

# Children conceived using ICSI do not have an increased risk of delayed mental development at 5 years of age\*

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**BACKGROUND:** Concerns about possible adverse outcomes for children conceived using ICSI were highlighted in 1998 when 1-year-old ICSI children were found to be at increased risk (relative risk = 9.2) of delayed mental development compared with children conceived naturally or using IVF. As the findings were biologically plausible, it was considered important to reassess child development when a more accurate measure of long-term cognitive ability could be obtained. **METHODS:** The mental development of 97 ICSI, 80 IVF and 110 naturally conceived (NC) children at 5 years of age was assessed using intelligence quotients (IQ) obtained from the Wechsler Preschool and Primary Scales of Intelligence. **RESULTS:** The mean full-scale IQ was  $110 \pm 18$  for ICSI,  $111 \pm 13$  for IVF and  $114 \pm 13$  for NC children ( $P = 0.21$ , non-significant). ICSI children were not at increased risk for delayed (full-scale IQ <85) cognitive development (ICSI 5.2%, IVF 2.5%, NC 0.9%;  $P = 0.18$ , non-significant). The only significant independent predictor of below-average full-scale IQ on multivariate analysis was lower maternal education level. **CONCLUSIONS:** These findings suggest that the genetic influence of parental cognitive ability is more important than the mode of conception in determining the long-term intellectual ability of children conceived using ICSI.

*Key words:* child development/conception mode/ICSI/intelligence quotient/IVF

## Introduction

It is now 10 years since the first report (Palermo *et al.*, 1992) of successful pregnancies achieved using ICSI. This technique was initially introduced for the treatment of severe male factor infertility, but it has become more widely used for the treatment of other forms of infertility. As a consequence, more than 50% of all children conceived in Australia using assisted reproduction techniques (ART) now result from the use of ICSI (Hurst and Lancaster, 2001).

Since ICSI was first introduced, concerns have been raised about possible adverse long-term health, psychosocial and developmental outcomes for the children conceived using this technique (De Braekeleer and Dao, 1991; Miesel *et al.*, 1993; Cummins and Jequier, 1995; Feichtinger *et al.*, 1995; Latham *et al.*, 1995; de Kretser, 1997; In't Velt *et al.*, 1997; Pryor *et al.*, 1997; Dowsing *et al.*, 1999; Hewitson *et al.*, 1999; Perry *et al.*, 1999; Vogt, 1999; Chan *et al.*, 2000). The issues raised by those expressing concern are biologically plausible, based on

the differences between this technique and both routine IVF and natural conception.

The results of the first controlled study of early mental development of ICSI children were published in 1998 (Bowen *et al.*, 1998). In this study, the group of children conceived using ICSI was found to have a significantly lower mean Bayley Mental Development Index (MDI) compared with both IVF and naturally conceived controls ( $96 \pm 11$  versus  $102 \pm 9$  and  $103 \pm 8$  respectively). Furthermore, ICSI children had a significantly increased risk of delayed mental development at 1 year compared with the control groups. The adjusted relative risk derived from the original study data (but not reported in the above-mentioned publication) for ICSI children compared with the two control groups was 9.2 (95% confidence interval = 2.7, 31.0). As this finding was biologically plausible, and potentially clinically significant, it was considered essential to follow these children further until they had reached an age when a more definitive assessment of cognitive development could be performed.

The purpose of the present study was thus to determine the developmental outcomes for children conceived using ICSI, compared with groups conceived naturally or using IVF, at 5 years of age. Only singleton or twin children were included.

\*The results of this study were presented in part at the 18th Annual Meeting of the European Society for Human Reproduction and Embryology in July 2002 (presentation received award for the best presentation by an established clinician) and the 21st Annual Meeting of the Fertility Society of Australia in October 2002 (presentation received award for the best clinical presentation).

