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The cognitive and socio-emotional development of 5-year-old children born after PGD

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STUDY QUESTION: Does PGD increase the risk on adverse cognitive and socio-emotional development?

SUMMARY ANSWER: The cognitive and socio-emotional development in children born after PGD seems to be normal when compared to control groups.

WHAT IS KNOWN ALREADY: A limited number of studies with small sample sizes indicate that the cognitive and socio-emotional development of (pre)school-aged children born after either PGD or PGS seem to be comparable to those of children born after IVF/ICSI and to naturally conceived (NC) children from the general population.

STUDY DESIGN, SIZE, DURATION: For this study we invited 72 5-year-old PGD children, 128 5-year-old IVF/ICSI children and 108 5-year-old NC children from families with a genetic disorder. All children were invited between January 2014 and July 2016.

PARTICIPANTS/MATERIALS, SETTING, METHODS: In total, 51 PGD children, 52 IVF/ICSI children and 35 NC children underwent neuropsychological testing (WPPSI-III-NL and AWMA). The children's parent(s) and teachers filled in questionnaires evaluating children's executive functioning (Behaviour Rating Inventory of Executive Functions; BRIEF) and socio-emotional development (Child Behaviour Checklist; CBCL and Caregiver-Teacher Report Form; C-TRF).

MAIN RESULTS AND THE ROLE OF CHANCE: The mean full-scale intelligence quotient scores ($P = 0.426$) and performance on the AWMA Listening Span task ($P = 0.873$) and Spatial Span task ($P = 0.458$) were comparable between the three groups. Regarding socio-emotional development, the teachers' scores revealed more externalizing ($P = 0.011$) and total problem ($P = 0.019$) behaviour in PGD children than for IVF/ICSI children; both groups did not differ significantly from the NC children ($P = 0.11$). More children (13%) with an affected first-degree family member (mostly parent) were included in the PGD group than in the NC group. Scores in all groups fell within the normal population range and should be considered normal.

LIMITATIONS, REASONS FOR CAUTION: The number of NC children from families with a genetic disorder was relatively small. Furthermore, the fathers' CBCL results were based on small samples.

WIDER IMPLICATIONS OF THE FINDINGS: PGD children show levels of cognitive and socio-emotional development at 5 years that are within the normal range, despite the biopsy involved in PGD and the potential extra psychological burden associated with the presence of a genetic disorder in the family.

†The authors consider that the first two authors should be regarded as joint First Authors.

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Introduction

PGD was first performed in 1990. It offers couples at risk of conceiving children with genetic disorders the opportunity to have an unaffected child of their own (Handyside *et al.*, 1990). IVF treatment with or without ICSI is required for PGD; this is followed by a biopsy of one or a few cells on Day 3, 5 or 6 after fertilization. This biopsy is obligatory in order to select embryos that are not affected by the familial genetic disorder (Handyside, 2010).

The indication for PGD is different from the indication for other ART treatment, the latter generally being offered as an infertility treatment. People opting for PGD either suffer from a specific genetic disorder themselves or are aware of a familial genetic disorder. It is conceivable that the presence of this type of disease in these families is associated with a higher level of psychological burden, which might pose a higher health risk for the whole family system, including the development of problem behaviour in their children (Waldboth *et al.*, 2016). The presence of chronic illness in siblings or parents has been shown to increase the risk of behavioural problems in otherwise healthy children (Romer *et al.*, 2002; Sieh *et al.*, 2010, 2012; Stoeckel and Weissbrod, 2015). There is thus a need to collect and compare data on cognitive and behavioural development of children born after PGD with data from children born after ART without PGD, and with data from naturally conceived (NC) children from families suffering from similar genetic diseases.

