A gradient relationship between low birth weight and IQ: A meta-analysis

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Multiple studies have reported that individuals with low birth weights (LBW, <2500 g) have a lower intelligence quotient (IQ) than those with normal birth weights (NBW, ≥2500 g). Based on 57 eligible individual studies including 12,137 participants, we performed a meta-analysis to estimate the association between low birth weight and individuals’ IQ scores (IQs). The pooled weight mean difference (WMD) in IQs between NBW and LBW individuals was 10 (95% CI 9.26–11.68). The WMD was stable regardless of age. No publication bias was detected. The mean IQs of the extremely low birth weight (ELBW, <1000 g), very low birth weight (VLBW, 1000–1499 g), moderately low birth weight (MLBW, 1500–2499 g) and NBW individuals were 91, 94, 99 and 104, respectively. Additionally, the WMD in IQs with NBW were 14, 10 and 7 for ELBW, VLBW, and MLBW individuals, respectively. Two studies permitted estimates of the influence of social determinants of health to the discrepancy in IQs, which was 13%. Since IQ is inherited and influenced by environmental factors, parental IQs and other factors contribute to residual confounding of the results. As the conclusion was based on population studies, it may not be applicable to a single individual.

Infants with low birth weight (LBW), very low birth weight (VLBW) and extremely low birth weight (ELBW) are considered to be at a high risk of cognitive dysfunction1–3, such as attention deficit4,5, executive function issues6–8 and low average to borderline intelligence quotient (IQ)4,6–8. With the development of perinatal care and neonatal medicine, the survival rates of LBW infants are greatly improved5, followed by an increasing number of LBW individuals with cognitive deficit2,9, which has become a serious public health burden5,10.

Numerous studies have focused on the cognitive outcomes of VLBW individuals in recent decades11. More than 50% of VLBW children required special education services, and approximately 20% of VLBW children repeated at least one grade12. ELBW individuals without major disabilities (mental retardation, cerebral palsy, deafness, or blindness)3 had subtle neurodevelopmental disabilities (language disorders, hyperactivity, behavioural problems, or motor dysfunction, etc.) in the school and teenage years13,14. Evidence from cohort studies in four western countries showed that more than 50% of adolescents with ELBW had learning difficulties (mathematics, writing, reading, or spelling)15,16. The effect of LBW accounted for a 0.4 standard deviation (SD) decrease in math and a 0.25SD decrement in reading17. Those cognitive disadvantages would lead to low school achievements and persist into early adulthood18–21, thus resulting in low socio-economic status (SES) in the future3.

The IQ score (IQs) is often used to indicate individuals’ cognitive outcomes worldwide22. The IQ is relatively stable and can be easily measured23. Additionally, there are some internationally recognized assessment scales which make it possible to compare the IQs in different populations. The consistent finding was that LBW individuals had lower IQs than those with normal birth weights (NBW)24–25. The size of this discrepancy varied across studies, ranging from 3 to 23 points23, and the discrepancy was directly proportional to their birth weight20 (R2 = 0.51; P < 0.001)3. Some studies found that a gradient relationship existed, in which lower birth weight was associated with lower IQs23,25. In other words, the ELBW individuals’ IQs were the lowest, followed by those with
VLBW and moderately low birth weight (MLBW)\(^{27,28}\). However, most of the previous individual studies were based on a small number of participants, so it was necessary to use meta-analysis to enlarge the sample size and assess the gradient relationship.

A recent meta-analysis containing 15 individual studies on the relationship between LBW and IQs in adolescent and early adulthood (age ≥ 13)\(^{29}\) found that LBW individuals scored an average of 8 IQ points lower than NBW individuals. As is already known, there have been more relevant studies focusing on preschool and school-aged children. We integrated those studies into our meta-analysis to identify the age-related change in IQs between LBW and NBW individuals.

Data from the US Centres for Disease Control showed that 45% of babies born preterm were < 2500 g\(^{29}\). Using 27 eligible individual studies published between 1980–2009, Kerr-Wilson et al.\(^{30}\) performed a meta-analysis on preterm delivery and intelligence, which showed that the preterm children had significantly lower IQs compared with term children. The weighted mean difference (WMD) was 12 [95% confidence interval (CI) 10.47–13.42]. The group's analysis included duplicated populations (Caldù\(^{31}\), Narberhaus\(^{32}\), and some control groups were used more than once in the model, which may enlarge the weight of some individual studies. Despite the overlap of LBW and prematurity, they may have different relationships with IQs\(^{29}\). To more specifically reflect on the relationship between LBW and IQs, we performed this meta-analysis on LBW and IQs.