## Materials and methods

Details of the enrolment of ICSI, IVF and naturally conceived control children have previously been published in a report on 1-year outcomes for this cohort (Bowen *et al.*, 1998). The original cohort consisted of 89 ICSI, 84 IVF and 80 naturally conceived children, and only included singleton or twin children. Attempts were made to contact all of those assessed at 1 year for further assessment at 5 years. Sixteen of the original 89 ICSI children were unavailable for assessment at 5 years (one child declined, six children were known to have moved overseas, three were known to have moved interstate, and six were uncontactable at their last known address). Four of the original 84 IVF children were unavailable for assessment at 5 years (one child declined, and three children were uncontactable at their last known address). Twenty of the original 80 naturally conceived children were unavailable for assessment at 5 years (all were uncontactable at their last known address). Additional ICSI and naturally conceived children were enrolled to ensure adequate power for the study to confirm the 1-year findings. The additional ICSI children enrolled at 5 years of age were the next singleton or twin children conceived in the same ART programme after those enrolled in the original study. Of the potential ICSI children available for study, there were only four who were not successfully enrolled—two because of parental refusal to participate, and two who were unable to be contacted due to change of address. The additional naturally conceived children were enrolled from preschools in communities that matched the demographics of the ICSI cohort. The preschools chosen were run by either the state or a church, and included children of diverse backgrounds. The principals of the preschools were requested to send out letters inviting participation in the study to the parents of first-born singleton children. There was a 12% response rate from parents contacted. One of the investigators then made telephone contact with those parents who indicated interest in the study to confirm eligibility for the study, and obtain demographic data for the family. Children were chosen from the resulting sample by one of the investigators in order to obtain a group with demographics that matched the ICSI cohort as closely as possible with respect to parental education and primary language spoken at home.

The study numbers provided 99% power to detect the same difference of six points in the mean full-scale IQ value at 5 years that was found for mean MDI values in the cohort at 1 year of age. The study numbers also provided 83% power to detect the actual difference of four points that we found at 5 years of age. A clinically significant difference in terms of educational needs was 7.5 points (half a standard deviation for the test reference), and these study numbers provided 100% power to detect such a difference. The study numbers also provided 97% power to detect the difference in percentages with delayed cognitive development at 5 years that was detected at 1 year (17% for ICSI versus 1.5% for the combined natural conception and IVF control groups). There was 80% power to detect a difference of 10 versus 1.5%, but only 30% power to detect the actual difference detected in the present study (5 versus 1.5%).

This study was approved by the Human Research Ethics Committee of Royal North Shore Hospital. Informed, written consent for participation was obtained from the parents of all children.

Assessment of development at 1 year of age was performed using the Bayley Scales of Infant Development (2nd edition) (BSID-II) (Bayley, 1993). The test consists of two major scales: mental, and psychomotor. The mental scale assesses memory, problem-solving and language skills, and the psychomotor scale assesses control of the fine and gross muscle groups. The child's performance on these scales is used to determine MDI and a psychomotor development index (PDI). Assessment of mental development at 5 years was performed

using the Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R) (Wechsler, 1989). This test consists of two major scales: verbal, and performance. The verbal scale includes vocabulary, comprehension and arithmetic skills. The performance scale includes visuo-spatial skills, copying designs and block patterns, and attention to visual detail. The child's performance on these scales is used to determine a verbal intelligence quotient (IQ) and a performance IQ. Additionally, a full-scale IQ is determined using a composite of both the verbal and performance IQ values. All scales of both the BSID-II and WPPSI-R have a mean of 100 and standard deviation of 15. Scores were categorized as accelerated when  $>1$  SD above the mean ( $>115$ ), normal when within 1 SD of the mean (85–115), and delayed when  $>1$  SD below the mean ( $<85$ ). The investigators testing the children were blinded to the 1-year results of those who were being re-assessed, and also to the study group.

Statistical analysis was performed using SPSS for Windows (version 10), and included chi-square and logistic regression for categorical variables, and analysis of variance for continuous variables. Appropriate demographic variables (prematurity, parental education and occupation, primary language spoken at home) were included as covariates in all analyses. A  $P$ -value  $\leq 0.05$  was considered statistically significant.

## Results

A total of 213 of the original cohort of 253 (84%) was re-assessed at 5 years of age, including 82% of the original ICSI group, 95% of the IVF group, and 75% of the naturally conceived controls. The demographic characteristics of those who were lost to follow-up between 1 and 5 years were not different from those who were re-assessed at 5 years. The mean ( $\pm$  SD) Bayley MDI at 1 year for children lost to follow-up was  $100 \pm 9.7$  compared with  $99.6 \pm 9.0$  for those reassessed at 5 years ( $P = 0.769$ , non-significant). Seventeen of the 19 children with a delayed ( $<85$ ) MDI at 1 year were re-assessed at 5 years.