The need for a cell biopsy and the effect of this biopsy on the (mental) health and cognitive development of the children has also been a point of concern ever since PGD treatment was instigated (Banerjee *et al.*, 2008; Desmyttere *et al.*, 2009; Liebaers *et al.*, 2010). To date, studies focusing on children born after ART have mostly included children born after IVF and/or ICSI. In general, there is evidence that children born after ART, especially multiples, have an increased risk of adverse perinatal outcome, such as prematurity and low/very low birthweight (Van Balen, 1998; Schieve *et al.*, 2002; Basatemur and Sutcliffe, 2008; Hansen *et al.*, 2013; Lu *et al.*, 2013; Eldar-Geva *et al.*, 2014). Prematurity and lower birthweight are associated with lower cognitive functioning and an increased risk of impaired behavioural development at follow-up in school-aged children (Bhutta *et al.*, 2002; Shenkin *et al.*, 2004; Sutcliffe and Ludwig, 2007), however, results from studies investigating cognitive outcomes in school-aged children conceived after ART are mostly reassuring (Middelburg *et al.*, 2008; Wagenaar *et al.*, 2008; Carson *et al.*, 2010; Barbuscia and Mills, 2017; Rumbold *et al.*, 2017).

To date, only a few systematic studies have assessed the cognitive and socio-emotional development of children born after PGD. Internationally, data from five PGD cohorts have been published (Banerjee *et al.*, 2008; Nekkebroeck *et al.*, 2008a, 2008b, 2011; Thomaidis *et al.*, 2012; Sacks *et al.*, 2015; Winter *et al.*, 2014, 2015).

Although these studies provide reassuring results concerning the cognitive and socio-emotional development of infants and (pre-) school-aged children born after PGD, there are large differences between the studies in age range (most included infants aged under 3 years), in the number and type of control groups, and in the constitution of the PGD group. With regards to the constitution of the PGD group, only Winter *et al.* (2014, 2015), Thomaidis *et al.* (2012) and Sacks *et al.* (2015) focused solely on PGD and compared them with either an ICSI and/or NC control group, though this latter control group consisted of families without a known genetic disorder, or they did not include a control group at all. The other studies included children born after PGD as well those born after PGS (Banerjee *et al.*, 2008; Nekkebroeck *et al.*, 2008a; 2008b, 2011), or PGS solely (Middelburg *et al.*, 2011; Schendelaar *et al.*, 2013). A cell biopsy is required for both PGD and PGS, however, the indications differ; PGS is a form of aneuploidy screening used to optimize pregnancy rates after IVF treatment, whereas PGD is a diagnostic test for couples with an increased risk of offspring with a genetic disorder. It is important to study PGD and PGS independently because potential differences in outcome between children born after PGS may not be attributable to the embryo biopsy, but to factors related to infertility or maternal age (Navot *et al.*, 1991; Sermon, 2006). Therefore, more research is needed that compares the cognitive and socio-emotional development of children born after PGD. This should specifically focus on older children and later cognitive and socio-emotional development and should include multiple control groups accounting for potential effects of the biopsy while accounting for general effects of undergoing ART treatment and the potential extra psychological burden associated with the presence of a genetic disorder.

The present study

We compared children born after PGD with two control groups: IVF/ICSI children to measure the impact of the fertility/ART treatment in general, and with NC children from families with a genetic disorder to measure the effect of a familial genetic disorder and its potential emotional/psychological impact on parents/children. Whereas many previous studies have only assessed children aged 2–3 years, we included 5-year-old children because cognitive functions such as intelligence quotient (IQ), working memory capacity and socio-emotional functioning can, due to speed of development and brain maturation, reliably be assessed from this age. We note that preschool scores on IQ and working memory capacity are highly predictive for future social and academic success (Baddeley and Hitch, 1974; Gathercole *et al.*, 2003; Alloway *et al.*, 2005; Alloway and Alloway, 2010).

Materials and Methods

Study population

The PGD group ($n = 51$) was compared with an IVF/ICSI group ($n = 52$) and a NC control group from families with a genetic disorder ($n = 35$). All children ($n = 138$) were Dutch speaking and born between May 2007 and April 2011. Prior to birth, parents of the PGD children had an initial consultation at the Maastricht University Medical Center+ (MUMC+) clinical genetics department, followed by IVF/ICSI treatment at either the MUMC+ or at one of the IVF transport-centres at the University Medical Center Utrecht (UMCU) or Groningen (UMCG). All biopsies were taken on day three, and all PGD analyses were performed at the MUMC+. The parents of the IVF/ICSI children underwent treatment at the MUMC+. The parents of the NC children either had an informative consultation regarding PGD but refrained from PGD treatment and became pregnant naturally, or had invasive prenatal testing (chorionic villus biopsy or amniocentesis) at the MUMC+ because of a high risk of transmitting a genetic disorder to their offspring.

