## Child Health

# The cognitive development from childhood to adolescence of low birthweight children born after medically assisted reproduction—a UK longitudinal cohort study

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## Abstract

**Background**: Previous research has documented that children conceived through medically assisted reproduction (MAR) are at increased risk of poor birth outcomes, such as low birthweight (LBW), which are risk factors for stunted longer-term cognitive development. However, parents who undergo MAR to conceive have, on average, advantaged socioeconomic backgrounds which could compensate for the negative effects of being born LBW. Previous studies have not analysed whether the negative effects of LBW are attenuated among MAR conceived children.

**Methods**: We draw on the UK Millennium Cohort Study (sweeps 1–6) which contains a sub-sample of ($N = 396$) MAR-conceived children. The dependent variable measures cognitive ability at around ages 3, 5, 7, 11 and 14. We examine the cognitive development of four groups of children: MAR-conceived low birthweight (MAR LBW); MAR-conceived non-low birthweight (MAR NLBW); naturally conceived low birthweight (NC LBW); naturally conceived non-low birthweight (NC NLBW). We estimate the two following linear regression models for each sweep: (i) a baseline model to examine the unadjusted association between cognitive development and low birthweight by mode of conception; and (ii) a model adjusted by socio-demographic family characteristics.

**Results**: In baseline models, MAR LBW children [age 3: $\beta = 0.021$, 95% confidence interval (CI): -0.198, 0.241; age 5: $\beta = 0.21$, 95% CI: 0.009, 0.418; age 7: $\beta = 0.163$, 95% CI: -0.148, 0.474; age 11: $\beta = 0.003$, 95% CI: -0.318, 0.325; age 14: $\beta = 0.156$, 95% CI: -0.205, 0.517], on average perform similarly in cognitive ability relative to NC NLBW at all ages, and display higher cognitive scores than NC LBW children until age 7. When we account for family characteristics, differences are largely attenuated and become close to zero at age 14.

**Conclusions:** Despite the higher incidence of LBW among MAR compared with NC children, they do not seem to experience any disadvantage in their cognitive development compared with naturally conceived children. This finding is likely explained by the fact that, on average, MAR children are born to socioeconomically advantaged parents.

**Key words:** Medically assisted reproduction, low birthweight, LBW, cognitive development, UK cohort study

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**Key Messages**

- We investigate the cognitive development of children conceived through medically assisted reproduction (MAR) who are born low birthweight (LBW), compared with naturally conceived (NC) children who are born LBW and non-LBW (NLBW), from early infancy to mid-adolescence.
- MAR LBW children, on average, perform similarly in cognitive development compared with NC NLBW children, and display higher cognitive scores compared with NC LBW children up to age 7.
- When family characteristics are accounted for, we find that differences are largely attenuated and become close to zero at age 14.
- MAR LBW children do not show any disadvantage in cognitive development compared with NC NLBW children, and family characteristics and resources may play a crucial role in hampering the effect of being born LBW.

## Introduction

In Europe, the proportion of children born through medically assisted reproduction (MAR) nearly doubled during the first decade of the new millennium.[1] Denmark has been a forerunner in this trend, with 9% of births being conceived through MAR in 2018.[2] Other countries have also witnessed a remarkable increase in the number of children born after MAR. In the UK for example, the Human Fertilization and Embryology Authority reported that a total of 1238 MAR-conceived babies were born in 1991, 9423 in 2001 and 19 728 in 2018. The rapid increase in MAR conceptions and births over time has motivated research about its consequences for children's well-being, in terms of both health at birth and later cognitive development.[3,4]

There is a large body of research showing that MAR children are at higher risk of experiencing adverse birth outcomes as compared with naturally conceived (NC) counterparts.[5–7] MAR children are four times more likely to be born low birthweight (LBW) and three times more likely to be born premature.[4] The mechanisms linking MAR to poor birth outcomes are not fully understood. Parental characteristics such as sub-fertility and advanced maternal age are factors that may lead parents to conceive using MAR, and they are considered risk factors for poor birth outcomes.[6,8] At the same time, MAR techniques increase the chance of multiple births, which is also associated with poor birth outcomes[9]. However, the difference in birth outcomes is only partially explained by the higher share of multiple birth among MAR-conceived children,[9] as singleton births also experience higher risks of adverse birth outcomes.[4] Overall, this evidence raises concerns regarding the longer-term cognitive development of MAR children, as poor birth outcomes such as low birthweight are linked to children's future cognitive development[10–14] through a number of biological mechanisms such as brain damage and hampered brain growth.[15,16]

