Meta-analysis of the association between preterm delivery and intelligence

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ABSTRACT

Background An increasing proportion of infants are born preterm, and their survival has improved. Therefore, their long-term sequelae are of increasing public health importance.

Methods We conducted a systematic review covering a 30 year period (1980–2009). A random effects meta-analysis provided a pooled estimate of the difference in IQ score between individuals born preterm and term. Small-study bias was examined using a funnel plot and Egger's test, and meta-regression was used to investigate possible causes of heterogeneity. Cumulative meta-analysis was used to determine if the magnitude of the association had changed over time.

Results The 27 eligible studies covered 7044 individuals; 3504 (50%) delivered preterm and 3540 (50%) at term. They provided 37 estimates of difference in IQ. All demonstrated a reduced IQ among those delivered preterm and all but four reached statistical significance. Overall, IQ score was 11.94 (95% CI: 10.47–13.42, $P < 0.001$) points lower among children born preterm. There was moderate heterogeneity (overall I^2 74.2%, $P < 0.001$), but no significant small-study bias ($P = 0.524$). The association between preterm delivery and IQ did not change significantly over time. There was a statistically significant, linear association across the gestational age range (adjusted coefficient: −0.91, 95% CI: −1.64, −0.17, $P = 0.018$).

Conclusions There is a strong and consistent body of evidence suggesting an association between preterm delivery and reduced IQ, with evidence of a dose–response relationship with gestational age.

Keywords intelligence, intelligence tests, meta-analysis, premature birth

Introduction

Worldwide, around 13 million infants are born preterm each year.[1] They account for an increasing proportion of deliveries. In Scotland, there has been a 17% relative increase in the proportion of live-born infants delivered preterm over 20 years.[2] Furthermore, preterm infants are being delivered at an increasingly early gestational age. The reasons for the increase in preterm deliveries include an increase in elective deliveries for medical indications,[2] increased use of caesarean section, increasing maternal age[1] and increased use of assisted reproductive technologies that often result in multiple births.[3]

Historically efforts have focused on reducing the risk of early adverse events and improving survival through interventions such as surfactant therapy, antenatal steroids and ventilatory assistance.[4] However, preterm infants are also at increased risk of long-term sequelae, including cognitive and behavioural impairment, cerebral palsy and hearing loss.[4] These areas have been relatively neglected[4] and, in light of the increasing numbers of preterm deliveries and improved survival, are an important public health concern.[1,5]

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It has been suggested that cognitive impairment may occur more frequently than motor, visual or hearing impairment.[6] Intelligence quotient (IQ) is easy to quantify and compare across different populations. Therefore, it has been studied more extensively than specific aspects of cognition, such as language and memory. A meta-analysis of all preterm deliveries was performed in 2002.[7] Since then obstetric and neonatal practice has changed, preterm deliveries have increased and more studies have been published. Therefore, we undertook an updated meta-analysis of all preterm deliveries to determine the strength of the association between preterm birth and IQ, and whether there was evidence of a dose–response relationship.

Methods

Systematic review

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[8] Systematic reviews were undertaken by two of the authors (C.O.K.W. and J.P.P.) using the Medline, Embase and PsychInfo databases. A title search was conducted using the terms preterm, low-birth weight, gestational age, date of delivery, prematur*, baby, babies or infan* combined with IQ, intelligence quotient*, cogni*, learning, neuro*, impair*, disorder, dysfunction*, disab*, delay, outcome*, status, development*, abilit* or performance. The search was limited to articles published in or translated into English, conducted on human subjects and published from 1980 to 2009 inclusive. Articles were included in the meta-analysis if they satisfied all the following criteria:

- IQ assessed at school age (four years of age) or older, using a validated test.
- Mean IQ score reported for children born preterm.
- Mean IQ score reported for children born at term.

Where multiple studies had been published based on the same cohort, only the most recent study was included in the meta-analysis. The reference lists of published articles were checked to identify additional relevant studies.

Data were extracted on the characteristics of the individual studies: the country in which the study was conducted, the years of birth and publication, the size of the study population, the mean gestational age and birth weight of the preterm and term subgroups, and the age, method and result of the IQ assessments. For those studies that expressed gestational age or birth weight only in terms of a range or cut-off, we used the distributions obtained from Scottish routine maternity data (Scottish Morbidity Record SMR02) for the relevant year(s) to estimate mean values (http://www.datadictionaryadmin.scot.nhs.uk/isddd/9066.html).