Study procedure

The children were included between January 2014 and July 2016 and were assessed at one of the participating hospitals, or in some cases, their parents' home.

The parent(s) first underwent a semi-structured interview. The date of birth, height, weight and the medical history of the parents, the child and potential siblings were recorded. Subsequently, the parents were asked to complete the Behaviour Rating Inventory of Executive Functions (BRIEF) and Child Behaviour Checklist (CBCL), as well as a questionnaire on their own educational level, marital status and additional information on the medical history of their child. Each child's teacher was asked to fill in two questionnaires (BRIEF and Caregiver-Teacher Report Form (C-TRF)).

The children underwent an auxological, physical and neurological examination, the results of which will be reported elsewhere. Neuropsychological tests were administered by a qualified psychologist.

Measurement instruments

Intelligence quotient

The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III-NL; Wechsler, 2009; Hendriksen and Hurks, 2010) is a widely used, standardized test for assessing IQ in children aged 2.6–7.11 years. A full-scale IQ-score (FSIQ) was obtained, consisting of a verbal IQ-score (VIQ) and a performance IQ-score (PIQ). Standardized scores were entered in the analyses. A score of 100 (population mean (M) = 100) is considered to be an average norm population score.

Working memory

The currently used standardized and norm-referenced screener version of the Automated Working Memory Assessment Battery (AWMA) (Alloway, 2007) consists of a Listening Span task, measuring verbal working memory capacity, and a Spatial Span task, measuring visuo-spatial working memory capacity. The AWMA provides age adequate norm scores for the age range 4–22 years. Standardized scores were entered in the analyses. A score of 100 ($M = 100$) is considered to be an average norm population score.

Executive functioning

The Dutch version of the BRIEF (Huizinga and Smidts, 2012), suitable for the 5–18 year age range was filled in by the children's parents and teachers. The resulting T-scores were entered in the analyses (population mean (M) = 50, SD = 10; a BRIEF total T-score of >65 is considered to be in the problem range).

Socio-emotional development

To assess internalizing behaviour (e.g. anxious, depressed) or externalizing behaviour (e.g. hyperactive, aggressive) and total problem behaviour, we asked the parents and teachers to complete the Dutch version of the CBCL (Achenbach and Rescorla, 2000) or the C-TRF (Achenbach and Rescorla, 2000). The resulting T-scores were entered in the analyses (population mean (M) = 50, SD = 10; a BRIEF total T-score of >65 is considered to be in the problem range).

Ethics

The study protocol was approved by the MUMC+ Medical Ethical Committee (NL43048.068.13/METC 13-2-010). Informed written consent was obtained from all parents prior to the examination.

Statistical analyses

Data analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) version 23.0 (SPSS Inc., Chicago, IL, USA). An alpha level of 0.05 (two-sided) was applied for all analyses.

To test for potential between-group differences in cognitive (IQ, working memory, executive functioning in daily life) and socio-emotional (CBCL/C-TRF) development between the groups, ANOVA was performed on all dependent measures (eta-partial squared reported as effect size measure). Significant ANOVA omnibus tests were followed by Bonferroni corrected post-hoc tests. First, a check for violations of the underlying assumptions for one-way ANOVA was carried out. Shapiro–Wilk's tests ($P < 0.05$) showed approximately normal distributions for FSIQ and VIQ, PIQ data from the WPPSI-III-NL and for the CBCL, C-TRF-Total scale and BRIEF questionnaire data. Data from the C-TRF-Internalizing scale, C-TRF-Externalizing scale and AWMA Listening and Spatial span test showed stronger deviations from normality. Therefore, for these dependent measures, ANOVA tests were also performed on (log)transformed data, but since the ANOVA results for the non-transformed and transformed data did not differ, we report on the non-transformed data. Outlier analyses were performed by inspection of boxplots and are reported in the results section. An outlier was defined as a score of either +3 SD or −3 SD or more, from the mean group score. Levene's test showed equality of error variances between the groups for all dependent measures except for the WPPSI-VIQ subscale, the WPPSI-FSIQ scale and father's Internalizing and Total CBCL scores.

