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## Abstract

**Objective:** To study self-reported well-being and self-esteem among adolescents born very preterm (VPT; <32 weeks of gestation) and moderate to late preterm (MLPT; 32-36 weeks of gestation) compared to those born full-term (FT) in an individual participant data (IPD) meta-analysis.

**Methods:** We obtained individual participant data from four data sources: The Avon Longitudinal Study of Parents and Children (ALSPAC; United Kingdom); the Millennium Cohort Study (MCS; United Kingdom); the Basel Study of Preterm Children (BSPC; Switzerland); and the Bavarian Longitudinal Study (BLS; Germany) and conducted two-step random-effects IPD meta-analysis. A total of 986 MLPT, 412 VPT and 12719 FT born adolescents reported on well-being and 927 MLPT, 175 VPT and 13312 FT born adolescents reported on global self-esteem.

**Results:** Adolescents born VPT or MLPT were not different from those born FT regarding general subjective well-being, and family, school and physical appearance related well-being, and global self-esteem. However, adolescents born VPT reported lower well-being in peer relationships than those born FT ( $\beta = -0.209$ , 95% CI = -0.336 to -0.082). There was no main effect of fetal growth restriction and no moderation by fetal growth restriction, sex, parental education, and ethnicity. No significant heterogeneity between cohorts was found even though some heterogeneity estimates were moderate.

**Conclusion:** Adolescents born preterm mostly report no lower well-being and self-esteem than adolescents born full-term. However, they perceive their peer relationships as poorer than those born full-term.

## **Introduction**

Preterm (PT) birth, defined as birth before completed 37th week of gestation, is associated with an increased risk for lower academic achievement,<sup>1</sup> higher mental health problems<sup>2,3</sup> and increased difficulties in social relationships<sup>4</sup> compared to those born full-term (FT). These effects have been found to get more severe with lower gestational age in a dose response pattern.<sup>1,3,4</sup> Notwithstanding these risks, many infants born PT do not develop academic, social or mental health problems.<sup>3</sup>

Even though there are several follow-up studies on adverse outcomes following PT birth, few have focused on the development of well-being or self-esteem,<sup>5</sup> which can foster positive adaptation of PT born children.<sup>6</sup> Since the onset of adolescence involves changing social demands, it has been noted that self-esteem may decrease during this period.<sup>7</sup> PT born adolescents may be at a particular risk for low self-esteem and well-being, but this has rarely been investigated.<sup>8-11</sup> Most previous studies focused on health-related quality of life (HRQoL), which is a related but a different construct that measures the impact of health on an individual's overall physical, psychological and social functioning.<sup>12</sup> These studies revealed that parents of PT borns report lower HRQoL,<sup>13,14</sup> however PT adolescents themselves report similar levels to full-terms,<sup>10,12,14</sup> except for one study where PT adolescents also reported having lower HRQoL compared to their FT born peers.<sup>15</sup> The few studies that investigated self-esteem in PT born adolescents reported mixed results, some found similar levels of self-esteem<sup>8,9</sup> whereas one study reported lower self-esteem for PT adolescents compared to FT borns.<sup>16</sup>

In addition to PT birth, there is evidence that fetal growth restriction (FGR) is a risk factor for increased emotional problems,<sup>2</sup> which might influence well-being and self-esteem of adolescents directly or might influence the role of PT birth on these outcomes. Other factors such as female sex, low parental education, and minority ethnicity status have

additionally been proposed as potentially critical moderators for understanding the relationship of PT with well-being and self-esteem.<sup>10-12</sup>

The few existing studies were mostly based on small samples and most considered only extremely PT infants,<sup>9,10</sup> thus, they did not investigate if there is a larger effect for those born with lower gestational age (i.e., dose-response pattern). One way to overcome the limitations of the previous studies is to undertake an individual participant data (IPD) meta-analysis, which enables using the same analysis procedure in each included study (e. g., using the same control variables), testing of the moderating effects with increased power, and including cohort studies where the specific research question has not been addressed.<sup>17</sup>

The main objective of the present study was to examine, whether being born very preterm [VPT: <32 weeks of gestation] or moderate to late preterm [MLPT: 32-36 weeks of gestation] is associated with lower subjective well-being and global self-esteem in adolescence compared to FT born adolescents [37-41 weeks of gestation]. Moreover, we investigated if the association follows a dose-response effect according to gestational age at birth, if FGR has an effect on these outcomes and whether the effects of PT birth are moderated by FGR, sex, parental education, ethnicity or multiple birth.

