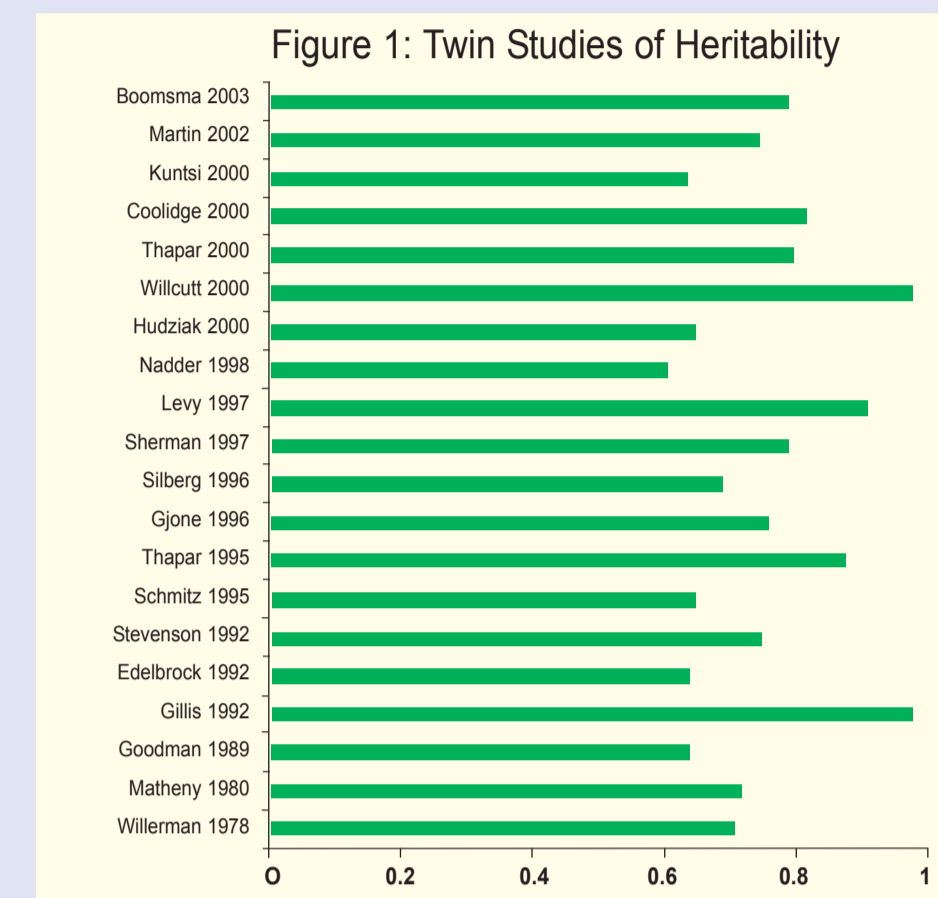


Attention Deficit Hyperactivity Disorder (DSM-IV Combined Subtype) Shows Familial Association with Continuous Measures of ADHD Symptom Scores in Co-Siblings

Wai Chan and IMAGE Consortium* MRC SGDP, Institute of Psychiatry, London, UK

Background:

- Twin studies have estimated the heritability of ADHD to be around 0.76, showing that genetic factors play a substantial role in the aetiology of ADHD (see Figure 1).
- Two recent linkage scans using an affected sibling pair strategy show only one region of partial overlap on chromosome 5. This reflects the low power of traditional linkage analysis to detect multiple genetic variation, while each conferring relatively small risks to the complex genetic disorder.



Study Objective:

- Here we describe a quantitative trait locus (QTL) linkage study, the International Multi-center ADHD Gene project (IMAGE), which aims to take advantage of QTL methods to potentially increase power over more traditional study designs.



- The QTL strategy in IMAGE hypothesizes that the correlation (familial association) observed in DZ twins from the community twin studies are analogous to that of the siblings and probands of the IMAGE sample, which has been selected from a clinic population with the diagnosis of DSM-IV 'Combined' subtype of ADHD.
- A requirement for QTL linkage analysis using the IMAGE sample is that this assumption is valid. Although this may be inferred from previous twin studies this has not been hitherto explicitly demonstrated.
- We therefore (1) review and report the findings of the 'siblings familiarity' or 'DZ correlation' in previous twin studies; and (2) utilize a modified method of DeFries-Fulker analysis to estimate the 'siblings familiarity' of the IMAGE sample.