Results

Participant-specific and socio-demographic characteristics

A total of 72 PGD children, 128 IVF/ICSI children and 108 NC children were invited to participate and 51 (including two twin pairs), 52 and 35 children, respectively, and their parent(s) were included. Participation rates were 70.8, 40.6 and 32.4% for PGD, IVF/ICSI and NC children, respectively.

Table I summarizes the relevant child-specific and parental characteristics at baseline. A significant age difference at assessment time was noted for the three groups ($F(2, 135) = 5.29$, $P = 0.006$, $\eta_p^2 = 0.073$), but as only 5-year-old children were invited for participation, the mean age differentiation in months was negligible. Furthermore, all dependent measures were age- (and mostly sex) standardized (T-) scores.

Table I Baseline characteristics of PGD, IVF/ICSI and naturally conceived children and their parents.

	PGD ($n = 51$)	IVF/ICSI ($n = 52$)	NC ($n = 35$)	Test	*P*-value	Effect size	Missing total (n)
Male/Female	28/23	21/31	17/18	$\chi^2(2) = 2.185$	0.335	$\eta_p^2 = 0.126$	/
Age at assessment in months[a]	64.98 ± 3.01	63.38 ± 1.36	64.54 ± 3.14	$F(2, 135) = 5.29$	0.006*	$\eta_p^2 = 0.073$	/
Birthweight (g)[a]	3364.63 ± 598.86	3272.62 ± 581.33	3422.79 ± 492.02	$F(2, 132) = 0.77$	0.464	$\eta_p^2 = 0.012$	3
Gestational age in weeks[a]	38.84 ± 2.24	39.17 ± 2.24	39.34 ± 1.37	$F(2, 135) = 0.68$	0.511	$\eta_p^2 = 0.01$	/
Birth order				$F(2, 135) = 1.28$	0.283		/
First	27	33	14				
Second	17	10	14				
Third	4	7	5				
Fourth	3	2	1				
Fifth	0	0	1				
Maternal age at birth (years)[a]	33.48 ± 3.21	33.65 ± 3.73	34.00 ± 4.71	$F(2, 135) = 0.20$	0.822	$\eta_p^2 = 0.003$	/
Maternal education level							
Low/medium/high	2/25/21	3/22/26	2/10/23	FET 4.850	0.292		4
Paternal age at birth (years)[a]	36.83 ± 3.70	37.76 ± 6.48	36.12 ± 5.31	$F(2, 135) = 1.04$	0.356	$\eta_p^2 = 0.015$	/
Paternal education level							
Low/medium/high	4/18/24	10/13/24	3/9/20	FET 4.515	0.340		13

Values are *n* unless otherwise stated.NC = naturally conceived.
[a]Values are mean ± SD.
*$P \leq .05$.
g = grams.
FET, Fisher's exact test, NC, naturally conceived.

Table II Genetic family characteristics of the PGD and NC groups.

	Invited		Participated		Participation % of total	
	PGD	NC	PGD	NC	PGD	NC
No affected first degree family member*	24	24	19 (79%)	14 (60%)	37%	40%
Affected first degree family member						
Parent	20[‡]	29[§]	13 (65%)	2 (7%)	25%	6%
Living sib	11	15	6 (55%)	4 (27%)	12%	11%
Deceased sib	8	15	7 (88%)	7 (47%)	12%	20%
Parent carrier of X-linked disorder	9	23	6 (67%)	8 (35%)	14%	23%
Invited child deceased	/	2	/	/	/	/
Total	72	108	51 (71%)	35 (32%)	100% ($n = 51$)	100% ($n = 35$)

Values are *n* unless otherwise stated. Values in parenthesis are percentage of responders to the invitation.
*Parent(s) is/are carrier of a genetic disorder; i.e. balanced chromosomal translocation or autosomal recessive disorder.
[‡]Nine parents were at risk for a late-onset disorder of whom four participated.
[§]17 parents were at risk for a late-onset disorder of whom two participated.