## **Methods**

This IPD meta-analysis was registered with the Open Science Framework (<https://osf.io/2jghs>) and conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines<sup>18</sup>.

### **Study Selection**

We included four cohort studies, which collected data on well-being and self-esteem in PT and FT born adolescents and for which we had access to the individual participant data (Table 1). None of these studies previously reported on well-being and self-esteem in adolescence

after PT birth. The ethical approval for the study was provided by the Ethics Committee of the University of Warwick (Approval number: 96/17-18).

## **Samples**

**The Avon Longitudinal Study of Parents and Children (ALSPAC).** ALSPAC is a UK birth cohort (1991-1992) of 13,988 children, which has been described in detail elsewhere.<sup>19</sup> ALSPAC recruited 14,541 pregnant women with expected delivery dates of 1st April 1991 to 31st December 1992. Of the initial pregnancies, there were 14,676 fetuses resulting in 14,062 live births; 13,988 children were alive at 1 year of age. A total of 13,978 children formed the original cohort. Ethical approval was obtained from the ALSPAC Law and Ethics committee and the local research ethics committee. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. From the first trimester of pregnancy, parents completed postal questionnaires about themselves and the study child. Children were invited to annual assessment clinics, including face-to-face interviews, and psychological and physical tests from 7 years onwards. The study website contains details of all data available through a fully searchable dictionary (<http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/>). The current study utilised the data on subjective well-being (N=3020) and self-esteem (N=3917) at 17 years of age.

**Bavarian Longitudinal Study (BLS).** BLS is a prospective geographically defined whole population sample of neonatal at-risk children born between January 1985 and March 1986 in Southern Bavaria (Germany) who required admission to a children's hospital within the first 10 days after birth (N= 7505).<sup>20</sup> This population ranged from very ill PT infants to term infants who required observation in the special care unit. Of the 7505 at-risk children, 682 were born VPT/VLBW (very preterm/very low birth weight). By 13 years of age, 181 VP/VLBW participants died and another 50 families either declined further participation

(n=7) or were non-German speakers (n=43). In addition, 916 healthy infants born at term in the same hospitals were recruited as controls. Of this control group, 350 children were randomly selected within two stratification variables (sex and family socioeconomic status) to be comparable to the VP/VLBW group after the first phase of the study (at age 6 years). At 13 years, 451 PT and 350 control children were eligible for follow up. Ethical approval for the study was granted by the ethics committees of the University of Munich Children's Hospital and the Bavarian Health Council. Informed consent was obtained from all participants. The present study utilizes data collected at age 13 years regarding well-being (N= 638).

**Basel Study of Preterm Children (BSPC).** The BSPC is a cohort study of children who were born between June 2001 and December 2006. The PT sample was drawn from an initial cohort of 260 prematurely born children, who were treated after birth at the University Children's Hospital of Basel <sup>21</sup>, while the FT sex- and age-matched control sample was recruited at an average of 8 years of age, based on official birth notifications. Detailed information on the sampling of the BSPC has been published previously<sup>21</sup> and can be found here: <https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/AYBAAN>. Ethical approval and written informed consent were obtained (Ethikkommission Nordwest- und Zentralschweiz, reference number 122/11). The present study utilizes data of participants reported on subjective well-being (N=132) and self-esteem (N= 138) at an average of 12 years of age.