Generally, studies show that MAR-conceived children perform better or similarly to naturally conceived children in terms of cognitive development.[3,17–19] To date, however, no studies have examined how specifically MAR children born with low birthweight (LBW) fare relative to their peers. This is an important research gap, given the large share of MAR-conceived children experiencing poor birth outcomes, which are determinants of long-term health and socioeconomic well-being.[12,13,20] We hypothesize that MAR children, regardless of whether they are born with poor birth outcomes, are advantaged relative to their naturally conceived peers. This may occur since parents who undergo MAR to conceive have, on average, a higher socioeconomic status (SES), which translates into higher cognitive scores among their children.[21,22] In addition, there is evidence that poor birth outcomes are less salient in advantaged families as they have more resources to invest in their children, which may compensate for the initial health disadvantage.[10,23]

This study has two aims. First, we compare cognitive development across early infancy and mid-adolescence in

four groups of children: MAR-conceived low birthweight (MAR LBW); MAR-conceived non-low birthweight (MAR NLBW); naturally conceived (NC) low birthweight (NC LBW); and naturally conceived non-low birthweight (NC NLBW). Although our focus is particularly to compare MAR LBW children with NC children (both LBW and NLBW), we also include MAR NLBW as we aim to provide a comprehensive perspective on children's cognitive development based on their mode of conception and birthweight status. Second, we investigate whether family characteristics play a role in explaining these differences. We draw on the UK Millennium Cohort Study (sweeps 1–6), which includes a sub-sample of MAR-conceived and naturally conceived children and detailed information on both their cognitive development and family sociodemographic characteristics.

## Methods

### Sample description

We use data from the Millennium Cohort Study (MCS), which is a longitudinal cohort study following a sample of about 19 000 children born between 2000 and 2002 in England, Wales, Scotland and Northern Ireland. The first interview was conducted when the children were approximately 9 months old. Follow-up interviews were conducted in 2003, 2005, 2007, 2012 and 2015 when the cohort members were around 3, 5, 7, 11 and 14 years old. The sample of the MCS is randomly selected at the electoral ward level, and it is stratified to ensure representation of disadvantaged groups. Given the complex sample design, in the analyses we use weights to account for the over-representation of participants from ethnically diverse and disadvantaged areas. In the analyses, we use data from sweeps 1–6.

The analytical sample includes all the singletons and twins with valid information on the variables of interest at each sweep in which the outcome is measured (2–6). We drop the triplets ($N = 30$ in 10 families). These inclusion criteria leads us to exclude 6.58% ($N = 966$) of cases at age 3; 2% ($N = 289$) of cases at age 5; 3.46% ($N = 455$) at age 7; 2.39% ($N = 302$) at age 11; and 8.2% ($N = 913$) at age 14. The final analytical samples consist of: $N = 13\ 716$ observation at age 3; $N = 14\ 175$ at age 5; $N = 12\ 714$ observations at age 7; $N = 12\ 336$ at age 11; and $N = 10\ 220$ at age 14. We do not find any systematic association between our key independent variables (MAR-conceived and LBW) and the risk of not being included in the sample (see Supplementary Figure 1, available as Supplementary data at *IJE* online). We find limited evidence, however, that the analytical sample is positively selected since having a non-White or non-university educated mother slightly increases the chance of not being included at each sweep. Yet, we do not find any evidence that MAR children born from low-educated mothers are more likely to not be included. Thus, only NC children may be positively selected.