Since no significant group differences were found for any of the other variables there was no need to include them as covariates in the ANOVA analyses.

Characteristics PGD and NC group

Six of the invited children in the NC group had a late-onset familial genetic disorder, but had an unknown genetic status. Only one of these children was included in the study. All other invited NC children were unaffected, as assessed by prenatal or postnatal testing. Further genetic characteristics of the PGD and the NC group are shown in Table II.

Cognitive development

IQ (WPPSI-III-NL)

Two cases were removed from the WPPSI-analysis, one in the PGD group due to a significant difference between VIQ and PIQ score, and one IVF/ICSI case who did not complete the tasks. Inspection of

Table III Between group differences in Intelligence and verbal and spatial working memory span scores.

	PGD	IVF/ICSI	NC	Min–max	ANOVA	*P*-value	Effect-size
WPPSI FSIQ ($n = 136$)‡	$n = 50$	$n = 51$	$n = 35$				
	107.98 ± 11.29	109.55 ± 14.18	106.06 ± 9.94	81–145	$F(2, 133) = 0.86$	0.426	$\eta_p^2 = 0.013$
WPSSI VIQ ($n = 136$)‡	$n = 50$	$n = 51$	$n = 35$				
	106.74 ± 9.92	109.16 ± 13.75	105.57 ± 9.91	80–142	$F(2, 133) = 1.12$	0.330	$\eta_p^2 = 0.017$
WPPSI PIQ ($n = 136$)‡	$n = 50$	$n = 51$	$n = 35$				
	106.38 ± 12.83	106.8 ± 13.13	104.37 ± 9.16	78–139	$F(2133) = 0.45$	0.637	$\eta_p^2 = 0.007$
AWMA ($n = 137$)‡	$n = 51$	$n = 51$	$n = 35$				
Listening span	104.14 ± 12.98	103.67 ± 14.55	105.26 ± 14.78	86–136	$F(2, 134) = 0.14$	0.873	$\eta_p^2 = 0.002$
AWMA ($n = 137$)‡	$n = 51$	$n = 51$	$n = 35$				
Spatial span	105.04 ± 12.90	102.77 ± 11.67	106.11 ± 13.03	83–139	$F(2, 134) = 0.79$	0.458	$\eta_p^2 = 0.012$

‡Mean standardized test scores ± SD (population mean (M) = 100) in PGD, IVF/ICSI and NC groups.
*$P \leq 0.05$.
WPPSI-III-NL, Wechsler preschool and primary scale of intelligence; FSIQ, full-scale intelligence score; VIQ, verbal intelligence score; PIQ, performance intelligence score.
AWMA, automated working memory assessment battery.
Min, minimum score; max, maximum score.

boxplots showed three outliers in the NC group for the verbal (VIQ) and full-scale (FSIQ) data) and one outlier in the IVF/ICSI group for the performance (PIQ) data (data not shown). The one-way ANOVA analyses (including outliers) showed no statistically significant differences in FSIQ, VIQ and PIQ between the three groups (Table III). All three groups scored above the population mean.

Removal of outliers did not change the ANOVA results and were thus retained, although the ANOVA omnibus test for VIQ became trend significant ($P = 0.089$), but Bonferroni corrected post-hoc tests revealed a non-significant trend only for higher IQ in the IVF/ICSI than in the NC group ($P = 0.08$).

Working memory capacity (AWMA tests)

One IVF/ICSI case was removed from the AWMA analyses because of incomplete data. There were no outliers in the Listening Recall data, but the Spatial Recall data showed six outliers; four in the PGD group and two in the IVF/ICSI group, all with higher scores than the population mean (>98th percentile) scores (data not shown). Removal of these outliers did not affect ANOVA results and they were retained. The one-way ANOVA analyses revealed no significant differences between the three groups on the Listening Span task and the Spatial Span task (Table III). Moreover, scores were within the normal population range for all groups.