An additional 24 ICSI and 50 naturally conceived children were enrolled for the 5-year assessments, so that a total of 97 ICSI and 110 naturally conceived children were assessed at 5 years. The children were seen at a mean age of 60.8 months for their 5-year assessments.

Demographic details for the children seen at 5 years are shown in Table I. There were no group differences with respect to premature birth. The percentage of twins in the natural conception group was significantly lower than for the IVF group ( $P = 0.001$ ) but not the ICSI group ( $P = 0.06$ , non-significant). The majority of parents in all groups had received tertiary education, and worked in either a skilled or professional occupation. ICSI mothers were less likely to have completed tertiary education than natural-conception mothers ( $P = 0.019$ ), but not IVF mothers ( $P = 0.077$ , non-significant). ICSI fathers were less likely to have a skilled or professional occupation than IVF fathers ( $P = 0.016$ ), but not natural-conception fathers ( $P = 0.061$ , non-significant). The percentage of families primarily speaking a language other than English was similar for both ICSI and IVF families, but significantly lower for the natural-conception group ( $P = 0.003$  versus ICSI and  $P = 0.031$  versus IVF). There were no group differences with respect to a family history of developmental problems.

The additional naturally conceived controls who were enrolled at 5 years were well-matched to the ICSI group with

**Table I.** Demographics of children assessed at 5 years\*

Variable	ICSI ( <i>n</i> = 97)	IVF ( <i>n</i> = 80)	Natural conception ( <i>n</i> = 110)	<i>P</i>
Born preterm	17.5	12.5	12.7	0.576 (NS)
Twins	22.7	32.5	12.7	0.005
Mother with diploma or degree	59.8	72.5	75.5	0.039
Father with diploma or degree	73.2	73.8	71.8	0.952(NS)
Mother with skilled occupation	92.9	88.8	88.2	0.506(NS)
Father with skilled occupation	84.5	96.2	92.7	0.018
Primary language not English	25.8	21.3	10.0	0.011
Family history of developmental problems	22.7	27.5	18.2	0.311(NS)

\*Values are percentage of children in group. Data were analysed using the chi-square test. *P*-values reported in Table I are from a 3×2 table including all three groups. Where there were group differences, the differences between individual groups are reported in the text.

NS = not significant.

**Table II.** Performance, verbal and full-scale IQ values\* for children assessed at 5 years

Variable	ICSI ( <i>n</i> = 97)	IVF ( <i>n</i> = 80)	Natural conception ( <i>n</i> = 110)	<i>P</i>
Performance IQ	112 ± 16 (79 <sup>a</sup> –155)	112 ± 13 (81–141)	114 ± 13 (79–146)	0.668 (NS)
Verbal IQ	107 ± 15 (78 <sup>a</sup> –148)	107 ± 12 (67–148)	111 ± 14 (77–148)	0.103 (NS)
Full-scale IQ	110 ± 18 (43 <sup>a</sup> –156)	111 ± 13 (77–149)	114 ± 13 (77–147)	0.209 (NS)

\*Values are mean ± SD (range).

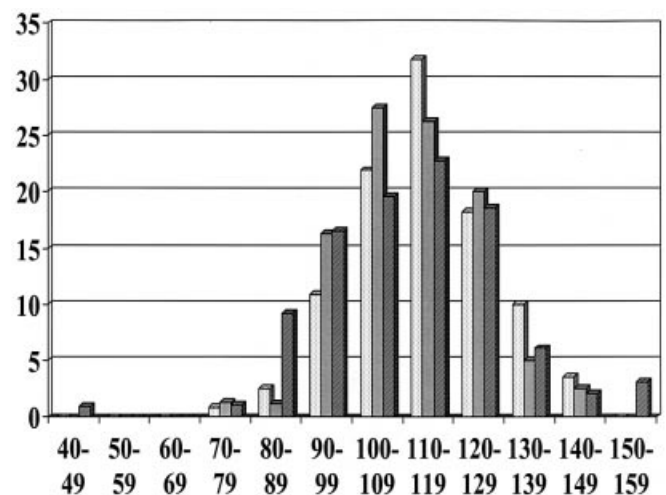
<sup>a</sup>One child unable to be tested using the WPPSI-R; hence no value was obtained for Performance or Verbal IQ; Full-scale IQ was determined using Griffiths Mental Development Scales.