### Variables

The outcome variable is children's verbal cognitive ability assessed with the British Ability Scales (BAS II). The British Ability Scales II (BAS II) is a battery of twelve core sub-tests of cognitive ability and educational achievement[24] and has demonstrated construct validity as a measure of cognitive ability[24,25] and high test-retest reliability.[25] Earlier work has found that BAS scores are associated with later educational attainment.[26] One of the advantages of the BAS II is its flexibility, since the core sub-tests of the battery are individually interpretable. In order to assess a child's level of performance, the child need not complete all of the tests in the battery.[25] The BAS II is therefore particularly suitable for the collection of data in a survey setting where the time is limited; the MCS cohort members have only completed a sub-set of the BAS II sub-tests.[27] Moreover, another main advantage is that children are presented with the test items that are most suitable for their age and ability, excluding items which are likely to be either too easy or too difficult. This works well in the MCS, where there is variation in children's ages at the time of interview (sometimes even several months). The raw scores are then converted into ability scores which take into account the specific set of items the cohort members were presented with.[27] At ages 3 and 5, children are assessed with the *naming vocabulary* scale; at age 7 with a *word reading* test; at age 11 with a *verbal similarity* test; and at age 14 with a *word activity* score. The scores are standardized (to a mean of 0 and a standard deviation of 1) and age-adjusted within each sweep (since there is variation in cohort members' age within each sweep).

We have two key independent variables: (i) mode of conception (MAR or NC); and (ii) whether the child was born LBW. First, we define a child as conceived with MAR if the mother underwent one of the following treatments to conceive: *in vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI), intrauterine insemination, or ovulation induction. The sample of MAR children consists of $N = 396$ children at age 3 and it reduces, because of attrition, to $N = 296$ at 14 years old. Despite the reduction of cases, the share of LBW children remains consistent across waves for both NC and MAR children (Supplementary Table 1, available as Supplementary data at *IJE* online). Second, following common practice in the literature, we

define LBW as birthweight less than 2500 g.[28] From this, we define four groups of children: MAR-conceived low birthweight (MAR LBW); MAR-conceived non-low birthweight (MAR NLBW); naturally conceived (NC) low birthweight (NC LBW); and NC non-low birthweight (NC NLBW).

We adjust the analyses for a series of confounders. As a measure of socioeconomic background, we use the level of education of the mother when the child was 6 months old. The variable is dichotomized between mothers with at least a university education (higher SES) and those with less than a university education (lower SES). We also conduct two sensitivity analyses: first, we replicated analyses using a detailed measure of maternal education; second, we used the highest occupational level among the parents (white collar vs others) measured with the National Statistics Socioeconomic Classification (NS-SEC), and results are consistent (see Supplementary Tables 2 and 3, available as Supplementary data at *IJE* online). As child characteristics, we adjust for sex, birth order (firstborn or higher) and twin births. As family characteristics, we adjust for maternal age at birth (continuous)[8,29]; marital status at birth (cohabiting/married and single); whether the mother accessed antenatal care before the 12th week of gestation; whether the mother is from an ethnic minority (White and non-White); and whether the mother smoked during pregnancy.[30,31]

## Statistical models

We estimate two linear regression models at each sweep, which were collected at around ages 3, 5, 7, 11 and 14 years. First, we estimate baseline models predicting cognitive ability at each age for each of the four groups mentioned above, including only controls for sex and twin birth. Second, we estimate models adjusting for maternal education, birth order, maternal age, maternal marital status, timing of the first prenatal visit, maternal minority group and whether the mother smoked during pregnancy. All analyses were conducted using Stata Statistical Software: Release 16 (StataCorp LP, College Station, TX).

## Results

### Descriptive results

Table 1 presents the descriptive statistics of the analytical sample at age 3, for all births and by mode of conception. In the total analytical sample, 2.9% of the children are MAR-conceived. We find that—consistent with the existing evidence—the prevalence of LBW varies considerably by mode of conception; more than one-fifth (21.9%) of

MAR-conceived children are LBW, whereas LBW is about 6% among NC children.

There are also differences in children's characteristics by mode of conception. Among MAR-conceived children, 66% are firstborn as compared with 41% among NC children. Most notably, 23% of MAR-conceived children are born in a multiple birth, whereas the corresponding figure is only 2% of natural conceptions.