Executive functioning in daily life (BRIEF)

Two outliers were found in the IVF/ICSI group in the mothers' BRIEF data and four outliers in the NC group for the fathers' BRIEF data (data not shown). The one-way ANOVA analyses including all children showed no significant differences between the PGD, IVF/ICSI and NC groups in BRIEF-total *T*-scores obtained from fathers and teachers (Table IV). Exclusion of outliers in the father's data did not change these results. For mothers, the ANOVA omnibus test showed a non-significant trend ($P = 0.07$) that became significant ($P = 0.035$) after removal of the two outliers. Bonferroni corrected post-hoc tests, however, only showed trend-significant differences between the PGD and the other groups ($P = 0.08$ for both contrasts), with higher scores in the PGD group (Table IV). Moreover, the mean BRIEF total *T*-scores from mothers, fathers and teachers were well below the population mean of $M = 50$ (lower scores indicating better executive functioning).

Socio-emotional development

CBCL (Parents)

Inspection of the mothers' boxplots revealed: one outlier (in IVF/ICSI group with score 73) on the Externalizing scale. Outliers in the fathers' data were: seven (all in the PGD group) on the Internalizing scale, three (two in the PGD and one in the IVF/ICSI group) on the Externalizing scale and one (in the PGD group) on the Total problem scale. The one-way ANOVA analyses including all children revealed no significant group differences between PGD, IVF/ICSI and NC groups in internalizing, externalizing and total problem behaviour, as reported by mothers and fathers (Table IV). Exclusion of outliers did not influence the fathers' results, and only influenced the result for the Externalizing problem scale as rated by mothers, now becoming significant (was borderline significant): F (2, 129) = 3,70, $P < 0.05$, $\eta_p^2 = 0.054$. However, Bonferroni corrected post-hoc tests revealed trend-significant differences between PGD and IVF/ICSI ($P = 0.055$) and NC ($P = 0.081$) groups, with higher scores in the PGD than in the other groups (Table IV). Mean *T*-scores in all groups were around or even below the normal population mean, lower scores indicating less problem behaviour.

C-TRF (Teachers)

Two outliers were found in the C-TRF-Externalizing data (one in the PGD and one in the IVF/ICSI group), one outlier in the C-TRF-Total data (PGD group, same outlier as in Externalizing data), and one outlier in the C-TRF-Internalizing data (NC group), all with relatively high scores. Removal of these outliers did not change the reported ANOVA omnibus test and post-hoc test results, so the outliers were

Table IV Between group differences in behaviour and teacher/caregiver *T*-scores.

	PGD	IVF/ICSI	NC	Min–max	ANOVA	*P*-value	Effect-size
Mothers ($n = 133$)	$n = 49$	$n = 51$	$n = 33$				
BRIEF total score‡	43.12 ± 10.24	39.98 ± 8.85	38.76 ± 6.79	24–64	$F(2, 130) = 2.72$	0.070	$\eta_p^2 = 0.04$
Fathers ($n = 65$)	$n = 30$	$n = 23$	$n = 12$				
BRIEF total score‡	41.23 ± 9.32	37.74 ± 9.47	41.92 ± 9.51	25–65	$F(2, 62) = 1.17$	0.318	$\eta_p^2 = 0.036$
Teachers ($n = 117$)	$n = 42$	$n = 43$	$n = 32$				
BRIEF total score‡	46.83 ± 7.75	43.30 ± 7.60	45.34 ± 7.40	35–63	$F(2, 114) = 2.31$	0.104	$\eta_p^2 = 0.039$
Mothers ($n = 133$)	$n = 49$	$n = 51$	$n = 33$				
CBCL Int. prob.‡,a	49.47 ± 9.68	48.00 ± 10.78	46.39 ± 9.32	29–70	$F(2, 130) = 0.94$	0.395	$\eta_p^2 = 0.014$
CBCL Ext. prob.‡,b	48.53 ± 9.42	44.75 ± 9.72	43.97 ± 8.66	28–73	$F(2, 130) = 3.03$	0.052	$\eta_p^2 = 0.054$
CBCL total problem score‡	48.04 ± 9.62	45.51 ± 9.60	44.55 ± 8.73	29–70	$F(2, 130) = 1.59$	0.208	$\eta_p^2 = 0.024$
Fathers ($n = 65$)	$n = 30$	$n = 23$	$n = 12$				
CBCL Int. prob.‡	48.53 ± 8.21	48.30 ± 11.65	47.50 ± 11.58	29–67	$F(2, 62) = 0.05$	0.956	$\eta_p^2 = 0.001$
CBCL Ext. prob.‡	48.80 ± 7.22	45.65 ± 9.01	44.75 ± 11.47	28–73	$F(2, 62) = 1.30$	0.279	$\eta_p^2 = 0.04$
CBCL total problem score‡	48.03 ± 6.94	45.87 ± 10.45	46.08 ± 11.41	29–70	$F(2, 62) = 0.42$	0.658	$\eta_p^2 = 0.013$
Teachers ($n = 118$)	$n = 42$	$n = 44$	$n = 32$				
C-TRF Int. prob.‡	47.52 ± 9.04	43.30 ± 8.15	46.09 ± 7.66	34–67	$F(2, 115) = 2.84$	0.062	$\eta_p^2 = 0.047$
C-TRF Ext. prob.‡	50.67 ± 9.02	45.68 ± 6.40	47.94 ± 6.98	36–75	$F(2, 115) = 4.65$	0.011*	$\eta_p^2 = 0.075$
C-TRF total problem score‡	49.17 ± 10.31	43.93 ± 7.20	46.63 ± 7.33	29–80	$F(2, 115) = 4.11$	0.019*	$\eta_p^2 = 0.067$

