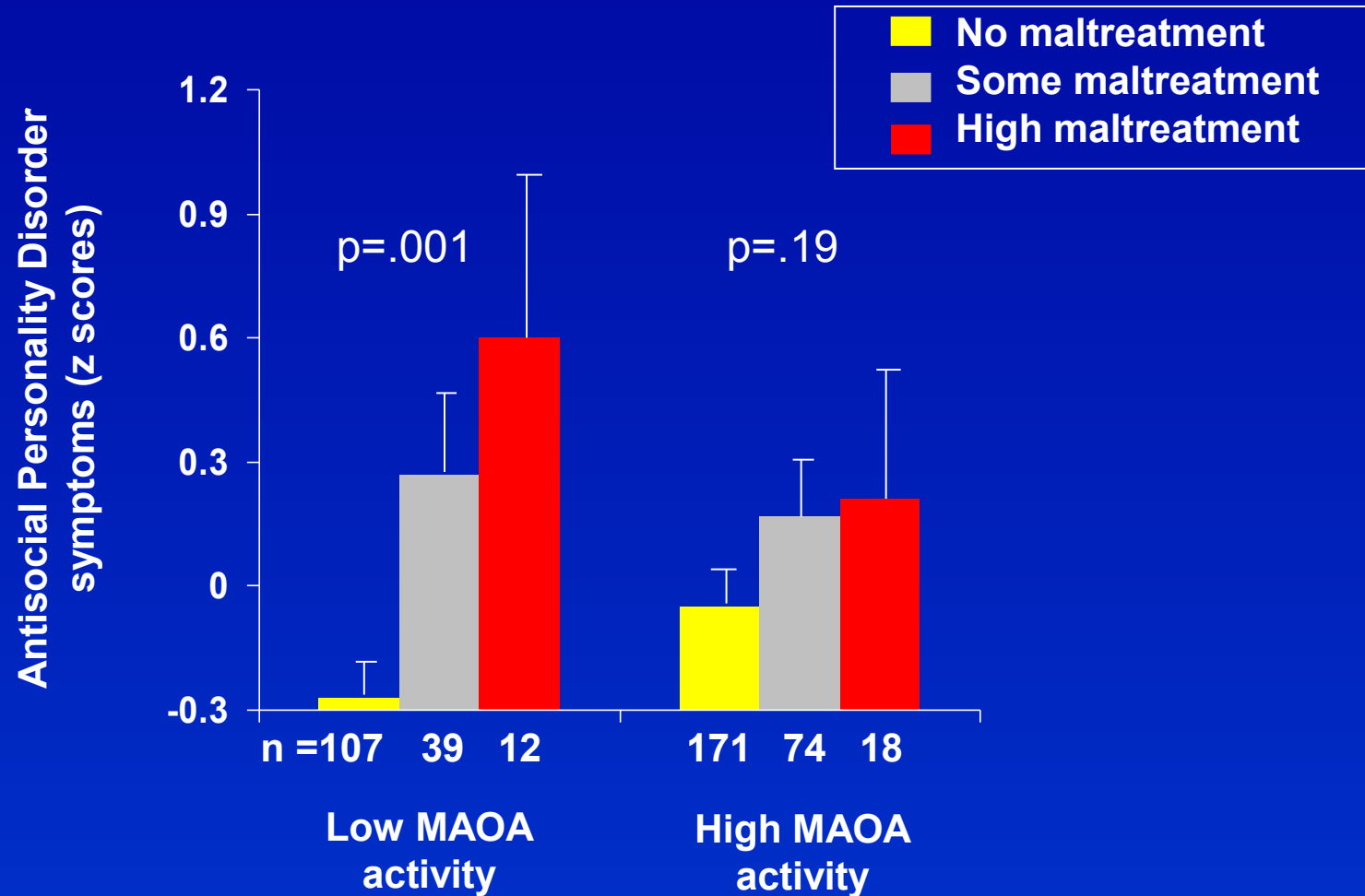




# **Antisocial personality disorder symptoms (informant report at age 26 years)**

- **Has problems controlling anger**
- **Blames others for own problems**
- **Does not show guilt after doing something bad**
- **Impulsive, rushes into things without thinking**
- **Good citizen (reversed)**
- **Does things against the law**
- **Gets into fights**