In this meta-analysis, we aimed to use 57 eligible individual studies to estimate the pooled discrepancy in IQs between LBW and NBW individuals and the changes in discrepancy across age. We also used subgroup analysis to assess the gradient relationship with IQs for the different levels of LBW.

**Results**

**Search results.** The search strategy generated a total of 3,124 potentially relevant papers. After reviewing the title and abstract, 2,548 papers were excluded because of irrelevance. Another 281 articles were also excluded because they were reviews (n = 40) or intervention studies (n = 14). Furthermore, 225 studies focusing on relevant factors for LBW and 2 studies in other than English were also excluded. Thus, we reviewed 295 articles with full text. Among them, 238 were excluded because they did not meet the inclusion criteria. The flow chart for exclusion/inclusion of individual studies is presented in Fig. 1.

**Characteristics of included studies.** There were 57 eligible studies published over 36 years based on our search strategies, four of which\(^{13,25,33,34}\) had two pairs of groups in the study population. Therefore, the meta-analysis included 61 study groups with 6,683 LBW individuals and 5,454 NBW comparisons. The participants included both children and adults, with ages ranging from 4 to 26. These studies were performed in 21 countries, including 18 developed countries, where most of the studies were conducted (n = 53). Forty-four studies used different versions of the Wechsler scale to measure IQ. Five studies used the K-ABC (Kaufman Assessment Battery for Children), whereas three used the Stanford-Binet intelligence scale. The MIQS (McCarthy IQ Scale) and BAS (British Ability Scales) were used in other studies. Most studies (n = 50) were cohort studies, and 7 were case-control studies. The descriptive information of the included studies is shown in Table 1.

**Overall analysis.** All studies revealed that the LBW individuals had lower IQs compared with the NBW group. The pooled WMD was 10 (Z = 17.12, P < 0.001), with a 95% CI of 9.26–11.68, which means that the LBW individuals’ IQs were significantly lower than those of the NBW controls (Fig. 2). Between-study heterogeneity was detected ([Q = 298.79 (P < 0.001) and I\(^2\) = 79.9% (P < 0.001)]. The mean IQs of the ELBW, VLBW, LBW and NBW individuals were 91, 94, 99 and 104, respectively. A gradient relationship was observed between birth weight and IQ.

**Sensitivity analysis and publication bias.** After excluding one study at a time, the sensitivity analysis confirmed the significant association between LBW and IQs (with 95% CI ranging from 0.68 to 0.76) (Figure S1). No publication bias was detected (Begg's test: P = 0.49 and Egger's test: P = 0.50). Figure 3 shows a basic funnel plot depicting potential bias.

**Sources of heterogeneity.** We used meta-regression models to probe the source of heterogeneity. The variables included sample size, birth year, age of assessment, and the birth weight of LBW individuals. The model showed that the birth weight of the LBW participants was associated with an IQ difference between NBW and LBW individuals (coefficient = −0.005, adjusted R\(^2\) = 13.22%, P = 0.003). Other variables did not reach the significance level (Table S1). Low birth weight contributed to 30.5% of the heterogeneity after further analysis, with T\(^2\) reduced from 17.10 to 11.88. Figure 4 shows the meta-regression model of the effect of low birth weight on IQ. The results from the Galbraith plot (Figure S2) indicated that two populations (Sereni\(^{14}\), Marlow\(^{14}\)) with the highest WMD may be the main cause of high heterogeneity. After excluding these two studies, the adjusted pooled WMD was 10 (95% CI 9.02–11.03, I\(^2\) = 67.4%, P < 0.01). Approximately 15.6% of the heterogeneity was attributable to these two studies.

**Subgroup analysis.** We performed subgroup analysis to examine whether a gradient relationship existed between different LBW levels and IQs. As shown in Table 2, the WMD was 7 (95% CI 4.76–8.89), 10 (95% CI 8.43–11.28), and 14 (95% CI 11.71–16.20) for MLBW, VLBW and ELBW, respectively (Figures S3–S5). To identify age-related changes in IQs between LBW and NBW individuals, all studies were divided into three groups, i.e., under 10 years, 10–18 years, and over 18 years. The WMD was 11 (95% CI 8.87–12.30), 10 (95% CI 7.88–11.75), and 11 (95% CI 8.42–11.68), respectively. Thus, the discrepancy was stable regardless of age (Table 2; Figure S6). Another subgroup meta-analysis was based on social determinants of health. The LBW and NBW groups were matched by social determinants of health in 39 individual studies, whereas other studies had different social determinant distributions for the two groups. The results showed that the WMDs between NBW and LBW individuals were 10 (95% CI 8.42–11.39) and 11 (95% CI 9.31–13.53) for social determinants between matched...
groups and non-matched groups (Figure S7), respectively. Therefore, approximately 13% of the IQ discrepancy was due to social determinants of health.