Meta-analysis

A classic random-effects meta-analysis was performed using the weight mean difference (WMD) in IQ between preterm and term infants. The individual study weights were derived using the inverse variance method and heterogeneity among studies was quantified using the I^2 measure.[9] Small-study bias was assessed visually using a funnel plot and then formally tested using Egger's regression asymmetry test for small-study bias.[10] We used univariate and multivariate meta-regression analyses to determine whether specific study characteristics were associated with effect size estimate and, therefore, were a potential source of between-study heterogeneity.[11] We tested for possible non-linear effects of continuous variables using a natural cubic spline. All regression analyses were subjected to 20 000 permutations to adjust for multiple testing. A cumulative meta-analysis was performed to examine whether the pooled estimate of effect size has changed over time, as new studies have been published.[12] Finally a meta-influence graph was produced to investigate the influence of any single study on the overall estimate of effect size. All analyses were performed using STATA 10.1 software (STATA Corp, College Station, Texas) and statistical significance was assumed at the 5% level.

Results

After removal of duplicates, the electronic search produced a list of 515 publications. Review of the abstracts enabled us to exclude 456 that were not relevant. The full texts were obtained for the remaining 59 and a further 32 were excluded because they did not satisfy the inclusion criteria. Five of the eligible studies provided results for subgroups. Therefore, the meta-analysis was based on 37 estimates of effect size obtained from the 27 eligible studies.[13–39] Together these studies comprised data on a total of 7044 children of whom 3504 (50%) were delivered preterm and 3540 (50%) at term. Thirteen studies were undertaken in Europe, eight in North America and six elsewhere (Table 1). Twenty-one (48%) studies used a version of the Wechsler scale to measure IQ, six (22%) used the Kaufman assessment battery, one used the British abilities scale and one the McCarthy scale.

The random-effects meta-analysis produced a pooled estimate suggesting an 11.94 (95% CI: 10.47–13.42) lower IQ score in children born preterm ($z = 15.87$; $P < 0.001$)

Table 1 Characteristics of studies examining the association between preterm delivery and IQ

Reference	*Country*	*Years born*	*Subgroup*	*Gestation at delivery (weeks)*		*n*	*Male %*	*Mean birthweight (g)*	*IQ (IQ)*		
				Range	*Mean*				*Test*	*Age (years)*	*Mean score (SD)*
Lloyd *et al.*[13]	UK	1975–79	Preterm	26–37	32	44	47	1302	BAS	7	93.1 (15)
			Term	40	40	44	47				100.4 (12.9)
McDonald *et al.*[14]	USA	–	Preterm	27–34	31	16	–	1776	WPPSI	5	112.7 (20.9)
			Term	40	40	18	–	3359			124.3 (12.6)
Smith and Knight-Jones[15]	UK	1981	Preterm	>28	–	43	47	1306	MIQS	5	88.6 (16.9)
			Term	>37	–	43	47	3342			101.0 (13.0)
Teplin *et al.*[16]	USA	1980	Preterm	25–31	28	28	50	905	KABC	6	86.3 (13.6)
			Term	≥37	40	26	–				98.7 (14.3)
Sommerfelt *et al.*[17]	Norway	1981–82	Preterm	–	31	29	62	1251	WISC–R	8	93.2 (16.0)
			Term	40	40	29	62	3650			104.2 (14.0)
Levy-Shiff *et al.*[18]	Israel	–	Preterm	25–35	29	90	–	1190	WISC-R	13	105.1 (10.5)
			Term	37–40	39	90	–	3225			114.4 (9.8)
Sommerfelt *et al.*[19]	Norway	1986–88	Preterm	–	32	144	51	1555	WPPSI-R	5	97 (14)
			Term	>37	40	163	55	>3000			104 (14)
Botting *et al.*[20]	UK	1980–83	Preterm	<37		138	–	<1500	WISC-III	12	89.7 (17.2)
			Term	≥37		163	–	>2500			97.8 (17.4)
Wolke and Meyer[21]	Germany	1985–86	Preterm	<32	30	264	56	1288	KABC	6	84.8 (17.4)
			Term	>36	40	264	56	3407			99.7 (11.2)
Stjernqvist *et al.*[22]	Sweden	1985–86	Preterm		27	61	41	1042	WISC-III-R	10	89.8 (15.1)
			Term		40	61	43	3648			106.5 (15.0)
Saigal *et al.*[23]	Canada	1977–82	Preterm		27	150	47	833	WISC-R	14	89 (19)
			Term		40	124	44	3395			102 (13)
Taylor *et al.*[24]	USA	1982–86	Preterm I		26	60	32	666	KABC	11	83.5 (19.7)
			Preterm II		30	55	31	1173			96.8 (14.4)
			Term	40	40	49	33	3300			106.2 (14.3)
Rickards *et al.*[25]	Australia	1980–82	Preterm		29	120	54	1167	WISC-III	14	96.2 (15.5)
			Term		40	41	61	3417			105.0 (13.3)
Magill-Evansal *et al.*[26]	Canada	–	Preterm	<37	34	20	70	2104	WISC-III	10	98.0 (14.9)
			Term		39	23	39	3515			101.5 (11.9)
Grunau *et al.*[27]	Canada	1982–87	Preterm	23–33	26	74	–	719	WISC-III	8–9	99.3 (10.9)
			Term	38–40		30	–	3540			117.3 (13.0)
Anderson *et al.*[28]	Australia	1991–92	Preterm	<28		258	47	<1000	WISC-III	8	95.5 (16.0)
			Term			220	47				104.9 (14.1)