NS = not significant.

respect to the important demographic factors of parental education and primary language spoken at home. Some 33 of 50 (66%) natural-conception mothers had a degree or diploma, compared with 58 of 97 (59.8%) of the ICSI mothers ( $P = 0.463$ , non-significant). Thirty-three of 50 (66%) natural-conception fathers had a degree or diploma compared with 71 of 97 (73.2%) of the ICSI fathers ( $P = 0.363$ , non-significant). The primary language spoken at home was not English for 10 of 50 (20%) natural-conception families compared with 25 of 97 (25.8%) of ICSI families ( $P = 0.475$  non-significant).

The results for developmental assessments at 5 years of age using the WPPSI-R are shown in Table II. Mean values for all three IQ scales were in the normal range for all three groups, and there was no between-group difference for any of the scales. There was one child in the ICSI group who was profoundly delayed and who could not be tested using the WPPSI-R; hence, the performance or verbal IQ scores for this individual could not be reported. However, a full-scale IQ was determined using an alternative measure and this value is included in the analysis.

The distribution of full-scale IQ scores for children in each group is shown in Figure 1. Delayed scores (IQ <85) were obtained for 5.2% of ICSI, 2.5% of IVF and 0.9% of natural-conception children; normal scores were obtained for 58.7% of ICSI, 61.2% of IVF and 56.4% of natural-conception children; and accelerated scores (IQ >115) were obtained for 36.1% of ICSI, 36.3% of IVF and 42.7% of natural-conception children. None of the differences between groups in any of the three



**Figure 1.** The distribution of full-scale IQ scores for ICSI, IVF and naturally conceived children. Column heights indicate the number of children in each group with an IQ value within each 10-point range of IQ values. Striped columns = ICSI children; solid grey columns = IVF children; dotted columns = naturally conceived children.

categories was significant. In particular, there was no significant increase in the likelihood of a delayed full-scale IQ score among the ICSI group compared with the other groups, either individually or in combination (Odds ratio for ICSI versus both control groups combined = 3.39; 95% CI = 0.79, 14.49;  $P = 0.125$ , non-significant). Children in the ICSI group were

**Table III.** Significant predictors of below-average scores on Performance, Verbal and Full-scale IQ on logistic regression analysis

Variable	Predictor	Odds ratio	95% CI	P
Performance IQ	Mother without tertiary education	6.13	1.86, 20.00	0.003
Verbal IQ	Primary language at home not English	3.84	1.56, 9.45	0.003
	Father without tertiary education	3.00	1.26, 7.19	0.013
Full-scale IQ	Mother without tertiary education	4.00	1.41, 11.36	0.009

CI = confidence interval.

also not less likely to have an accelerated score on the full-scale IQ (Odds ratio for ICSI versus both control groups combined = 0.85; 95% CI = 0.51, 1.40;  $P = 0.608$ , non-significant).

For the children who were assessed at both 1 and 5 years, the mean full-scale IQ was significantly higher than the mean Bayley MDI ( $111.6 \pm 14.1$  versus  $100.0 \pm 9.7$ ; mean difference = +11.6; 95% CI = 9.8, 13.5;  $P < 0.001$ ). The magnitude of the increase in value was similar for all three groups. The percentage of children with a delayed full-scale IQ at 5 years was significantly lower than the percentage with a delayed Bayley MDI at 1 year for the ICSI group (5.2 versus 16.9%; Odds ratio = 0.31; 95% CI = 0.12, 0.81;  $P = 0.019$ ), but not significantly different for either the IVF (2.5 versus 3.5%; Odds ratio = 0.72; 95% CI = 0.12, 4.18;  $P = 0.53$ , non-significant) or naturally conceived (0.9 versus 1.3%; Odds ratio = 0.73; 95% CI = 0.05, 11.45;  $P = 0.67$ , non-significant) control groups.

Children in the ICSI group who had a delayed Bayley MDI had a significantly lower mean full-scale IQ than those who had a normal MDI ( $97 \pm 16$  versus  $112 \pm 15$ ;  $P = 0.002$ ), and were at significantly increased risk of having a delayed full-scale IQ (Odds ratio = 16.8; 95% CI = 1.6, 178.1;  $P = 0.019$ ). Nevertheless, only 23.1% of ICSI children who had a delayed MDI at 1 year also had a delayed full-scale IQ at 5 years.