**Discussion**

Our study supported the evidence that individuals’ low birth weight had a negative association with IQ4,29. The lower birth weight categories had lower IQs on average. The average IQs of ELBW individuals were the lowest, followed by VLBW individuals and those with MLBW. Specifically, low birth weight individuals had approximately 10–11 points lower IQs than NBW individuals from childhood to adulthood (4–26 in age). There was a gradient relationship between low birth weight and the discrepancy in IQs between LBW and NBW individuals, with the WMDs from large to small being 14 (ELBW), 10 (VLBW), and 7 (MLBW). In addition, social determinants of health were associated with individuals’ IQs, which explained approximately 13% of the IQ difference between LBW and NBW individuals.

The gradient relationship obviously depicted the IQ gap between individuals with different levels of LBW and those with NBW. The M LBW infants were closer to preterm (<37 weeks)29, while the VLBW and ELBW infants tended to be less than 32 weeks in gestational age. Because of the high degree of immaturity of respiratory organs and the nervous system, they were susceptible to bronchopulmonary dysplasia35, neonatal brain injury (cerebral palsy, periventricular leukomalacia, hydrocephalus, hypoxic-ischaemic encephalopathy)9,35–37, and other medical complications, which may result in cognitive impairment. Additionally, children born with low birth weight had less connected and less complex brain networks38, smaller brain volumes39–41, and less cortical surface area42 compared with NBW children. The different degree of neonatal immaturity in LBW infants is considered to be associated with cognitive outcomes34,43.