**Millennium Cohort Study (MCS).** MCS is a national birth cohort of 18,818 children born between September 2000 and January 2002 in England, Wales, Scotland, and Northern Ireland.<sup>22</sup> The first sweep of interviews with cohort members' mothers took place when the infants were 9 months old and 7 sweeps were completed so far. The interviews included questions on a wide variety of topics, including health, education, social, family and economic status of the cohort members' households. Detailed information on the sampling and scope of

MCS is available at: <http://www.cls.ioe.ac.uk/>. Ethical approval and written informed consent of all participants were obtained (London - Hampstead Research Ethics Committee, REC reference 14/LO/0868). Current analyses included those who provided data on subjective well-being (N= 10327) and self-esteem (N= 10359) at the 14 years assessment.

## Measures

**Gestational age (GA).** GA in full weeks plus days was extracted from medical records and was recoded into a categorical variable: FT (37-41 weeks of gestation); MLPT (32-36 weeks of gestation); VPT (< 32 weeks of gestation).

**Subjective well-being.** Participants reported on their well-being in four cohorts. In ALSPAC and BSPC, the Warwick-Edinburgh Mental Well-being Scale (WEMWBS)<sup>23</sup> and the KIDSCREEN-52<sup>24</sup> were used, respectively, which are widely used measures. On the other hand, in MCS and BLS, subjective well-being was assessed with scales that were specifically devised for the studies (Supplemental Table 1). Given the differences in measurement of well-being in the four cohorts, the scales were z-standardised within each cohort to allow for comparability, which is a common practice in data harmonization. Five well-being subscales were analysed including *family relations* (six items in BSPC; one item in MCS; and four items in BLS), *peer relations* (six items in BSPC; one item in MCS; and four items in BLS), *school environment* (six items in BSPC; two items in MCS; and three items in BLS), *physical appearance* (five items in BSPC, one item in MCS, two items in BLS), and *general well-being* (six items in BSPC, one item in MCS, fourteen items in ALSPAC; there was no item measuring general well-being in BLS). All scales had good reliability to measure overall well-being (ALSPAC:  $\alpha = 0.95$ ; BLS:  $\alpha = 0.83$ ; BSPC:  $\alpha = 0.88$ ; MCS:  $\alpha = 0.86$ ). Higher scores reflect higher well-being.

**Global self-esteem.** Participants reported on their self-esteem in three cohorts (ALSPAC, BSPC, MCS) using the Bachman Revision of Rosenberg Self-Esteem Scale<sup>25</sup> in ALSPAC and

Rosenberg Self-Esteem Scale<sup>26</sup> in BSPC and MCS. We included 5 items (Supplemental Table 1), which were the same across cohorts which allows to make item level harmonization across the cohorts. Higher scores reflect higher self-esteem and the scales had good reliability (ALSPAC:  $\alpha = 0.82$ ; BSPC:  $\alpha = 0.82$ ; MCS:  $\alpha = 0.91$ ).

***Fetal growth restriction (FGR).*** As a measure of fetal growth, birth weight z-scores were computed via the model proposed by Hadlock.<sup>27</sup>

***Covariates.*** Participants' age at the assessment of the outcome, gender, ethnic group, multiple birth, parity, neurosensory impairment, and the highest level of education of either parent at participants' birth. Neurosensory impairment was indicated by the presence of either (a) an IQ score for fluid reasoning of 3 standard deviations below the mean identified between 5-11 years, (b) parent- or school-reported visual or hearing impairment, or (c) severe congenital malformations identified during the child's first year of life.

## **Statistical Analysis**

All statistical analyses were conducted with Stata, version 15.0 (StataCorp, 2017). We conducted a two-step random-effects IPD meta-analysis using the `ipdmetan` command. In the first step, we fitted the hierarchical linear regression models to the data from each cohort (Supplemental Table 2), and in the second step the results were combined in a meta-analysis. The DerSimonian and Laird procedure was used to compute the pooled effects and 95% confidence intervals (CIs). Between-study heterogeneity was tested using the Cochran's Q statistic and quantified by the  $I^2$  value. All analyses were adjusted for the covariates. Furthermore, subgroup analysis was undertaken comparing the estimates of VPT and MLPT groups to test the dose-response effect. Moderator analyses were conducted with 5 variables: FGR, female sex, minority ethnic group, education below tertiary and multiple birth.