Family attributes also differ by mode of conception. Mothers who underwent MAR are on average almost 4 years older than mothers who conceived naturally. They are also more likely to be married or cohabit (98%) compared with NC mothers (85%). MAR mothers are also more likely to have a university degree compared with NC mothers, 45% and 33%, respectively. MAR mothers are also more likely to be White than NC mothers, a difference of about 5% age points. There are also differences in health behaviours, with MAR mothers being less likely to smoke during pregnancy and likely to access antenatal care earlier compared with mothers of NC children.

### Regression analyses

Table 2 shows the standardized regression coefficients [and 95% confidence intervals (CIs)] by mode of conception (MAR or NC) and weight status at birth (LBW or NLBW). The reference category is naturally conceived children born non-low birthweight (NC NLBW). The full model results are presented in Supplementary Tables 4 and 5, available as Supplementary data at *IJE* online. Figure 1 reports the predicted cognitive scores for the four groups.

Panel A of Figure 1 reports coefficients estimates from the baseline (or unadjusted) models, which include controls for the cohort members' sex and multiple birth (Figure 1, left panel). MAR LBW children show equal or slightly higher cognitive scores compared with NC NLBW conceived children. At age 3, there are no differences between MAR LBW and NC NLBW children ($\beta = 0.021$, 95% CI: -0.198, 0.241). At age 5, MAR LBW children show higher cognitive ability scores ($\beta = 0.21$, 95% CI: 0.009, 0.418). Starting at age 7, the differences become smaller in magnitude and MAR LBW do not show notable differences in cognitive ability as compared with NC NLBW children (age 7: $\beta = 0.163$, 95% CI: -0.148, 0.474; age 11: $\beta = 0.003$, 95% CI: -0.318, 0.325; age 14: $\beta = 0.156$, 95% CI: -0.205, 0.517). When NC LBW children are used as the reference category (results not shown), the group showing the lowest cognitive ability scores at any age, MAR LBW display higher cognitive ability scores up to age 7 (at age 3: $\beta = 0.293$, 95% CI: 0.690, 0.517; at age 5: $\beta = 0.430$, CI: 0.218, 0.641; at age 7: $\beta = 0.381$,

**Table 1** Child and family characteristics by mode of conception

|  | Total | NC | MAR |
|---|---|---|---|
| Birth outcomes |  |  |  |
| LBW (%) | 7 | 6.6 | 21.9 |
| Child characteristics |  |  |  |
| Female (%) | 49.8 | 49.7 | 51.6 |
| Firstborn (%) | 42.3 | 41.5 | 66.1 |
| Twin (%) | 2.7 | 2.1 | 23.2 |
| Family characteristics |  |  |  |
| Maternal age at birth (mean/SE) | 29.7 (0.13) | 29.6 (0.12) | 33.1 (0.34) |
| Mother is married or cohabiting at birth (%) | 86.3 | 85.9 | 97.8 |
| Mother of White ethnic origin (%) | 90 | 89.9 | 94.5 |
| Mother has a university degree (%) | 33.5 | 33.1 | 45.5 |
| Mother smoked during pregnancy (%) | 21.4 | 21.8 | 9.3 |
| Mother used antenatal care before 12th week (%) | 43.3 | 42.9 | 55.4 |
| N (%) | 13716 (100) | 13320 (97.1) | 396 (2.9) |

Descriptive statistics refer to the analytical sample at age 3.

SE, standard error.