![Flow chart of meta-analysis for exclusion/inclusion of individual studies. ‘Deficiency of data cited references63–95.](image-url)
| No. | Study | Country | Years of Birth | LBW (n) | Birth Weight (g) | Gestational Age (week) | Measurement Tool | Age at evaluation | IQ Scores | Study Design |
|-----|-------|---------|---------------|---------|-----------------|----------------------|-----------------|------------------|-----------|--------------|
|     | Yi KH et al. 96, 2016 | Korea | 2003–2009 | L 46 | 2110(315) | ≥37 | WISC-III | 12 | 100.52(15.24) | case-control study |
|     | Serenius et al. 98, 2016 | Sweden | 2004–2007 | L 37 | 779(170) | 25.41(0.7) | WISC-IV | 6.5 | 83.4(14.8) | cohort study |
|     | Breeman et al. 99, 2015 | Germany | 1985–1986 | L3 216 | 131(320) | <32 | WISC-III | 26 | 86.2(20.25) | cohort study |
|     | Molloy et al. 100, 2014 | Australia | 1994–1995 | L 22 | 88(161) | 26.6(2.0) | WASI | 18 | 95.18 (16.33) | cohort study |
|     | Ritter et al. 101, 2014 | Switzerland | 1998–2003 | L 5 | <1500 | <32 | WISC (HAWIK-IV) | 10 | 109.28(77.7) | cohort study |
|     | Guarini et al. 102, 2014 | Italy | 1998–2001 | LI 6 | 1155(331) | 29.8(2.3) | K-BIT | 6 | 93.4(10.5) | case-control study |
|     | McNicholas et al. 103, 2013 | Ireland | 1995–1997 | L 52 | 1172(219) | 29.9(2.8) | WISC-IV | 11 | 89.7(12.5) | cohort study |
|     | Cheong et al. 104, 2013 | Australia | 1991–1992 | L 148 | 897(177) | 25.8(1.1) | WASI | 18 | 95.7(15.9) | cohort study |
|     | Hutchinson et al. 105, 2013 | Australia | 1997 | L 189 | 833(164) | 26.5(2.0) | WISC-IV | 8 | 93.9(16.1) | cohort study |
|     | Lundequist et al. 106, 2013 | Sweden | 1988–1993 | L 145 | 1050(266) | 28.1(2.8) | WPPSI-R | 5 | 95.7(16.1) | case-control study |
|     | Aarnoudse-Moens et al. 107, 2013 | Netherlands | 1996–2004 | L 200 | 1013(287) | 28.1(4.4) | WISC-III | 8 | 93.3(15.8) | cohort study |
|     | Munck et al. 108, 2012 | Finland | 2001–2006 | L 124 | 1061(260) | 28.7(2.8) | WPPSI-R | 5 | 99.3(17.7) | cohort study |
|     | Pyhala et al. 109, 2011 | Finland | 1978–1985 | L 103 | 1140(217) | 29.3(2.3) | WAIS-III | 25 | 102.2(15.3) | case-control study |
|     | Potharst et al. 110, 2011 | Netherlands | 2002–2004 | L 104 | 1045(254) | 28.7(1.6) | WPPSI | 5 | 92(17) | cohort study |
|     | Ni et al. 111, 2011 | China | 2002–2003 | L 27 | 1158(266) | 29.5(2.8) | WISC-IV | 6 | 100.1(10.7) | cohort study |
|     | Lohaugen et al. 112, 2010 | Norway | 1986–1988 | L 55 | 1217(233) | 29.1(2.5) | WAIS-III | 19 | 88(13) | cohort study |
|     | Soria-Pastor et al. 113, 2009 | Spain | 1996–1998 | L 20 | 1794 | 30–34 | WISC-IV | 9 | 105.8(13.8) | case-control study |
|     | Aarnoudse-Moens et al. 114, 2009 | Netherlands | 1998–2000 | L 50 | 1042(31) | 28.0(4.1) | WPPSI-R | 6 | 92.5(17.5) | case-control study |
|     | Woodward et al. 115, 2009 | New Zealand | 1998–2000 | L 14 | 807(233) | <28 | WPPSI-R | 4 | 93.86(17.57) | cohort study |
|     | Mu et al. 116, 2008 | China | 1995–1997 | L 130 | 1163(238) | 29.5(2.7) | WISC-III | 8 | 93.14(16.33) | case-control study |
|     | Gaddlin et al. 117, 2008 | Sweden | 1987–1988 | L 59 | 1214(212) | 30.7(2.4) | WISC-III | 15 | 84.9(17.5) | cohort study |
|     | Allin et al. 118, 2008 | UK | 1982–1984 | L 94 | <2500 | <33 | WASI | 19 | 96.6(13.7) | cohort study |
|     | Lauvalainen et al. 119, 2007 | Finland | 1984–1986 | L 35 | 1440(440) | 30(2) | WISC-R | 9 | 96.3(11.3) | cohort study |
|     | Nosarti et al. 120, 2007 | UK | 1979–1982 | L 61 | 1296(295) | 29.5(1.8) | WASI | 22 | 103.14(11.99) | cohort study |
| No. | Study | Country | Years of Birth | LBW(n) | Birth Weight (g) | Gestational Age (week) | Measurement Tool | Age at evaluation | IQ Scores | Study Design |
|-----|-------|---------|----------------|---------|-----------------|-----------------------|-----------------|------------------|-----------|--------------|