Continued

Table 1 Continued

Reference	*Country*	*Years born*	*Subgroup*	*Gestation at delivery (weeks)*		*n*	*Male %*	*Mean birthweight (g)*	*IQ (IQ)*		
				Range	*Mean*				*Test*	*Age (years)*	*Mean score (SD)*
Cooke *et al.*[29]	UK	1991–92	Preterm	23–32	30	268	56	1467	WISC-III	7	89.4 (14.2)
			Term			198	53				100.5 (13.7)
Taylor *et al.*[30]	USA	1982–86	Preterm I		26	48	33	660	WISC-III or WAIS-III	16	82.5 (18.9)
			Preterm II		29	47	34	1165			91.4 (19.8)
			Term			52	39	3422			97.9 (16.2)
Marlow *et al.*[31]	UK	1995	Preterm	<25		241	50		KABC	6	82.1 (19.2)
			Term			160	44				105.7 (11.8)
Caravale *et al.*[32]	Italy	1998	Preterm	30–34	32	30	–	1755	Stanford	3–4	110.8 (10.4)
			Term			30	–		Binet		121.0 (10.6)
Hack *et al.*[33]	USA	1992–95	Preterm		26	200	41	811	KABC	8	87.8 (8.0)
			Term			176	–				99.8 (15.0)
Caldú *et al.*‡[34]	Spain	1983–94	Preterm	<33	30	25	60	–	WISC-R or WAIS-III	13	96.0 (16.8)
			Term		40	25	52	–			113.3 (12.2)
Narberhaus *et al.*[35]	Spain	1983–94	Preterm I	25–27	26	9	78	899	WISC-R or WAIS-III	14	91.4 (14.4)
			Preterm II	28–30	29	19	42	1140			100.5 (16.2)
			Preterm III	31–33	32	25	44	1534			103.2 (15.7)
			Preterm IV	34–36	35	11	64	2446			112.7 (13.8)
			Term	37–43	40	53	49	3419			113.6 (11.5)
Mu *et al.*[36]	Taiwan	1995–97	Preterm		30	130	45	1165	WISC-III	8	93.1 (16.3)
			Term		40	59	48	3312			111.1 (14.8)
Roberts *et al.*[37]	Australia	1979–80	Preterm I		27	77	46	871	WISC-R	8	96.3 (15.0)
		1985–87	Preterm II		27	192	42	866			94.2 (16.9)
		1991–92	Preterm III		27	209	46	834	WISC-III	8	94.9 (15.8)
		1997	Preterm IV		27	149	49	789			94.1 (14.3)
		1997	Term			199	–	>2499			105.5 (12.4)
Soria-Pastor *et al.*[38]	Spain	1996–98	Preterm	30–34	33	20	55	1754	WISC-IV	9	105.8 (13.8)
			Term		40	22	64	3392			121.9 (15.3)
Woodward *et al.*[39]	New Zealand	1998–2000	Preterm I	23–33		105	51	1062	WPPSI-R	4	94.9 (15.5)
			Preterm II	23–27		43	47	808			93.9 (17.6)
			Preterm III	28–33		62	53	1238			95.7 (13.9)
			Term	38–41		107	56	3575			104.7 (13.5)

BAS, British Abilities Scale; KABC, Kaufman Assessment Battery for Children; MIQS, McCarthy IQ Scale; WASI, Wechsler Abbreviated Scales of Intelligence; WAIS-III, Wechsler Adult Intelligence Scale, Third Edition; WISC-III, Wechsler Intelligence Scale for Children; WISC-R, Wechsler Intelligence Scale for Children, Revised; WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition; WPPSI, Wechsler Preschool and Primary Scales of Intelligence Test; WPPSI-R, Weschsler Preschool and Primary scale of intelligence, Revised.