# Antisocial Personality Disorder symptoms (informant reports) by MAOA gene activity and childhood maltreatment

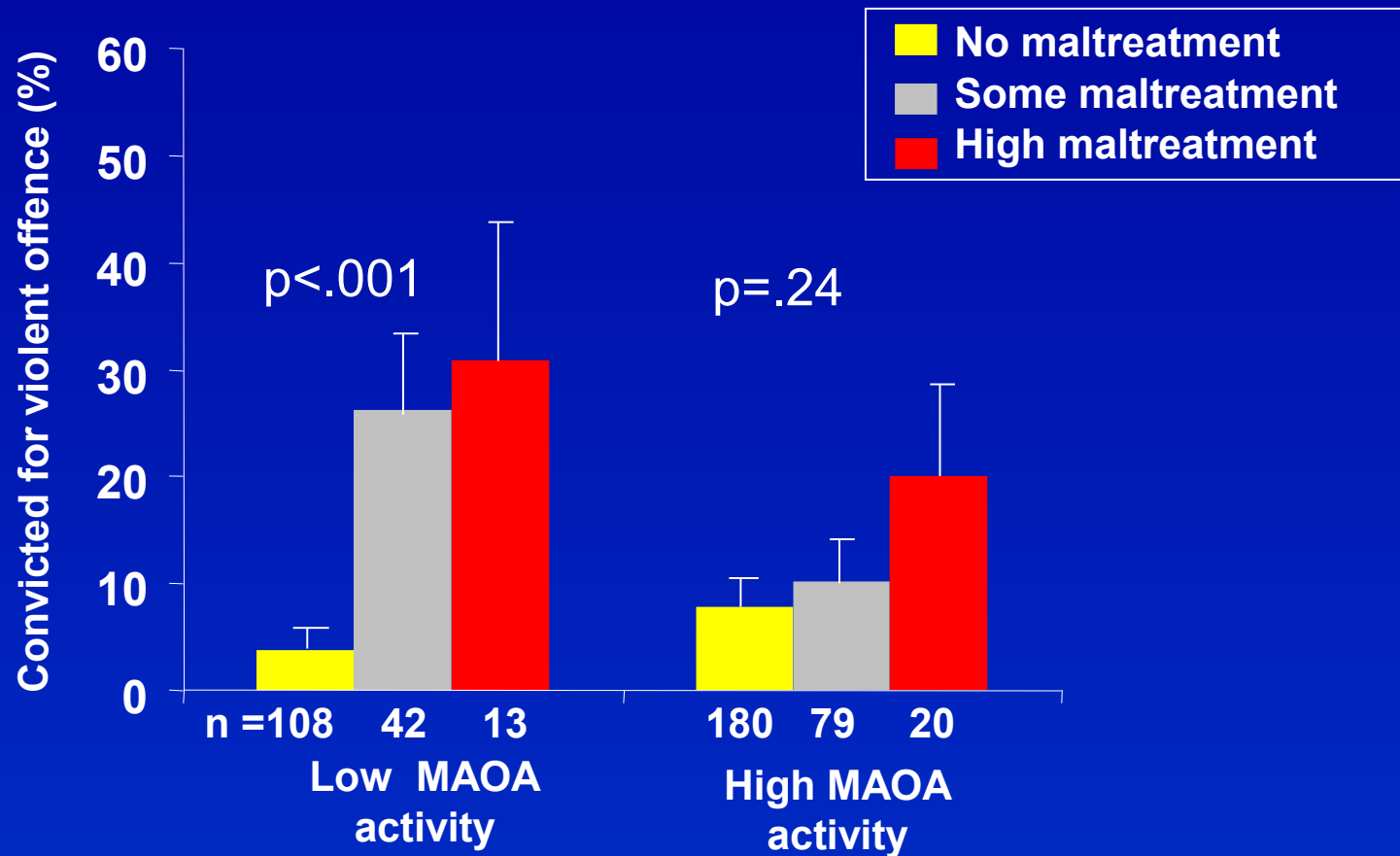


# Conviction of a violent crime by age 26

- **Court records searched for all Study members**
- **25% of Study males received 987 criminal convictions**
- **11% of Study males received 172 convictions for violent crimes**