| 25  | Narberhaus et al.\(^\text{13}\), 2007 | Spain | 1983–1994 | L1 9 | 899 | 26.4 | WISC-R or WAI-S-III | 14 | 91.4(14.4) | case-control study |
| 26  | Hoff et al.\(^\text{107}\), 2006 | Denmark | 1994–1995 | L 191 | 922(167) | 27.5(1.8) | WPPSI-R | 5 | 96.4(14.1) | cohort study |
| 27  | Martinez-Cruz et al.\(^\text{17}\), 2006 | Mexico | 1997 | L1 25 | 875(107) | 31.4(1.7) | Stanford-Binet | 6 | 95.3(1.3) | case-control study |
| 28  | Hack et al.\(^\text{28}\), 2005 | USA | 1992–1995 | L 219 | 810(124) | 26.4(2) | K-ABC | 8 | 87.8(18) | cohort study |
| 29  | Lefebvre et al.\(^\text{23}\), 2005 | France | 1976–1981 | L 69 | 912(79) | 28.5(2.4) | WAIS | 18 | 94(12) | cohort study |
| 30  | Marlow et al.\(^\text{22}\), 2005 | UK | 1995 | L1 243 | <2500 | <26 | K-ABC | 6 | 82(19.2) | cohort study |
| 31  | Kilbride et al.\(^\text{28}\), 2004 | USA | 1983–1990 | L 25 | 702(76) | 26.0(1.6) | Stanford-Binet | 4 | 95(11) | cohort study |
| 32  | Short et al.\(^\text{18}\), 2003 | USA | 1989–1991 | L 75 | 1256(176) | 30.2(2) | WISC-III | 8 | 91.7(16) | cohort study |
| 33  | Cooke et al.\(^\text{16}\), 2003 | UK | 1991–1992 | L 268 | 1467 | 29.8 | WISC-III | 7 | 89.4(14.2) | cohort study |
| 34  | Grunau et al.\(^\text{11}\), 2002 | Canada | 1982–1987 | L 74 | 718(480–800) | 26.0(23–33) | WISC-R | 9 | 99.3(10.9) | cohort study |
| 35  | Magill-Evans et al.\(^\text{11}\), 2002 | Canada | NA | L 20 | 2104 | <37 | WISC-III | 10 | 98(14.9) | cohort study |
| 36  | Breslau et al.\(^\text{23}\), 2001 | USA | 1983–1985 | L1 231 | <2500 | <26 | WISC-III | 11 | 90.7(14) | cohort study |
| 37  | Rickards et al.\(^\text{23}\), 2001 | Australia | 1980–1982 | L 120 | 1167(215) | 29.3(2.0) | WISC-R | 14 | 96.2(15.5) | cohort study |
| 38  | Nadeau et al.\(^\text{14}\), 2001 | Canada | 1987–1990 | L 61 | 1024(204) | 27.4(1.1) | MHSQ | 5 | 100(19.1) | cohort study |
| 39  | Taylor et al.\(^\text{13}\), 2000 | USA | 1982–1986 | L 61 | 665(68) | 25.7(1.8) | RABC | 11 | 83.49(19.7) | cohort study |
| 40  | Tandon et al.\(^\text{13}\), 2000 | India | 1985–1995 | L1 60 | 1175(217) | 29.4(2.4) | Stanford-Binet | 8 | 105.6(13.4) | cohort study |
| 41  | Saigal et al.\(^\text{12}\), 2000 | Canada | 1977–1982 | L 150 | 833(126) | 27.2(2.4) | WISC-R | 14 | 89(19) | cohort study |
| 42  | Hughes et al.\(^\text{12}\), 1999 | USA | 1979–1981 | L1 95 | 964(208) | 28.5(2.1) | WISC-R | 9 | 86.16(17.67) | cohort study |
| 43  | Stjernqvist et al.\(^\text{14}\), 1999 | Sweden | 1985–1986 | L 61 | 1042(242) | 27.1(1.03) | Stanford-Binet | 10 | 89.8(15.1) | cohort study |
| 44  | Botting et al.\(^\text{13}\), 1998 | UK | 1980–1983 | L 138 | <1500 | NA | WISC-III | 12 | 89.7(17.2) | cohort study |
| 45  | Whitlefield et al.\(^\text{10}\), 1997 | Canada | 1974–1985 | L 90 | 731(520–800) | 26.23–28 | WISC-R | 9 | 89.7(12.6) | cohort study |
| 46  | Rose et al.\(^\text{13}\), 1996 | USA | 1979–1981 | L 50 | 1154(233) | 31.2(1.8) | WISC-R | 11 | 89(6.13) | cohort study |
| 47  | Sommerfelt et al.\(^\text{13}\), 1995 | Norway | 1986–1988 | L 144 | 1555(368) | 32(5) | WPPSI-R | 5 | 97(14) | cohort study |
We also found a stable difference in IQs between LBW individuals and NBW individuals. The discrepancy was approximately 10–11 points regardless of the age of assessment. This finding was inconsistent with previous reports that showed that the discrepancy would decrease over time. Some LBW individuals may have cognitive catch-up growth, but it is not a universal rule among those with LBW. A long-term follow-up study on a population sample aged from 3 months to 26 years showed that the IQs were more stable in very preterm (VP)/VLBW individuals than in term-born individuals across all time points. However, this conclusion was based on the entire LBW group and may not be applicable to a single individual.