‡Mean BRIEF and CBCL/C-TRF T-scores (± SD) in PGD, IVF/ICSI and NC groups.
*$P \leq 0.05$.
[a]Internalizing problems. [b]Externalizing problems.
BRIEF, Behaviour Rating Inventory of Executive Functions; CBCL, Child Behavioural Check List; C-TRF, Caregiver-Teacher Report Form.

retained. The one-way ANOVA analyses yielded significant Group effects for externalizing behaviour and total problem behaviour and a non-significant trend for internalizing behaviour (Table IV). Bonferroni corrected post-hoc tests showed that C-TRF-Externalizing and Total scores were higher in the PGD than in the IVF/ICSI group (difTRF_EXT = 4,98 (SE = 1,6), $P = 0.003$, LCI 1,75 HCI = 8,22 and dif C_TRFTotal = −5,23 (SE = 1,8), $P = 0.015$), LCI = −9,67, HCI = −0,80)), however, both groups did not differ significantly from the NC group. Mean *T*-scores of all groups were around or below the normal population mean of $M = 50$ (lower scores indicating less problem behaviour).

Discussion

In this study, we evaluate the cognitive and socio-emotional development of 5-year-old children born after PGD in the Netherlands. Overall, our findings are reassuring and comparable to those reported for PGD cohorts from other countries (Banerjee *et al.*, 2008; Nekkebroeck *et al.*, 2008a, 2008b, 2011; Thomaidis *et al.*, 2012; Sacks *et al.*, 2015; Winter *et al.*, 2014, 2015).

We found no evidence for an adverse effect of PGD on the cognitive development of the children. No significant differences in verbal, performance or full-scale IQ-scores between the three groups were found and all three groups had mean IQ-scores above the population average. A possible explanation for the higher IQ-score is the relatively high educational level of the parents. Earlier studies have reported that ART couples are often more highly educated compared to the general population (Leunens *et al.*, 2006; Place and Englert, 2003), and their results were supported by Winter *et al.* (2014), who also found no differences in IQ-scores between children born after PGD or ICSI, and NC children. Compared to previous work, our study incorporated two extra working memory tests, however, we found no differences in verbal and visuo-spatial working memory capacity among the three groups. This is a promising result considering the predictive value of children's working memory capacity for future cognitive and socio-emotional development and academic success (Baddeley and Hitch, 1974; Kusche, Cook and Greenberg, 1993; Gathercole *et al.*, 2003; Alloway *et al.*, 2005; Alloway and Alloway, 2010; Dunn, 2010; Diamond and Lee, 2011).