**Table 2** Linear models regressing cognitive ability (standardized) on mode of conception and birthweight status

|  | Age 3 BAS naming vocabulary $\beta$ (95% CI) | Age 5 BAS naming vocabulary $\beta$ (95% CI) | Age 7 BAS word reading $\beta$ (95% CI) | Age 11 BAS verbal similarity $\beta$ (95% CI) | Age 14 BAS word activity $\beta$ (95% CI) |
|---|---|---|---|---|---|
| Panel A: Baseline models[a] |  |  |  |  |  |
| NC NLBW | Reference | Reference | Reference | Reference | Reference |
| NC LBW | -0.272 | -0.216 | -0.218 | -0.121 | -0.105 |
|  | (-0.348, -0.196) | (-0.306, -0.127) | (-0.303, -0.133) | (-0.210, -0.032) | (-0.208, -0.001) |
| MAR NLBW | 0.181 | 0.324 | 0.345 | 0.228 | 0.226 |
|  | (0.052, 0.311) | (0.211, 0.437) | (0.232, 0.457) | (0.093, 0.358) | (0.068, 0.384) |
| MAR LBW | 0.021 | 0.213 | 0.163 | 0.003 | 0.156 |
|  | (-0.198, 0.241) | (0.009, 0.418) | (-0.148, 0.474) | (-0.318, 0.325) | (-0.205, 0.517) |
| Panel B: Adjusted models[b] |  |  |  |  |  |
| NC NLBW | Reference | Reference | Reference | Reference | Reference |
| NC LBW | -0.200 | -0.118 | -0.182 | -0.093 | -0.062 |
|  | (-0.267, -0.132) | (-0.196, -0.040) | (-0.266, -0.097) | (-0.179, -0.008) | (-0.161, 0.051) |
| MAR NLBW | -0.067 | 0.046 | 0.115 | 0.002 | -0.028 |
|  | (-0.192, -0.058) | (-0.060, 0.153) | (0.004, 0.226) | (-0.130, 0.126) | (-0.180, 0.123) |
| MAR LBW | -0.198 | 0.017 | -0.074 | -0.162 | -0.023 |
|  | (-0.401, 0.005) | (-0.159, 0.193) | (-0,369, 0.220) | (-0.472, 0.148) | (-0.386, 0.339) |
| N | 13716 | 14175 | 12714 | 12336 | 10220 |

NC NLBW, naturally conceived born non-low birthweight; NC LBW, naturally conceived born low birthweight; MAR NLBW, conceived with medically assisted reproduction and born non-low birthweight; MAR LBW: conceived with medically assisted reproduction and born low birthweight.

[a]Baseline models include: sex, multiple birth.

[b]Adjusted models include: sex, multiple birth, maternal education, whether the child is firstborn, maternal age at the time of birth, maternal marital status at the time of birth, timing of the first prenatal visit, ethnic origin, whether the mother smoked during pregnancy.

95% CI: 0.069, 0.693); however, after age 7, the advantage is attenuated. MAR NLBW children show the highest predicted scores and higher scores than NC NLBW and NC LBW children at all ages, but compared with MAR LBW children, differences are smaller in magnitude, and the confidence intervals overlap at all ages.