Social determinants of health, such as social class, parental/maternal education and occupation, marital status, etc., are known to contribute to suboptimal cognitive development of LBW children. Previous studies have indicated that LBW continues to be associated with cognitive disadvantage at each SES level and that the risk of impaired cognitive development increases with decreasing SES. A study by Sommerfelt et al. reported that 23% of the variance in child’s IQ at age 5 could be attributed to parental and family variables in Norway.

Our results showed that social determinants of health explained approximately 13% of the lower IQ values. Because of the diversity of social determinants in different societies and the variations in study design, the common practice of simply matching social determinants of health (social class, occupation, parental/maternal education) may result in an underestimation of cognitive impairment caused by social determinants of health or other similar risk factors.

Intelligence is a product of genetic and environmental variables. Genetic variation is the main cause of individual differences in IQ. Previous studies have reported that the “heritability” (h²) for IQ ranges from 20% in infancy, to 40–50% by late adolescence and to 60–80% in adulthood. Environmental factors, such as perinatal factors, schooling, family environment, nutrition and so on also contribute to individuals’ IQs. The aetiology of LBW individuals’ lower IQs is complex and unclear. Various adversities occur among LBW infants, such as preterm birth, the stress of intensive care and more frequent morbidities, which may also affect individuals’ IQs. It may be that low birth weight is an event along this causal pathway. However, two cohort studies from Denmark and Estonia demonstrated the associations between birth weight and IQs, and the associations remained significant after controlling for a wide range of confounders. These correlations were modest, ranging from 0.05 to 0.13.

As poor cognitive outcomes may be related to lower school achievements, inferior SES, an unhealthy lifestyle, and even some chronic diseases, improving the cognitive outcome of LBW infants is essential and urgent. Previous evidence showed that the LBW individuals can benefit from early interventions for cognitive outcomes. Some randomized controlled trials, such as the Newborn Individualized Developmental Care...
Figure 2. Random-effect analysis of the association between low birth weight and IQs. WMD: weight mean difference; CI: confidence interval.

Table 1. Study characteristics

| Study                 | WMD (95% CI) | % Weight |
|-----------------------|--------------|----------|
| Yi et al. (2016)      | 0.00 (0.00, 0.00) | 1.00     |
| Seres et al. (2018)   | 1.00 (1.00, 1.00) | 2.00     |
| Bremer et al. (2015)  | 2.00 (2.00, 2.00) | 3.00     |
| Molly et al. (2014)   | 3.00 (3.00, 3.00) | 4.00     |
| Ritter et al. (2014)  | 4.00 (4.00, 4.00) | 5.00     |
| Guernsey et al. (2014)| 5.00 (5.00, 5.00) | 6.00     |
| Guernsey et al. (2014)| 6.00 (6.00, 6.00) | 7.00     |
| Mcanhuijzen et al. (2013)| 7.00 (7.00, 7.00) | 8.00     |
| Cheong et al. (2013)  | 8.00 (8.00, 8.00) | 9.00     |
| Hutcheson et al. (2013)| 9.00 (9.00, 9.00) | 10.0      |
| Lundequist et al. (2013)| 10.0 (10.0, 10.0) | 11.0     |
| Aarnouw et al. (2013) | 11.0 (11.0, 11.0) | 12.0     |
| Munck et al. (2012)   | 12.0 (12.0, 12.0) | 13.0     |
| Pyhala et al. (2011)  | 13.0 (13.0, 13.0) | 14.0     |
| Pothdar et al. (2011) | 14.0 (14.0, 14.0) | 15.0     |
| Ni et al. (2011)      | 15.0 (15.0, 15.0) | 16.0     |
| L’Heuguet et al. (2010)| 16.0 (16.0, 16.0) | 17.0     |
| Sorin et al. (2009)   | 17.0 (17.0, 17.0) | 18.0     |
| Aarnouw et al. (2009) | 18.0 (18.0, 18.0) | 19.0     |
| Woodward et al. (2009)| 19.0 (19.0, 19.0) | 20.0     |
| Mu et al. (2008)      | 20.0 (20.0, 20.0) | 21.0     |
| Gaddin et al. (2008)  | 21.0 (21.0, 21.0) | 22.0     |
| Gaddin et al. (2008)  | 22.0 (22.0, 22.0) | 23.0     |
| Ali et al. (2008)     | 23.0 (23.0, 23.0) | 24.0     |
| Savelainen et al. (2007)| 24.0 (24.0, 24.0) | 25.0     |
| Nosari et al. (2007)  | 25.0 (25.0, 25.0) | 26.0     |
| Narberhaus et al. (2007)| 26.0 (26.0, 26.0) | 27.0     |
| Hoff et al. (2007)    | 27.0 (27.0, 27.0) | 28.0     |
| Martinez-Cruz et al. (2006)| 28.0 (28.0, 28.0) | 29.0     |
| Haris et al. (2005)   | 29.0 (29.0, 29.0) | 30.0     |
| Lefort et al. (2005)  | 30.0 (30.0, 30.0) | 31.0     |
| Marlowe et al. (2005) | 31.0 (31.0, 31.0) | 32.0     |
| Kline et al. (2004)   | 32.0 (32.0, 32.0) | 33.0     |
| Short et al. (2003)   | 33.0 (33.0, 33.0) | 34.0     |
| Cooke et al. (2003)   | 34.0 (34.0, 34.0) | 35.0     |
| Gnau et al. (2002)    | 35.0 (35.0, 35.0) | 36.0     |
| Magill-Evans et al. (2002)| 36.0 (36.0, 36.0) | 37.0     |
| Breed et al. (2001)   | 37.0 (37.0, 37.0) | 38.0     |
| Beslau et al. (2001)  | 38.0 (38.0, 38.0) | 39.0     |
| Richards et al. (2001)| 39.0 (39.0, 39.0) | 40.0     |
| Nadeau et al. (2001)  | 40.0 (40.0, 40.0) | 41.0     |
| Taylor et al. (2000)  | 41.0 (41.0, 41.0) | 42.0     |
| Tardoo et al. (2000)  | 42.0 (42.0, 42.0) | 43.0     |
| Saigal et al. (2000)  | 43.0 (43.0, 43.0) | 44.0     |
| Hughes et al. (1999)  | 44.0 (44.0, 44.0) | 45.0     |
| Sjørensen et al. (1999)| 45.0 (45.0, 45.0) | 46.0     |
| Bolding et al. (1998) | 46.0 (46.0, 46.0) | 47.0     |
| Whitfield et al. (1979)| 47.0 (47.0, 47.0) | 48.0     |
| Ross et al. (1998)    | 48.0 (48.0, 48.0) | 49.0     |
| Sommerfell (2015)     | 49.0 (49.0, 49.0) | 50.0     |
| Levy-Strab (1994)     | 50.0 (50.0, 50.0) | 51.0     |
| Sommerfell (1993)     | 51.0 (51.0, 51.0) | 52.0     |
| Hack et al. (1992)    | 52.0 (52.0, 52.0) | 53.0     |
| Tepf et al. (1991)    | 53.0 (53.0, 53.0) | 54.0     |
| Smith et al. (1990)   | 54.0 (54.0, 54.0) | 55.0     |
| McDonald et al. (1989)| 55.0 (55.0, 55.0) | 56.0     |
| Klein et al. (1999)   | 56.0 (56.0, 56.0) | 57.0     |
| Portnoy et al. (1988) | 57.0 (57.0, 57.0) | 58.0     |
| Lloyd et al. (1988)   | 58.0 (58.0, 58.0) | 59.0     |
| Knip et al. (1980)    | 59.0 (59.0, 59.0) | 60.0     |
| Overall               | 60.0 (60.0, 60.0) | 61.0     |