***Attrition and Power Analyses.*** Attrition analysis using birth cohorts showed a significant association between drop-out and gestational age group ( $\chi^2(2) = 13.308, p < .001$ ), where



65.9% of VPT, 56.9% of MLPT and 56.4% of FT participants were missing. Power analysis using Gpower (version 3.1.9.4) revealed high statistical power to detect a modest effect size of  $d = 0.20$  (0.99 for MLPT and 0.98 for VPT in well-being).

**Sensitivity Analyses.** First, main analyses were repeated after excluding participants with neurosensory impairments. Second, we examined if the main findings would differ when moderate preterm (MPT; 32- 33 weeks of gestation) and late preterm (LPT; 34-36 weeks of gestation) groups were analyzed separately. Third, we repeated our main analyses using multiply imputed (20 imputations) data to examine whether drop-out led to biased results. Fourth, we repeated the main analyses using gestational age as a continuous variable.

## Results

In the current study, 986 MLPT, 412 VPT and 12719 FT born adolescents reported on well-being and 927 MLPT, 175 VPT and 13312 FT born adolescents reported on self-esteem (Table 1). The age of participants ranged from 12 to 17 years. Characteristics of MLPT, VPT, and FT born adolescents are shown in Table 2.

### Differences in Subjective Well-Being and Self-Esteem between Preterm and Full-Term Adolescents and The Role of Foetal Growth Restriction

Adolescents born MLPT (Supplemental Table 3) and VPT (Supplemental Table 4) were not significantly different from FT born adolescents on overall well-being and self-esteem. On the subscales of well-being, VPT born adolescents reported lower well-being in peer relationships than FT ( $\beta = -0.209$ , 95% CI = -0.336 to -0.082,  $p = 0.001$ ), whereas there was no evidence of differences in other subscales of well-being. Although some of the heterogeneity effect sizes were moderate in the subscales of subjective wellbeing and self-esteem, no significant heterogeneity existed between the study cohorts in all analyses ( $I^2 < 67.0\%$ ,  $p > 0.05$  in all analyses) (Table 3). The main findings remained the same across all sensitivity analyses (Supplemental Tables 5,6,7).

When comparing MLPT and VPT born adolescents, findings were the same as the main analyses (Supplemental Table 8). FGR had no significant main effect on wellbeing and self-esteem (Table 4). Moderator analyses revealed that FGR, sex, parental education, minority ethnicity and multiple birth did not moderate the findings (Supplemental Table 9). Moreover, there were no significant associations between continuous gestational age and the outcomes (Supplemental Table 10).

### **Discussion**

Findings of the current study show that those born MLPT, VPT and FT reported similar levels of overall subjective well-being and global self-esteem. The findings were similar for all subjective well-being sub-scales (i.e., family relationships, school environment, physical appearance, general well-being), except that those born VPT reported less well-being in peer relationships than both MLPT and FT born adolescents. Sensitivity analyses excluding individuals with neurosensory impairments, conducting the analyses with imputed data and investigating the MPT and LPT groups separately did not alter the main findings. Further, there was no main effect of FGR on well-being and self-esteem. Differences between VPT and FT born adolescents in well-being in peer relationships were not accounted for by sex, low parental education, minority ethnicity, multiple birth or FGR.