Sample and methods:

- The International Multi-center ADHD Gene project (IMAGE) is an international collaborative study involving: Belgium, Germany, Holland, Ireland, Israel Spain, Switzerland, UK, USA. The probands have been recruited through the specialist ADHD clinics, with a diagnosis of DSM-IV 'Combined' sub-type of ADHD.
- All children (probands and siblings) are: between age 6 to 18, of IQ=70 or above, of European descent, and with access to one or both biological parents for DNA collection. Exclusion criteria (apply to both probands and siblings) include autism, epilepsy, general learning difficulties, brain, medical and genetic disorders that mimic ADHD.
- Probands are diagnosed by structured parent interview (Parental Account of Childhood Symptoms, PACS), with Strengths and Difficulties Questionnaires (SDQ) and Conners' rating scale (parent and teacher).
- Dimensional scores of ADHD symptoms in the siblings are derived from Strengths and Difficulties Questionnaires (SDQ) and Conners' rating scale (parent and teacher).
- We carried PubMed search for past publications on twin studies. In addition, we estimated the correlation (r) between trait liability and the clinical disorder; (r = [sibling mean - population mean]/[proband mean] - [population mean]), a method modified from traditional DeFries-Fulker twin analysis.

Results:

(1) Our review of published DZ twin correlations from twin studies shows a wide range of familial association, from -0.05 to 0.49 (see Figure 2 and 3). It appears that the variabilities are dependent on both the raters and the behavioural rating measures used. Figure 2 illustrates those using teacher-rated measures.

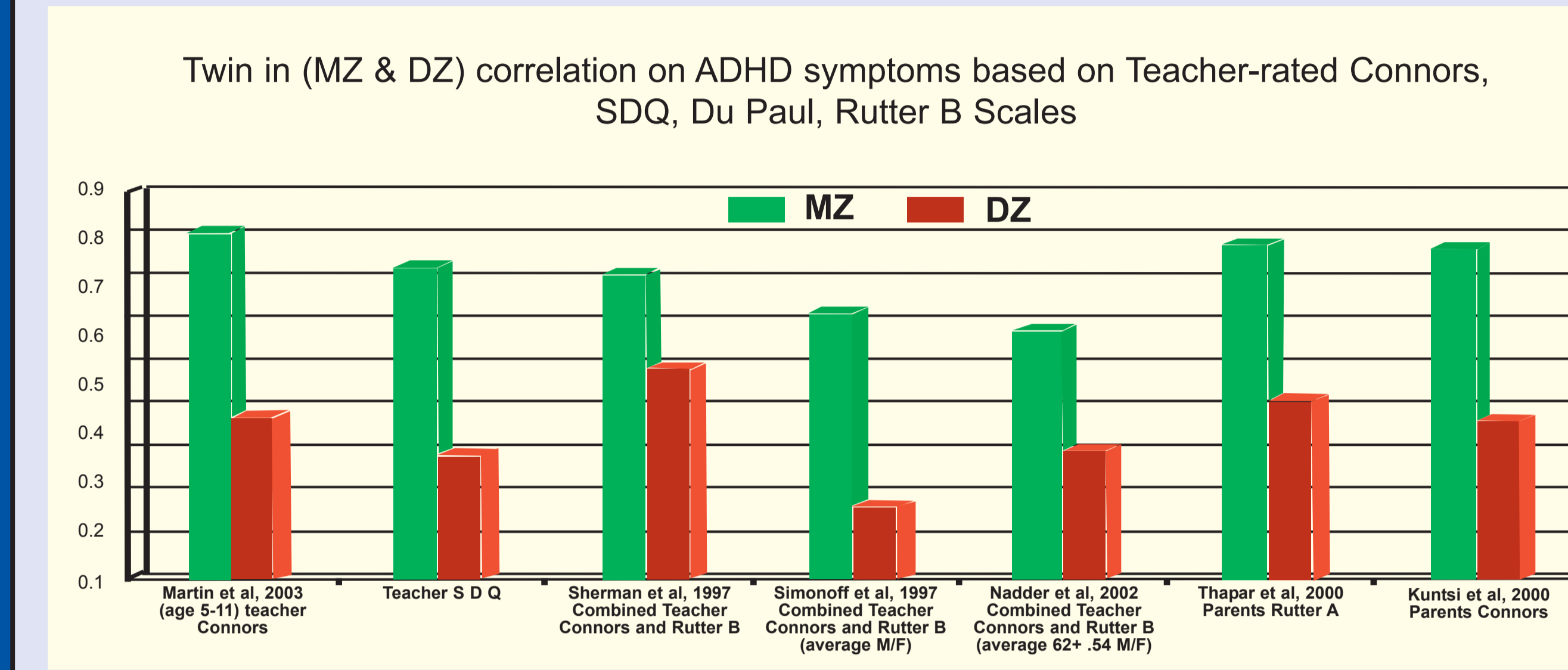
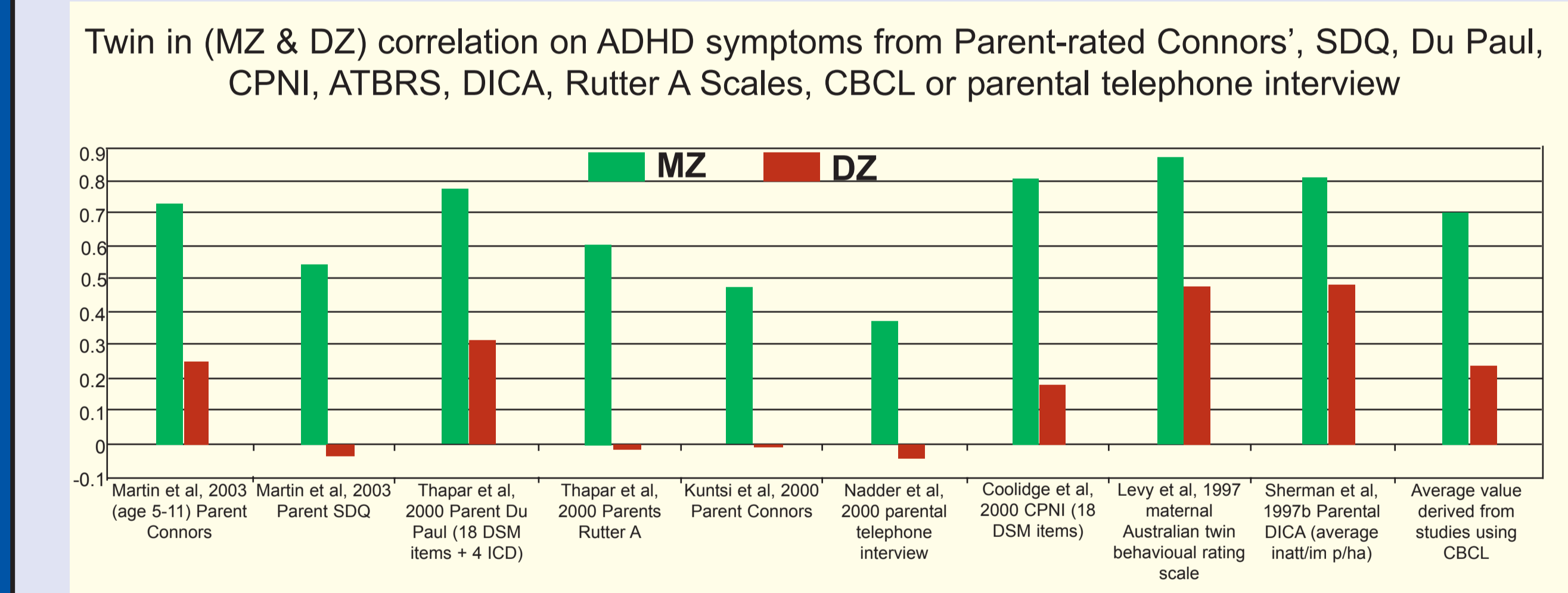