For the ICSI group, mean full-scale IQ was not related to the nature of the defect in paternal sperm (i.e. abnormal morphology, motility or numbers). Similarly, the mean full-scale IQ of the children whose father had a triple sperm defect was not significantly different from that of children whose fathers had normal sperm ( $110 \pm 16$  versus  $110 \pm 17$ ;  $P = 0.9$ , non-significant).

Multivariate logistic regression analysis was performed (including the demographic covariates indicated in Materials and methods) to determine which variables independently predicted performance below the average range (90–110 on the test reference values) on each of the IQ scales. The significant independent predictors of below-average performance on each of the scales are shown in Table III. ICSI was not a significant independent predictor of low values for any of the three IQ scores. Lower scores on both performance and full-scale IQ were related to lower levels of maternal education. The strongest predictor of lower scores on the verbal IQ was primary language spoken at home not being English, while the other independent predictor was a lower level of paternal education.

## Discussion

The results of the present study provide some reassurance for the parents of children conceived using ICSI with respect to their longer-term intellectual development.

The few previous controlled studies of mental development of ICSI children have provided conflicting results (Bowen *et al.*, 1998; Bonduelle *et al.*, 1998; Sutcliffe *et al.*, 1999). During the earlier stages of the present study, the mean Bayley MDI of the ICSI group was significantly lower than for both the IVF and naturally conceived control groups at 1 year of age. By contrast, others (Sutcliffe *et al.*, 1999) found the mean Griffiths Mental Development Scales General Quotient (GQ) of ICSI children not to be significantly different from that of naturally conceived controls, although the ICSI children did perform significantly less well on the eye-hand coordination sub-quotient. In another study (Bonduelle *et al.*, 1998), the results of which were published as a research letter, no statistical analyses were reported and the findings were expressed as differences between test and chronological ages rather than as mean MDI values. Nevertheless, singleton ICSI children did not appear to perform quite as well as singleton IVF controls.

These different findings may relate to differences in the way the studies were designed, including differences in the tests used to assess mental development and in the selection of controls. The Bayley Scales MDI was used by both the present authors and others (Bonduelle *et al.*, 1998) to assess mental development, albeit using two different editions of the test; a newer second edition and a Dutch revision of the original edition respectively, whereas others (Sutcliffe *et al.*, 1999) used a recent revision of the Griffiths Scales GQ. With respect to the Griffiths Scales GQ, it should be noted that there is a decrease in the range of maximum scores achievable when infants are aged over 20 months. As some of the infants studied (Sutcliffe *et al.*, 1999) were aged 21–22 months, it is possible that the group mean scores could have been dampened, thus tending to reduce the likelihood of finding significant between-group differences.

In the present study, two control groups were used—one conceived naturally and one conceived using IVF—whereas controls in other studies were conceived using IVF (Bonduelle *et al.*, 1998), or were all conceived naturally (Sutcliffe *et al.*, 1999). There were some demographic differences between the ICSI group and controls in both the present study and the latter investigation (Sutcliffe *et al.*, 1999), whereas no demographic data were provided by others (Bonduelle *et al.*, 1998). All

relevant demographic factors were included as covariates in the present analyses to allow for these differences, and ICSI remained a strong independent risk factor for delayed mental development at 1 year (relative risk = 9.2; 95% CI = 2.7, 31.0). It is not clear whether others (Sutcliffe *et al.*, 1999) allowed for the differences in maternal age, birth weight and gestational age in their analyses, and it is possible that such differences may have confounded the findings.

It is important to acknowledge that all of the above studies were performed on children during the first 2 years of their life, when tests of cognitive ability are not necessarily reliable predictors of long-term intelligence (McCall, 1979; Bayley, 1993; Bowen *et al.*, 1996). For this reason, it was considered essential to evaluate further the children at an age when a more reliable estimate of long-term intellectual ability could be obtained. This was considered important because if the difference in mental development observed at 1 year was maintained at school age, this would be clinically significant because of the increased likelihood of the ICSI children requiring additional educational assistance when compared with the IVF and naturally conceived children.

In the present study, the mean values for all three IQ scales for all three groups of children were within the normal range. In fact, in all cases the mean values were above the test reference mean of 100, perhaps reflecting the demographics of the present study population. Of particular importance was the observation that mean values for the ICSI group were not significantly different from either the IVF or naturally conceived control groups. This finding is similar to the findings in the study of others (Sutcliffe *et al.*, 1999). It is also reassuring that, among the present ICSI group, no association was found between the child's IQ and the presence or nature of any abnormality in the paternal sperm.