Executive functioning in daily life, as reported by the parents and teachers, was comparable in all three groups. All mean group scores were around or even below the population mean; lower scores indicate better executive functioning. Our results are thus in line with the findings by Sacks *et al.* (2015).

The socio-emotional development scores did show some differences between PGD children and the control groups. Whereas fathers' CBCL scores did not reveal group differences, the mothers' CBCL scores showed trend-significant ($P < 0.1$) higher scores on externalizing problem behaviour in the PGD group compared to the IVF/ICSI and NC group. Furthermore, the PGD children's teachers reported significantly higher scores on Externalizing and Total problem behaviour scales compared to those of IVF/ICSI children, but reported similar scores for the NC children. It is important to realize that analyses were performed on standardized scores, and mean problem

behaviour scores on all scales fell well within (even below) that of the normal population range and were thus not indicative of any problem behaviour in all three groups.

Normal socio-emotional development, though without group differences, has also been reported by other researchers (Nekkebroeck *et al.*, 2008b; Middelburg *et al.*, 2011; Sacks *et al.*, 2015; Winter *et al.*, 2015). It seems unlikely that the presence of a familial genetic disorder in PGD families could account for teacher's higher Externalizing behaviour scores, since no difference was seen in teachers' ratings between the NC (also marked by the presence of genetic disorders) and IVF/ICSI groups. It is worth noting that the participation rate was higher in the PGD group compared to the NC group and, whereas NC and PGD groups had largely similar family backgrounds in terms of genetic disease, the PGD group included 13% more children with a first-degree family member (mostly parent) affected with a genetic disorder. Although we consider it unlikely, we cannot exclude that this might have influenced the somewhat higher rating of Externalizing behaviour scores on the CBCL in the PGD group as evaluated by the teachers. We postulate that, the Externalizing behaviour scores in NC children may have been even higher if more children with an affected first-degree family member had been included, indicating a possible effect of a familial genetic disorder on the children's socio-emotional development. Based on our results, it is unlikely that the embryo biopsy had an effect on the somewhat higher Externalizing behaviour scores since no difference was seen between the PGD and NC groups. Replication of the present results in PGD and NC groups of children with even more closely matched genetic disease family backgrounds is thus highly desirable.

Strengths and limitations

The strength of our study is the inclusion of exclusively PGD (and not PGS) children and the comparison with a group of NC children with a familial genetic disorder. This approach enabled us to focus on potential consequences of the PGD treatment (the biopsy) on children's cognitive and socio-emotional development and on the possible effect of the presence of a genetic disease in the family. Moreover, by administering tests on executive functioning and working memory, especially at the age of 5 years, we were able to give a more comprehensive evaluation of the possible effect of PGD on a child's cognitive development. Furthermore, adding a non-subjective rater (teacher) provided us with multi-informant data, giving even more insights in a child's socio-emotional and behavioural development.

The higher response rate of the PGD group and the higher presence of affected first-degree family members in this group is a possible limitation. The difference in response rate can, in our view, be best explained by the higher affinity of parents in the PGD group for the research question because they had a child born after PGD. The slightly different genetic background of the PGD and NC children could have influenced the socio-emotional development scores, resulting in higher Externalizing behaviour scores in PGD children and lower Externalizing behaviour scores in NC children. Another possible limitation regarding the evaluation of children's socio-emotional development is that we included far fewer fathers than mothers. This led to uneven and small groups and made analysis of the father's data less reliable.

We conclude that the results of this study are reassuring since our sample of 5-year-old children born after PGD showed cognitive and socio-emotional development within the normal population range on all normed measurement instruments. The higher scores on Externalizing and Total problem behaviour scales on the C-TRF in the PGD group, as reported by their teachers, were the most striking finding. In future studies it would be worthwhile exploring these problem behaviour scales in older PGD children.

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Authors' roles

All authors have made substantial contributions to the study's conception and design. M.H. and M.v.d.S. included all the study subjects. L.V. and L.J. analysed the data, and M.H., L.V., L.J. and C.d.D.-S. interpreted the data. All authors have made substantial contributions to revising the article and given final approval of the version to be published.

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Conflict of interest

None of the authors have any competing interests to declare.

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