NOTE: Weights are from random-effects analysis.

Figure 3. Begg’s funnel plot of individual studies included in the analysis according to random-effect WMD estimates.
and Assessment Program (NIDCAP)\(^57\) and a sensitizing parental intervention programme\(^58\), showed that breastfeeding\(^59\) and kangaroo care had beneficial effects on LBW infants’ cognitive outcomes. It is recommended to assess the cognitive ability of LBW individuals first in order to determine the need for interventions. Periodic cognitive assessment of LBW children can evaluate the intervention’s effectiveness, thus providing more accurate interventions for each individual\(^60\). The cognitive benefits from early intervention may persist into preschool age or adolescence\(^58\). Therefore, long-term interventions may play a role in the long run. Although there were few long-term intervention programmes reported, it is necessary for child care centres and parents to offer long-term neuropsychological rehabilitation to LBW individuals even if they do not suffer from severe cognitive disabilities.

**Strengths and limitations.**  
*Strengths.* Compared with previous meta-analyses of LBW/preterm individuals’ IQs, we included more eligible and recent individual studies, with a total of 12,137 participants and without a duplicated study population. We conducted subgroup analyses to show the gradient in the IQ gap between individuals with different levels of LBW and those with NBW, as well as the stability of the difference in IQs between LBW and NBW individuals. Although the selected studies used different cognitive tests to measure individuals’ IQs, each test/scale had similar normative data (mean = 100; SD = 15), which made the results from different studies comparable.

*Limitations.* We tried to include all relevant studies, but some studies may be missed in this meta-analysis due to our search strategies or incomplete databases. Additionally, grey literature publications were not included. However, the large sample size of this study made the results more stable and credible.