Panel B reports coefficients for the adjusted models, in which we include controls for family sociodemographic characteristics (Figure 1, right panel). In contrast to the unadjusted estimates, we find that differences between NC and MAR (LBW and NLBW) conceived children become largely attenuated and close to zero at age 14. The only
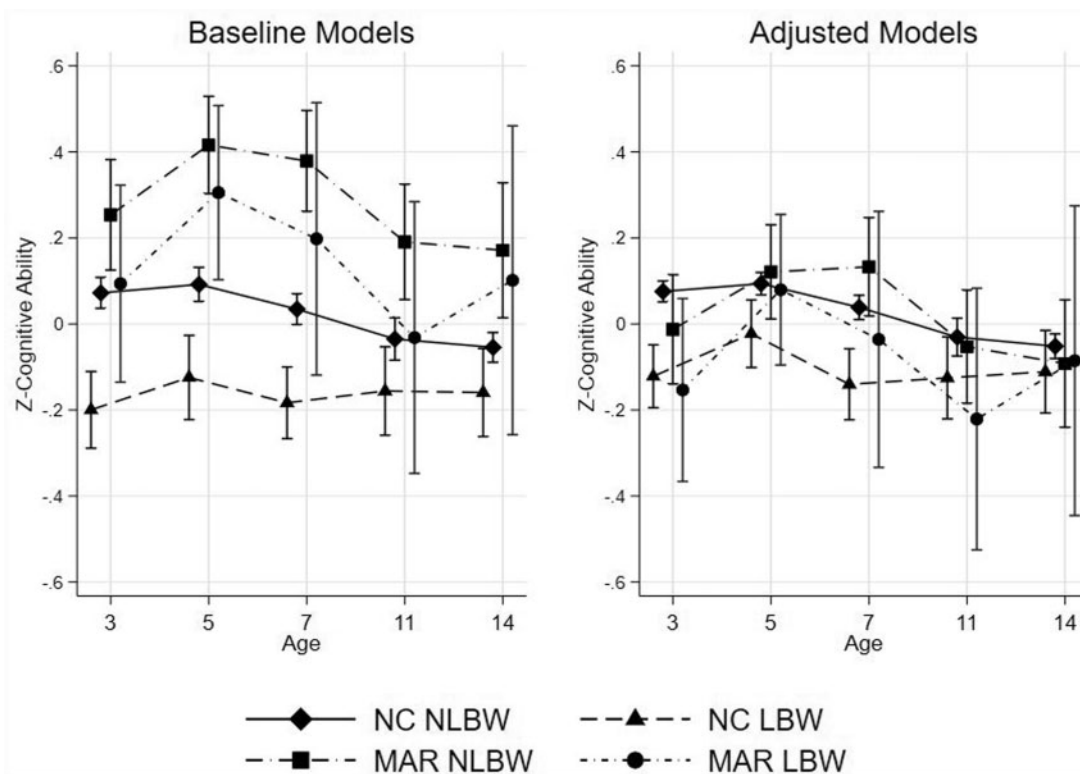
**Figure 1** Predicted scores in cognitive development and 95% confidence intervals of MAR and naturally conceived children by their weight status at birth at different age points. Baseline models include: sex, multiple birth. Adjusted models include: sex, multiple birth, maternal education, birth order, maternal age, maternal marital status, timing of the first prenatal visit, ethnic origin, whether the mother smoked during pregnancy. NC NLBW, naturally conceived born non-low birthweight; NC LBW, naturally conceived born low birthweight; MAR NLBW, conceived with medically assisted reproduction and born non-low birthweight; MAR LBW, conceived with medically assisted reproduction and born low birthweight.

group of children showing a persistent negative cognitive performance are NC LBW children, who continue to show the lowest predicted cognitive ability until age 7.

### Sensitivity analyses

We performed several sensitivity analyses. First, we replicated our analyses on the subgroup of MAR-children conceived with IVF and ICSI, since these procedures are more strongly associated with adverse birth outcomes.[4,32] This analysis yielded similar results. Second, we restricted the analyses to only children included in all waves of the survey, to account for attrition in our analytical sample. Our results are unchanged. Third, research has recently questioned the use of LBW as an indicator of birth outcomes and developmental potential.[33,34] We replicated analyses using an indicator of small for gestational age, and results are consistent. Fourth, we replicated our analyses using a more detailed definition of LBW, distinguishing very LBW (<1500 g) and LBW (between 1500 g and 2500 g), and our results are consistent. Finally, we re-performed the analyses controlling for maternal drinking in pregnancy, and results are consistent. The results of these sensitivity

analyses are presented in Supplementary Tables 6–13, available as Supplementary data at *IJE* online.

## Discussion

Medically assisted conceptions and births have increased considerably in recent decades, with over than 8 million MAR children born since the first treatment in the 1978.[35] Previous research has shown that MAR-conceived children are at higher risk of being born with poor birth outcomes, such as low birthweight,[4] raising concern about their future well-being including their cognitive development. Research has shown that MAR children perform as well as or better than naturally conceived children in cognitive ability, but one important aspect that has been overlooked is whether the MAR advantage is consistent for those born with LBW. MAR children, on average, come from socio-economically advantaged backgrounds,[36] which may compensate for the negative consequences of being born LBW.[23] We used a representative UK longitudinal cohort study to investigate the cognitive development of MAR children who were born LBW compared with NC (low birthweight and non-low birthweight) children from

infancy to mid-adolescence, before and after the adjustment for parental characteristics.

There are two main findings from this study. First, the results from the unadjusted models show that MAR-conceived children born LBW have similar or slightly higher cognitive ability scores compared with naturally conceived children. Specifically, MAR LBW children show cognitive ability scores that are similar to those of NC NLBW children and higher than NC LBW children up to age 7. Second, differences in cognitive ability between MAR and NC children are explained after adjustment for parental characteristics.