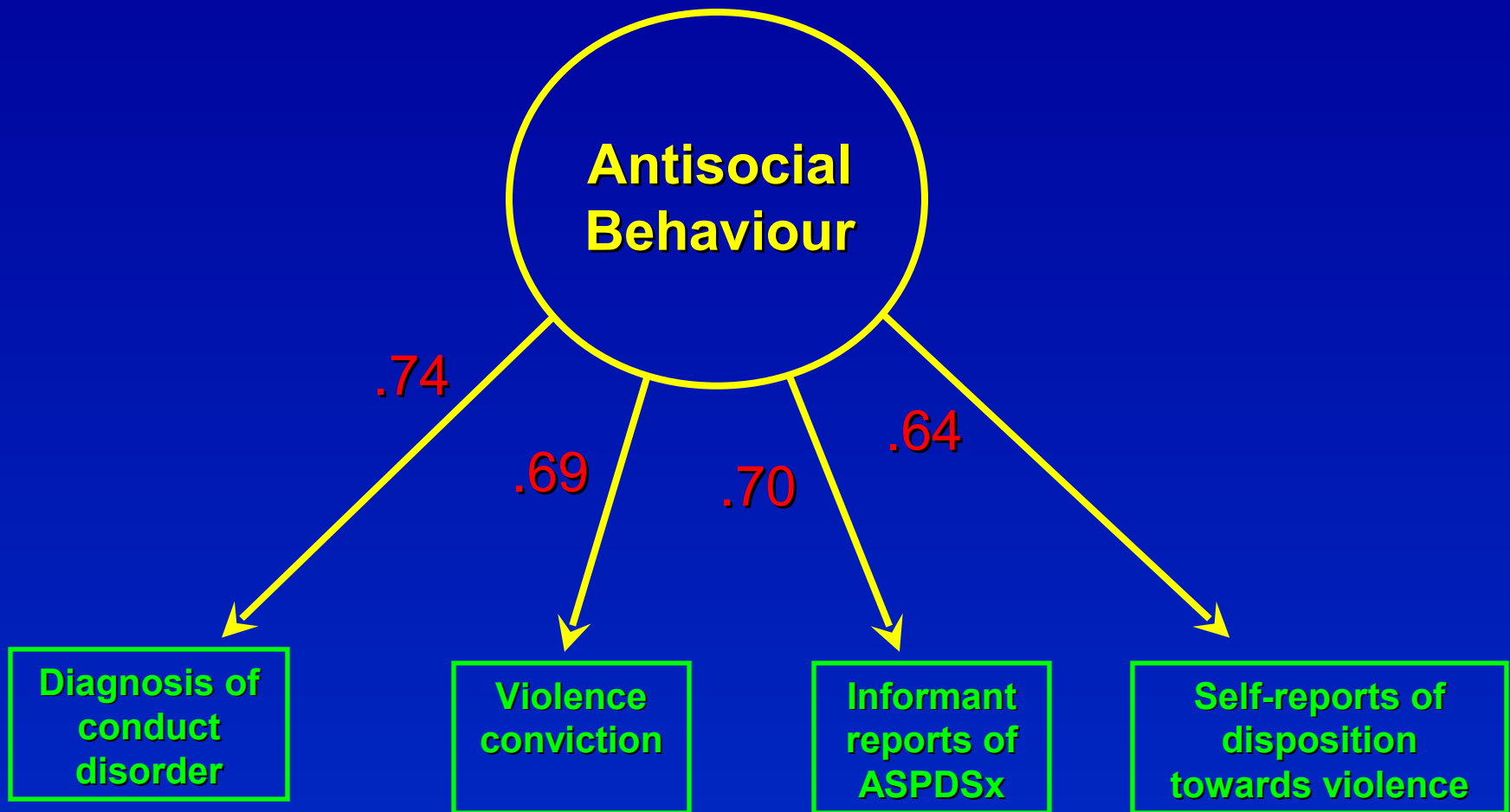
- **Common assault**
- **Assault with intent to injure**
- **Manslaughter**
- **Rape**
- **Indecent assault on female**
- **Aggravated cruelty to animal**