According to individual studies, parental/maternal education was either a variable of socio-economic status or an independent social determinant. Three individual studies only matched by parental/maternal education were also included in the social determinant-matched group. Since there is not a perfect fit between education and socio-economic status, residual confounding may exist in the subgroup analysis based on social determinants of health.

IQ is a complex trait that is influenced by genetic and environmental factors, such as parental IQs\(^17,45\), medical complications\(^61\), early home environment, schooling, and so on\(^36,60,62\). We didn’t take this residual confounding...
into account. These factors may also contribute to the heterogeneity. The association between these factors and LBW IQs will be explored in a further study.

Methods

Literature and search strategy. We searched the PubMed and the Embase databases for full-text articles in English published between January 1980 and November 2016. The following terms were used to perform the literature search: “low birth weight” or “preterm” or “premature”, and “intelligent quotient” or “IQ” or “cognition” or “neurodevelopmental” or “mental” or “psychological” or “outcome”.

Inclusion criteria. Each study should meet all of the inclusion criteria.

1) Participants with LBW (< 2500 g) were compared with those with NBW (≥ 2500 g).
2) The individuals’ ages were ≥ 4 years.
3) Full-scale IQ was measured by a standardized and global scale with the mean and standard deviation of the IQs listed.
4) Full-text articles were available from the two databases.

We excluded reviews, studies of the non-LBW group, and those without NBW individuals as a control group. If more than one study was based on the same cohort, only the study with the larger sample was included in the meta-analysis. When the study had two or more LBW groups, we calculated the weighted mean and deviation to represent the LBW individuals’ IQs in the meta-analysis (Figure S8). For the subgroup analysis, we used the raw data from each study.

Data extraction. The following information was extracted from each study:

1) first author’s name; (2) year of publication; (3) country of origin; (4) birth year of the participants; (5) size of study population; (6) birth weight; (7) gestational age; (8) measurement tools; (9) age at assessment; and (10) mean and standard deviation of the IQs.

Statistical analysis. A random-effects meta-analysis was performed using the WMD in IQs between LBW and NBW individuals. The significance of the WMD was determined using a Z test (P < 0.05) was statistically significant. To assess the heterogeneity, we consulted the Cochrane Q test and I^2 statistics. Publication bias was assessed by Begg’s test and Egger’s test. We also used a funnel plot to depict the potential publication bias.

We constructed meta-regression models and a Galbraith radial plot to probe the source of heterogeneity.

The subgroup analysis was conducted based on birth weight, age at assessment and social determinants of health. In the first subgroup analysis, we divided the studies into three subgroups according to the LBW participants’ birth weight, i.e., moderately low birth weight (MLBW, 1500–2499 g), very low birth weight (VLBW, 1000–1499 g) and extremely low birth weight (ELBW, <1000 g). Then, we grouped individual studies into three groups by the subjects’ age at assessment (under 10 years, 10 to 18 years, 18 years or older) in the second subgroup analysis. Because social determinants of health are associated with individuals’ IQs, we compared the social determinant-matched group with the social determinant-unmatched group to evaluate how much of the lower IQ values were due to social determinants of health. All analyses were conducted using STATA version 11 (StataCorp LP, College Station, Texas, USA).

Conclusion

Individuals with LBW had lower IQs compared to those with NBW, and the discrepancy was approximately 10–11 points from childhood to adulthood (4–26 in age). We also demonstrated a gradient relationship between different levels of LBW and IQs. The social determinants of health explained approximately 13% of the IQ difference. These findings contribute to our understanding of the association between LBW and IQs. Our results will help physicians and parents to pay more attention to regular cognitive assessment and early intervention, as well as to long-term neuropsychological rehabilitation for LBW infants.

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Acknowledgements
This research was supported by National Natural Science Foundation of China (81673194) to S.R. and Project from Health and Family Planning Commission of Hubei Province (WJ2015MB019).

Author Contributions
G.H. and S.R. designed the research; G.H and W.L. wrote the paper; G.H., W.L., L.L., H.E., L.X., W.J., M.H., and D. P. reviewed and extracted data from eligible studies; Z.J. and W.L. performed the statistical analysis; L.J. and L.G. prepared the tables and figures. All authors have reviewed and approved the manuscript as submitted.
Additional Information
Supplementary information accompanies this paper at https://doi.org/10.1038/s41598-017-18234-9.

Competing Interests: The authors declare that they have no competing interests.

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