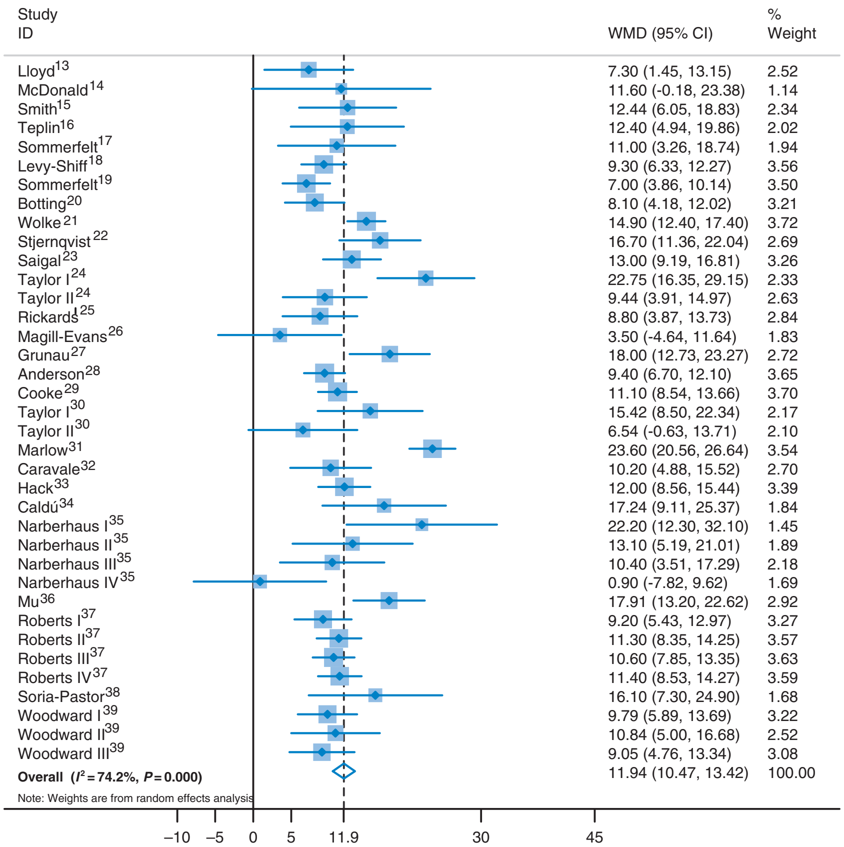

Fig. 1 Random-effects meta-analysis of the association between preterm delivery and IQ. Individual study weights were derived using the inverse variance method. WMD weighted mean difference; CI, confidence interval.

(Fig. 1). The chi-square test for heterogeneity was significant ($X^2 = 139.57$, df = 36, $P < 0.001$). This was supported by an I^2 value of 74.2%, consistent with a moderate level of heterogeneity.[40] The funnel plot was relatively symmetrical, suggesting a low probability of small-study bias (Fig. 2). This was confirmed when formally tested using Egger's method ($P = 0.890$). The cumulative meta-analysis did not indicate any significant change in effect size over time. Nor did any individual studies have a significant impact on the effect size when assessed visually using a meta-influence plot. In the meta-regression analysis, there was a significant association between gestational age and IQ (coefficient −0.88, 95% CI: −1.37, −0.40, adjusted $R^2 = 34.39\%$, $P = 0.001$, multiplicity adjusted $P = 0.001$) (Fig. 3). There was no significant association with year of delivery (coefficient 0.09, 95% CI: −0.16, 0.34, adjusted $R^2 = -1.5\%$, $P = 0.454$, multiplicity adjusted $P = 0.454$). Using a natural cubic spline to assess non-linearity of mean gestational age resulted in insignificant spline terms confirming that a linear term was the most appropriate way to model this variable. We re-ran the meta-analysis stratified by mean gestation age. Among studies with a mean gestational age <28 weeks, the pooled weighted mean difference was 13.9 (95% CI: 11.5–16.2, $P = 0.001$, $I^2 = 66.5\%$). Among studies with a mean gestational age of 28–31 weeks, the pooled weighted mean difference was 11.4 (95% CI: 9.7–13.2, $P = 0.022$, $I^2 = 48.4\%$) and among studies with a mean gestational age of ≥32 weeks it was 8.4 (95% CI: 6.6–10.2, $P = 0.314$, $I^2 = 14.1\%$).