There are a range of mechanisms that potentially underlie our results. First, MAR parents' characteristics, resources and behaviours may account for the MAR advantage.[37] MAR parents could be more committed to parenting, due to the difficulty of conceiving thorough MAR and the desire to become parents.[38] Moreover, since MAR parents are on average socioeconomically advantaged, they may give their children the chance to take part in a wider range of stimulating extra-curricular activities alongside school[39];they may spend more time reading to their children[40]; they may provide their children with better child care (i.e. less day care and more adult-child interactions, which have long-lasting benefits in childhood)[41]—all of which are linked to positive cognitive development. Taken together, these characteristics and behaviours might enable MAR parents, by virtue of their higher SES, to compensate for the possible initial disadvantage of being born LBW.[42,43] This is in line with research showing how poor birth outcomes are associated with cognitive impairments later in life primarily among families with a lower socioeconomic background.[10,42]

Second, it may be possible that we do not observe any disadvantage of being born LBW among MAR children, since the determinants of being born LBW differ between MAR and NC children. For example, in the MAR-conceived group, the risk of LBW may be more related to the experience of sub-fertility[6] and less to other causes, such as unobserved health behaviours during pregnancy,[44,45] which is more common among parents who conceive naturally. In line with this, the proportion of firstborn children—firstborn children are at higher risk of LBW than second- or later-born children[46]—in the MAR-conceived group is higher than in the NC group (66% vs 42%, see Table 1). The larger share of LBW children in the MAR group could be an indicator of physiological rather than pathological differences in birthweight. Ultimately, differences in the determinants of LBW could translate in differences in the developmental risk associated with being born LBW.

This study has also a secondary result. In the unadjusted models, we observe that MAR NLBW children have higher

cognitive ability with respect to the NC group until age 7, when the gap is attenuated. Similarly, MAR LBW children show higher cognitive ability with respect to NC LBW children up to age 7, at which point the difference fully attenuates. These patterns may have two explanations. First, they could be explained by school entry, as schools may work as an equalizer for the cognitive development across groups.[47] That is, the role of parents is more crucial at the earliest ages since they spend more time at home; once children enter schools, the influence of teachers and peers attenuates differences across groups. A similar pattern of narrowing differences in cognitive development is observed for SES gaps, where differences in cognitive ability between high- and low-SES children increase before entering school and remain stable thereafter.[21,48] Second, it may be possible that we observe a convergence as the negative effect of being born LBW for NC conceived children fades away over time, which is consistent with previous studies documenting that the negative effect of LBW become smaller as children grow older.[23,49,50]

Our results partially differ from those of a previous study which has analysed the cognitive development of MAR children using the same data until age 11.[3] Our results are consistent with theirs until age 7, after which they differ since we find that MAR NLBW show consistently higher cognitive ability with respect to all other groups before accounting for family characteristics. This difference is likely driven by the fact that we distinguish between NLBW and LBW children, whereas the other study considered MAR children in general.

This study is not free of limitations. First, the sample size of MAR children is small, which may affect the precision of our estimates. This is particularly the case in the later sweeps where, due to attrition, the confidence intervals become wider, making it difficult to interpret statistical differences between groups. Second, due to few children being conceived after MAR, we were required to combine all the children who were conceived through different MAR techniques, although the consequences of these procedures may differ.[32] We repeated the analyses focusing only on a sub-sample of children conceived through IVF and ICSI (the most invasive techniques), and results were consistent. Third, our study focuses on the UK context, where the subsidization of MAR treatments through the National Health System is less generous compared with other contexts (such as Northern Europe), resulting in the majority of treatments taking place in the private sector and the MAR group being particularly selected. Results should be generalized to other contexts with caution, especially those where the subsidies are more generous.[51] This study has nonetheless also considerable strengths. First, we investigate the consequences of MAR across

children's developmental stages, providing evidence on both early childhood and mid-adolescence, which are often understudied.[17] Second, the richness of the data allows us to control for a large set of confounders, which enables us to further understand the mechanisms underlying the results.