Figure 3 includes those findings using parent-rated measures. The DZ correlation of teacher-rated measures has a narrower range: 0.17 to 0.42 (see Figure 2); while that of parent-rated measures range from -0.05 to 0.49 (see Figure 3).



(2) We analyzed the first set of families for whom we have completed ascertainment (n=129). The following table summarizes our findings on siblings correlations (familial associations) of the IMAGE sample by using modified DeFries-Fulker Analysis.

	Sibling Correlations	Confidence Intervals	p=
Teacher Connors'	30.30%	20.87 - 39.68%	0.000
Teacher SDQ	34.11%	23.22% - 45.01%	0.000
Parent Connors'	19.83%	11.36 - 28.16%	0.000
Parent SDQ	-0.86%	-12.76% - 10.97%	0.88

Discussion:

(1) There is a wide range of DZ sibling correlation: from -0.05 to 0.49.

Despite this, certain patterns emerge:

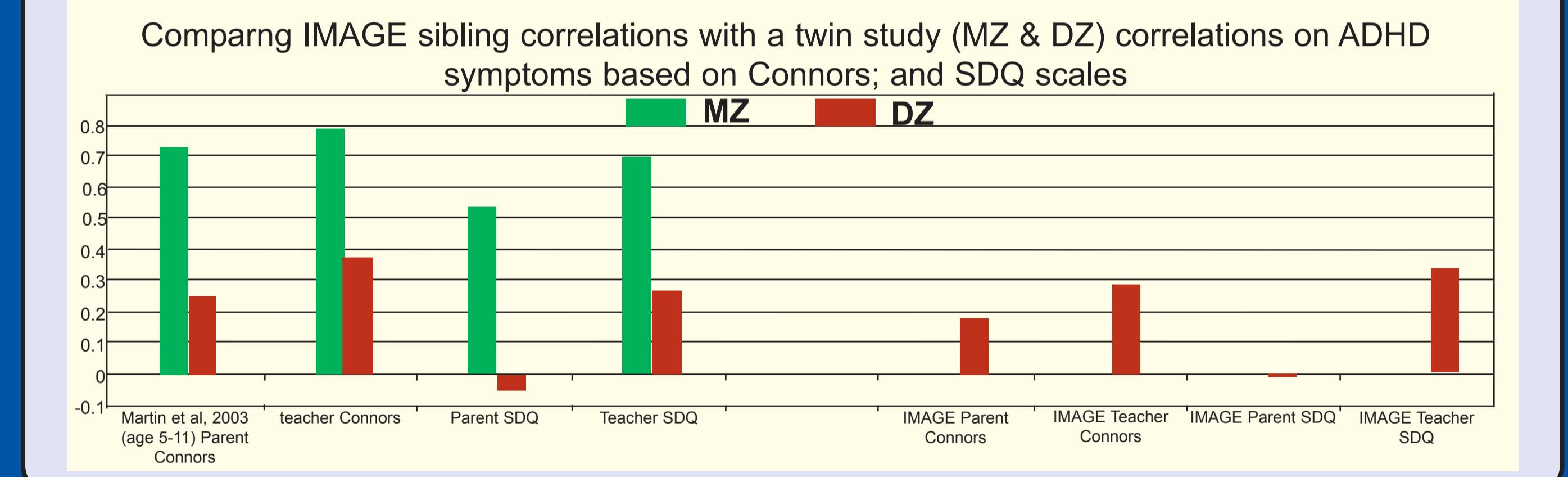
- there is generally a narrower range of sibling correlation derived from measures rated by teachers, i.e. 0.17 to 0.42 (see Figure 2);
- there is greater variability amongst parent-rated questionnaires, i.e. from -0.05 to 0.49 (see Figure 3);
- amongst the parental measures, those containing DSM-IV 18-items yield higher sibling correlation, than those with fewer items, such as SDQ and Rutter A.

Near zero DZ sibling correlations are incompatible genetic aetiology of a disorder. It is likely to be attributable to the either contrast effect in observer bias or sibling interactions.

Teacher measures show higher correlations and suggest that teacher measures may be more informative for QTL linkage.

(2) The 'siblings familiarity' or sibling correlations observed in the IMAGE study are comparable to published sibling correlations in DZ twin pairs (Martin et al, 2003) using the same measures: SCQ and Connors' (parent and teacher) (see Figure 4).

- Parent Connors' was 0.25 (or 25%), which is within the 95% CI of 11.36% - 28.16% of IMAGE data;
- for Teacher Connors' was 0.38 (or 38%), which is within the 95% CI of 20.87% - 39.68% of the IMAGE data;
- Parent SDQ was -0.04 (-4%), which is within the 95% CI of -12.76% - 10.97% of the IMAGE data;
- Teacher SDQ was 0.29 (29%) which is within the 95% CI of 23.22% - 45.01% of the IMAGE data.



Conclusion:

The findings demonstrate that the familial relationships between sibling ADHD symptoms scores and combined type diagnosis in probands (twin studies using group heritability suggest this is predominantly due to shared genes), are analogous to those of DZ twin correlations.

The IMAGE sample ascertained via probands recruited from specialist ADHD clinics can be used for QTL analysis.

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*IMAGE Consortium: Senior investigator: Philip Asherson, Tobias Banaschewski, Jan Buitelaar, Wai Chan, Jacques Eisenberg, Richard Ebstein, Steve Faraone, Michael Gill, Peter McGuffin, Iris Manor, Ana Miranda, Fernando Mulas, Bob Oades, Robert Plomin, Herbert Roeyers, Aribert Rothenberger, Pak Sham, H. C. Steinhausen, Joseph Sergeant, Edmund Sonuga-Barke, Etsu Taylor, Margaret Thompson. Contributors: P. Andreou, Renée Arnold, Fris Boer, Cathelijn Buschgens, Louise Butler, Hanna Christiansen, Liat Feldman, Karin Fleischman, Ellen Filiers, R. Howe-Fortbes, Abigail Ggolofero, Alexander Heise, Gabriela Isabel, Jo Knight, Jonna Kuntsi, Isabelle Lubetzki, Rafaela Marco, She'era Medad, Ruud Minderaa, Ueli Müller, Aisling Mulligan, Karina Rabin, Nanda Rommelse, Vahesha Sethna, Jean Sorohan, Henrik Uebel.

†This work was funded by NIMH Grant R01MH062873 to S. Faraone.