# Violent convictions to age 26 by MAOA gene activity and childhood maltreatment



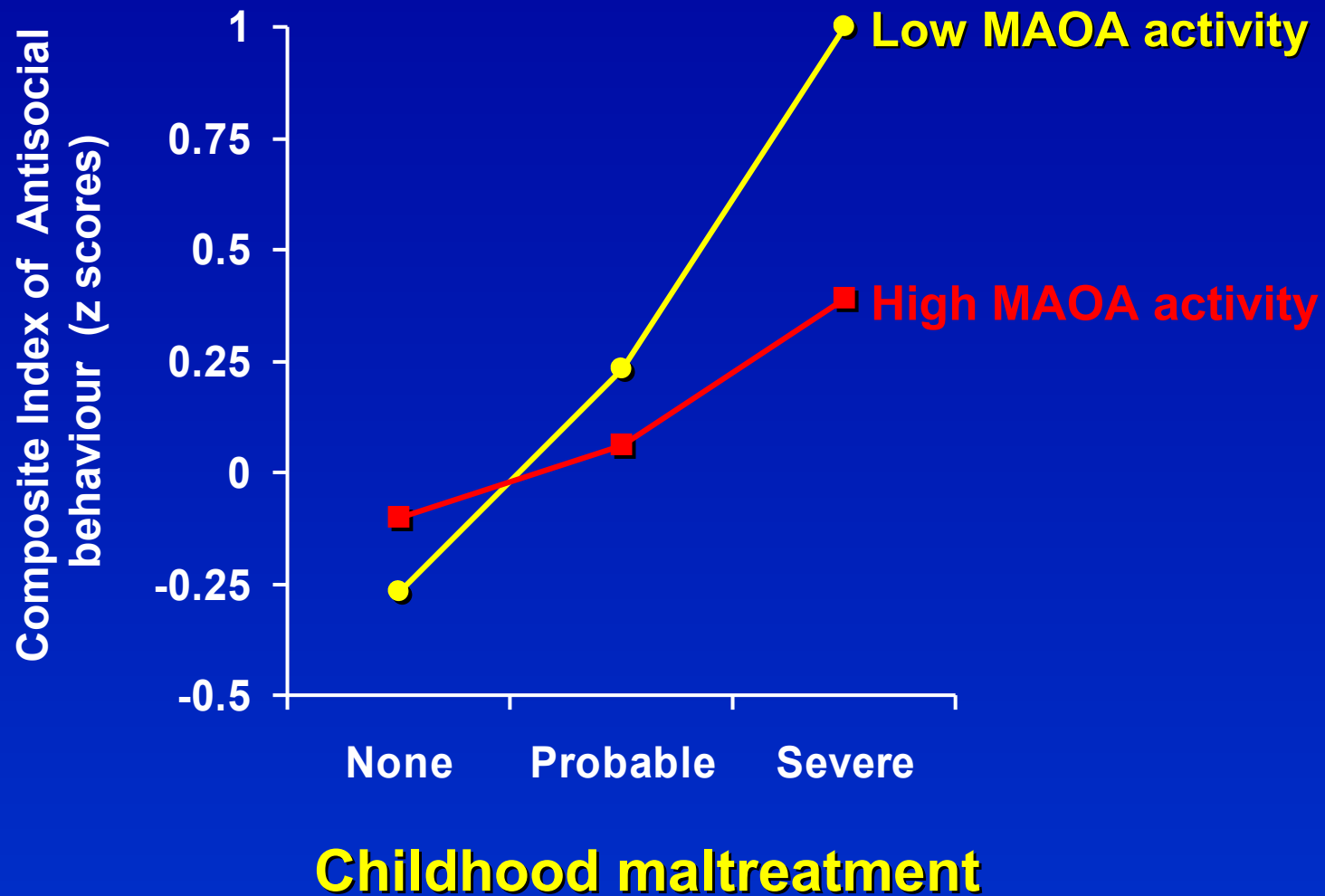
**Step 3**

# Multiple Indicator Model of Antisocial Behaviour



$\chi^2(2) = 2.56, p=.28, CFI=.99, RMSEA=.02$

# The Interaction between MAOA and Childhood Maltreatment



# Research implications

- Genes are assumed to create vulnerability to disease, but from an evolutionary perspective they are equally likely to protect against environmental insult.
- Bivariate association (main effect) studies are not the way forward. Two-way, three-way, four-way... interactions are the future.

# Intervention implications

- Pharmacological and genetic treatments remain a long way off. Old fashioned fixes are supported.
- Population screening inappropriate.
- Impact upon (↑or↓) a person's sense of responsibility for their own wellbeing and behaviour.



# Legal implications

- Courts – Is there a case for mitigation in sentencing, i.e. lighter versus harsher sentencing linked to genes.
- Discrimination by insurance companies or employers? Require legislation to prevent this.

# Social implications

- Are designer babies inevitable?
- Pre-implantation and pre-natal diagnosis for positive and/or negative attributes.

# Moral/ethical implications

- **Reducing versus increasing stigmatisation.**
- **Social inequalities are not justified by the Bell Curve.**

**“There is a special obligation to guard against allowing research aimed at increasing knowledge and reducing suffering from being hijacked by the desire to justify the status quo.” (Parens, 2004)**

# Acknowledgements

- This on-going research would not have been possible without the co-operation and commitment of the Study members, their families and friends over a long period of time.
- Core funding for the Dunedin Multidisciplinary Health and Development Research Unit comes from the Health Research Council of New Zealand.

For copies of research articles referred to in this presentation or other information on the Study, contact Michelle McCann:

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[http://www.otago.ac.nz/dunedin study](http://www.otago.ac.nz/dunedin_study)