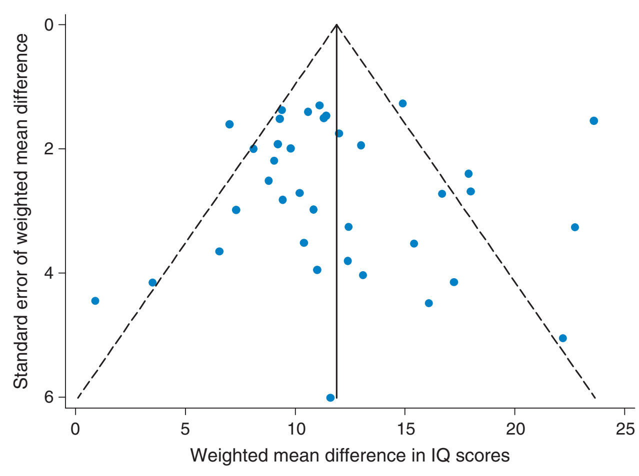

Fig. 2 Funnel plot of the association between preterm delivery and IQ.

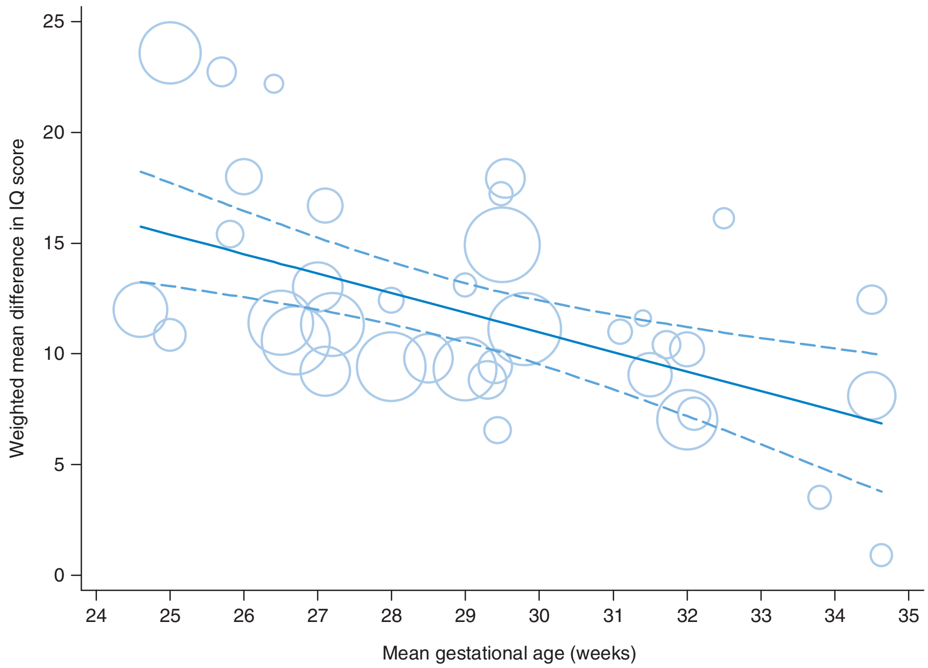

Fig. 3 Bubble-plot of the association between mean gestational age at delivery and IQ. The size of the bubbles is proportional to the weight of studies in the meta-analysis (——, regression line; - - - -, 95% confidence intervals).

Discussion

Main findings of this study

Preterm delivery is associated with a 12-point reduction in IQ score. This effect is sufficient to impact on school performance and educational achievement. Data from the USA suggest that a 10-point reduction in IQ score from the mean score of 100 to 90 equates with an increase in the risk of dropping out of high school from 6 to 35%, and an increase in the risk of living in poverty from 6 to 16%.[41] In our meta-analysis, there was evidence of a linear dose–response relationship, with IQ falling steadily for each 1 week decrease in gestation. As a result of improvements in neonatal care, survival following preterm delivery has increased.[4] However, our study showed that the impact of preterm delivery on IQ has not improved over time.