Our findings are similar to those of previous studies reporting similar levels of quality of life in extremely PT born adolescents in comparison to those who were born FT.<sup>10,11,13</sup> It is an encouraging finding that PT born adolescents show the same levels of well-being as FT born adolescents despite the association between PT birth and increased mental health problems.<sup>3</sup> Even though mental health and subjective well-being have conceptual overlaps, they are different constructs with recent evidence showing only a weak correlation between mental health problems and subjective well-being.<sup>28</sup>

The only lower well-being score in PT born adolescents compared to the FT group was in peer relationships. Our findings suggest a threshold effect because the significant association between PT birth and well-being in peer relationships was only evident in the VPT group and there were no significant association between continuous gestational and well-being in peer relationships. Thus, 32 weeks of gestation might be a breaking point for the development of skills required for peer relationships. This finding is in line with previous literature that highlights that VPT born children have fewer friends at the ages of 6 and 8,<sup>29</sup> are more likely to be bullied by peers,<sup>30</sup> and during adolescence they are less likely to participate in social and leisure activities in comparison to those born FT.<sup>31</sup> These findings suggest a continuing negative impact of VPT birth specifically on relationships with peers despite the similarity in well-being between VPT and FT born individuals in other domains.<sup>14</sup> This finding could be due to interaction between several factors related to VPT birth such as reduced hippocampal volumes which is related to social competence<sup>32</sup>, impaired cognition<sup>33</sup> and withdrawn personality<sup>34</sup>.

Furthermore, there were no differences in the level of self-esteem of MLPT and VPT born adolescents compared to FT born adolescents. This finding is in line with the studies showing similarities between PT and FT born adolescents' self-esteem despite being at a higher risk for functional impairments.<sup>8,9</sup> However, it is in contrast to the finding of a previous study, which found lower levels of self-esteem in very low birth weight adolescents than normal weight borns<sup>16</sup>. The participants of that study were born between 1980 to 1982, at a time when neonatal procedures were different than the cohorts reported on self-esteem in the current study which included participants born between 1990 and 2006<sup>35</sup>.

Although there is evidence that FGR increases the risk for poor academic performance and increased behavioral problems,<sup>2</sup> our findings suggest that it has no significant influence on subjective well-being and self-esteem during adolescence, which is in line with studies

reporting no association between FGR and quality of life during adulthood.<sup>36</sup> Despite the fact that PT born individuals who were also born with FGR might be at an elevated risk for mental health problems,<sup>2</sup> they are as likely as FT born individuals to have good well-being and self-esteem. Moreover, female sex, multiple birth, low parental education, and minority ethnicity did not alter the association between PT birth and subjective well-being and self-esteem.

The current study has several strengths including the large sample size combining IPD across four cohorts, high power to detect statistically significant differences, investigation of the same moderators across cohorts and accounting for the role of drop-out rates on the results via repeating the analyses with imputed data. However, there are also limitations of the study. First, only three of the four cohorts had data on self-esteem while four cohorts had data on subjective well-being. Second, different scales were used to measure subjective well-being in each cohort with the scales used in BLS and MCS being designed for the specific study, where participants reported on single-item scales of well-being. Given these differences, moderate heterogeneity between the cohorts was found in some of the analyses even though it was statistically not significant, which suggests that differences between either the scales or the cohorts (e.g., differences between countries) might have had an impact on the results for subjective well-being. In addition, it is important to note the difference in the birth years of the included cohorts, which was ranging from 1985 to 2006, a timespan during which medical advances and changes in neonatal care were introduced<sup>35</sup>. These improvements might have contributed to the heterogeneity between cohorts. Nevertheless, the pattern of findings was consistent among cohorts. Third, we were unable to control for the role of prenatal maternal smoking since it was reported retrospectively and at differing time points across the cohorts. Last, physical growth and pubertal age are additional covariates which could have an impact on the outcomes. We could not include these variables as covariates since they were not

measured across all cohorts. However, the impact of these variables on well-being and self-esteem of preterm born adolescents may be the focus of future studies.

To conclude, despite being at risk for increased physical and mental health problems, PT born adolescents show similar levels of well-being and self-esteem compared to those born FT. However, VPT adolescents are feeling worse about their relationships with peers compared to FT adolescents. Therefore, interventions to enhance well-being in VPT born adolescents may in particular focus on improving peer relationships in childhood and adolescence.

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