It is considered that the magnitude of the difference between the mean full-scale IQ scores of the ICSI group and the natural conception controls (4 points) is unlikely to be of any clinical significance. There are two reasons for this. The first is that the absolute mean was above the test reference test mean, so the group as a whole is likely to perform well within the normal range educationally. Second, a mean difference of at least one half of the test standard deviation of 15 would be required to indicate a likely group difference in need of educational assistance.

At 1 year of age, a higher percentage of the ICSI group was found to have delayed mental development compared with both the IVF and naturally conceived control groups, and ICSI was also found to be a significant independent predictor of delayed mental development. At 5 years the percentage of ICSI children with cognitive delay was significantly lower than was observed at 1 year (5 versus 17%), and ICSI was no longer an independent predictor of delayed development. However, the explanation for these differences may lie in differences between the types of test used to assess these abilities at the two ages. Assessments of mental/intellectual function, such as the Bayley Scales of Infant Development, which can be performed on infants within the first 2 years of life, provide a better assessment of perceptual motor skills than of true intellectual abilities (Slater, 1997), whereas tests such as the

WPPSI-R provide a robust assessment of long-term intelligence. It may be that there were some real differences with respect to early perceptual motor skills in the present ICSI cohort at 1 year that are not reflected in differences in actual intellectual ability at 5 years. The finding of demographic factors such as parental education to be the strongest predictors of below-average cognitive ability at 5 years of age are consistent with the results of other population-based studies of non-ART children (Kagan *et al.*, 1978; Bee *et al.*, 1982; Rickards *et al.*, 1988; Kramer *et al.*, 1995; Sommerfelt *et al.*, 1995).

With respect to differences in the percentage of children with delayed IQ scores, the present study was designed to confirm the relatively large difference that had been observed at 1 year of age in this cohort. The study also had 80% power to show statistical significance for a finding of 10% delay in the ICSI cohort, but only 30% power to show such a difference when the percentage with delay in the ICSI group was only 5%, as was found in the present study. It is acknowledged that if the sample size had been increased three-fold, then the difference that was observed at 5 years may have reached statistical significance. Nevertheless, it is doubtful that such a finding would be of clinical significance because the absolute risk for delay in the ICSI group was low at only 5%—a risk that most prospective parents might be expected to accept. On the other hand, if the 1-year findings (where the absolute risk was 17%) had been confirmed, this would be much more likely to be of concern to prospective parents.

It is acknowledged that there were some group differences in the method of recruitment of the children assessed at 5 years of age, which could potentially have influenced the results. All of the IVF children were from the original cohort were recruited prospectively during pregnancy, and the additional ICSI children were the next children conceived in the same ART programme after those in the original cohort. On the other hand, the additional naturally conceived controls were enrolled from preschools that were likely to match the ICSI cohort with respect to parental education and primary language spoken at home. This was done because of concerns expressed by some about group differences in the demographics among the present cohorts assessed at 1 year. Because only 12% of potentially eligible children from these preschools could be enrolled, it is possible that the motivation of the parents who agreed to their child's participation in the study may (potentially) have biased the results. Parents who had concerns about their child's educational performance may have agreed to participate in order to receive guidance about appropriate additional educational assistance, and this could have resulted in a lowering of the mean IQ for the natural conception group. Alternatively, parents who considered their child to be gifted may have sought confirmation of this through participation in the study, and this could have resulted in an increase in the mean IQ for the natural-conception group. A review of the individual results of these additional recruits did not reveal any consistent bias in either direction, and their mean results were similar to those of the originally recruited naturally conceived controls. Furthermore, the demographic backgrounds of these additional, naturally conceived controls were well-matched to

those of the ICSI children, and the mean IQ values for all three groups was also well within the normal range. Therefore, it was not considered that the different method used to recruit additional naturally conceived controls would bias the study findings.

In conclusion, the results of the present study provide some reassurance for parents of children conceived using ICSI, with respect to the child's long-term cognitive development. The present findings suggest that the genetic influence of parental cognitive ability is more important than the mode of conception in determining the long-term cognitive ability of children conceived using ICSI.

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## Conflict of interest statement

Professor Saunders is a Director of North Shore ART (now IVF Australia, North Shore), which provided some financial support for the conduct of this study. None of the other authors have any potential conflict of interest.

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