What is already known on this topic and what this study adds

Bhutta *et al.* published a previous meta-analysis, in 2002, based on the 15 eligible studies available at that time.[7] They showed a significant association between preterm delivery and childhood IQ. Over the past decade, there have been changes in obstetric and neonatal practice that have resulted in increasing numbers of early term, preterm and extreme preterm deliveries and an increase in the proportion of extreme preterm infants who survive to childhood. An additional 12 eligible studies have been published since the previous meta-analysis. Therefore, we felt that it was important to update the meta-analysis to determine whether the strength of association has changed over time. Our finding of a 12-point difference in IQ score is very similar to the 11-point difference reported by Bhutta *et al.*,[7] and year of publication was not a significant predictor of effect size in our study. Therefore, the strength of the association between preterm delivery and childhood IQ has not changed over time with improvements in obstetric and neonatal practice.

Strengths and limitations of this study

Our meta-analysis included all eligible studies published over a 30 year period. Together these measured IQ on over 7000 children. The random-effects method was chosen, in preference to a fixed effect method, because it allows for between-study heterogeneity. Of the 13 studies that reported retention rate,[17,19–21,23–25,27,28,30,36,37,39] only one fell below 70%.[36]

Some published studies used birth weight as a proxy indicator of preterm birth. However, low birth weight may also result from intra-uterine growth restriction. Therefore, our meta-analysis included only studies that reported gestational age. Our meta-analysis used aggregated data from the individual studies. We did not approach investigators for individual level data since some of the studies were published more than 30 years ago. Four studies reported gestational age as only a range, and did not report the mean.[20,28,31,39] The same limitation applied to birthweight.[20,28,31,34] Therefore, we had to use the Scottish distribution of gestational age, or birthweight, in the equivalent year(s) to determine the mean value for the range quoted. There were some variations in the inclusion criteria used by individual studies. Some included all preterm survivors,[14–16,20–25,27–30,33,37,39] whilst others excluded those with major sensory impairments,[13,17–19,26,27,32,34–36,38] and some applied a lower limit for IQ.[27,38] The exclusion of the most severely affected individuals from some studies suggests that our pooled estimate may be an underestimate of the true association between preterm delivery and reduced IQ. As with all observational studies, residual confounding may be present. IQ is influenced by a multitude of factors including parental intelligence, maternal age and socioeconomic status.[42] Individual studies differed in the extent to which they adjusted for these. Some did not adjust for paternal[13,16,18,22,24,27,29–35,37,39] or socioeconomic factors.[14,20,23,25,26,38] Where these were taken into account, preterm delivery remained a significant, independent predictor of IQ[17,21] Similarly, in a meta-regression analysis (results not presented), the results of studies that adjusted for socioeconomic status were not significantly different from those that did not ($P = 0.316$). Demonstration of an association in observational studies does not necessarily infer causality. Nonetheless, a causal relationship between preterm delivery and reduced IQ is biologically plausible. Because brain growth is most rapid at term,[33] preterm infants have significantly less grey and white matter, and demonstrate regional vulnerability.[38]

Implications

The results of the meta-analysis have clinical, public health and educational implications. The evidence of a dose–response relationship suggests that the timing of elective preterm delivery should be carefully considered. Historically, the focus has been on improvements in neonatal care. These efforts have reduced early complications and improved survival, but long-term sequelae have not been addressed. Further emphasis is required on prevention and long-term management. Possible preventative measures include capping the number of embryos transferred during assisted reproduction, smoking cessation interventions for pregnant women, tight control of maternal conditions, such as diabetes, seizures, asthma and hypertension, breast-feeding and a positive parental attitude. In the educational sector, preterm infants may benefit from screening, enabling earlier detection of and support for learning difficulties, and age of entry to school should be adjusted for children born preterm. Finally, we require a better understanding of the underlying mechanisms predisposing to preterm delivery *per se* and to reduced IQ thereafter, and better methods to identify at-risk pregnancies.

Authors' roles

J.P.P. had the original idea. C.O.K.W. and J.P.P. undertook the systematic review. C.O.K.W. and D.F.M. performed the statistical analyses. All authors contributed to interpreting the results. C.O.K.W. and J.P.P. drafted the manuscript. All authors reviewed and revised the manuscript, and approved the final version. J.P.P. is the guarantor.

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