In this study we show that, before adjustment for family characteristics which enable us to assess the actual well-being of different sub-population groups, MAR-conceived children born LBW do not show any disadvantage in cognitive development from infancy to mid-adolescence, but rather better cognitive performance than NC LBW and similar performance to NC NLBW children. The findings suggest that this is not a result of MAR per se, but because of selection into MAR and the advantaged profile of MAR families.

Our findings are important for two main reasons. First, the facts that the proportion of MAR-conceived children is increasing rapidly and a considerably high proportion are born LBW might constitute a concern and an impediment to their longer-term development. Overall, the findings provide a reassuring picture on the development of MAR-conceived children despite the increased risk of being born low birthweight. Second, by focusing on a subgroup of children born LBW to socially advantaged parents, our results corroborate earlier work showing that the impact of LBW on cognitive development is less consequential than the social context in which children are growing up.[23]

Future research should replicate the analyses using different data, especially in contexts—such as the Nordic countries—where the selection into MAR might be less pronounced because of a higher subsidization of MAR treatments through the public health system than in the UK. Future research should also further investigate if there are (and if so, which) family characteristics and behaviours specific to the MAR families which may be able to ameliorate the consequences of being born low birthweight.

## Supplementary data

Supplementary data are available at *IJE* online.

## Ethics approval

Ethical approval was not required as the study used anonymized, publicly available data.

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## Author contributions

A.G. with M.C. and S.A. conceptualized the study. M.C. performed the statistical analyses, S.A. and A.G. advised on the study design and interpretation of the results. M.C. wrote the first draft. S.A. and A.G. read, reviewed and revised the manuscript. All the authors contributed to subsequent drafts. All the authors approved the final manuscript.

## Data availability

Data and code are available upon reasonable request to the corresponding author.

## Conflict of interest

We have no conflict of interest to declare.

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# Commentary: Context matters for the postnatal sequelae of being born low birthweight

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As the proportion of children being born as a result of medically assisted reproductive (MAR) technologies increases rapidly across the globe, epidemiologists are increasingly interested in understanding how these complex and evolving interventions that have provided welcome solutions to subfertility for so many parents also contribute to offspring wellbeing beyond the perinatal period.

In some European countries, births after MAR now represent ∼10% of all births, so understanding the impact of MAR on life-course wellbeing outcomes is not trivial.[1]

Understanding the impact that MAR has on childhood cognition is especially important because of the associations with whole-of-life-course wellbeing and productivity.[2]

Children born after MAR are known to have a greater chance of experiencing poorer perinatal outcomes, including being born with a low birthweight (LBW) compared with naturally conceived births. In naturally conceived births, LBW usually predisposes offspring to relative cognitive disadvantage.[3]

However, after MAR, children are not generally disadvantaged cognitively compared with their naturally conceived peers according to a recent systematic review.[4] The review also highlighted that only a handful of the hundreds of studies that investigated this association were ranked as being of high quality. Common limitations of studies included the lack of large and detailed life-course data sets used and selection bias in the populations included, with a bias towards the exclusion of children at greatest risk of cognitive impairment.[4]

Evaluating postnatal outcomes for offspring born after MAR is particularly challenging because the underlying reasons for parental subfertility and the need for MAR are also poorly understood. Additionally access to MAR is not equitably distributed according to need. Parents who are able to access MAR, especially in the UK, tend to be more socio-economically advantaged than the general reproductive population .

Cozzani *et al.* begin to address some of these challenges in their recent paper.[5] They extend the previous analyses which demonstrated that when cognitive scores for offspring born after MAR offspring were compared with those of their naturally conceived peers, in a richly characterized UK cohort up to the age of 11 years, there was no evidence that children born after MAR were cognitively disadvantaged.[6] Analyses are extended to cognitive scores at 14 years and MAR offspring are stratified into LBW and non-low-birthweight (NLBW) groups to assess the impact of MAR and LBW together on cognitive scores.[5]

The comparisons of cognitive scores demonstrate that MAR LBW offspring perform more like naturally