**Identifying factors associated with adverse pregnancy outcomes in women with reduced fetal movements in the third trimester of pregnancy: An Individual Participant Data Meta-Analysis**

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**Abstract**

**Objectives**: Women experiencing reduced fetal movements (RFM) have an increased risk of adverse pregnancy outcome (APO). Single-population studies may introduce bias and limiting generalisability. This study aimed to identify factors most strongly associated with APO, including stillbirth, fetal growth restriction (FGR), and admission to neonatal intensive care unit in women with RFM.

**Design and settings**: Individual-level data from multiple sites in Manchester and Leicester were synthesised and analysed.

**Population or Sample:** 1,175 women between 28+0 and 41+0 weeks’ gestation with singleton pregnancies.

**Methods:** Factors associated with APO were assessed by two-stage individual participant data meta-analysis (IPD-MA).

**Main Results**: 7.7% of RFM pregnancies ended in APO, with the most common complication being FGR (birthweight ≤3rd centile) in 4.6%. Maternal past medical history (adjusted Odds Ratio, aOR = 2.28, 95% CI 1.08-4.83) and smoking status (aOR = 2.52, 95% CI 1.20-5.29) were most strongly associated with APO. Estimated fetal weight (EFW) percentile (aOR = 0.97, 95% CI 0.96-0.99) and maternal age (aOR = 1.05, 95% CI 1.01-1.09) were also significant risk factors, though high heterogeneity between studies in EFW percentile was observed (I2 = 76.84%, Tau2 = 0.0004, Q-statistic p-value = 0.0007).

**Conclusions**: IPD-MA allowed amalgamation of patient-level data across studies, and more accurate and reliable associations were found by accounting for heterogeneity. Further work is required to investigate the model’s generalisability across diverse populations and settings.

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**Keywords:** Individual Participant Data Meta-Analysis; Adverse pregnancy outcome; Stillbirth; Fetal Growth Restriction; Perinatal mortality; Decreased Fetal Movement

**Introduction**

Pregnancies in which there is subjective perception of reduced fetal movements (RFM) are more likely to end in adverse pregnancy outcomes, including stillbirth (approximately 2.3-fold increased risk)1 and fetal growth restriction (FGR) which occurs in 20-23% of cases.2-5 Up to half of stillbirths reported RFM before a diagnosis of intrauterine fetal death.6-9 In addition, interventions following RFM can lead to increased rates of induction of labour (IOL), caesarean section, and neonatal unit admission.10-13 Some of this intervention is likely to be iatrogenic, in an attempt to avoid rare, serious outcomes such as stillbirth and perinatal asphyxia. Thus, identifying factors that best predict adverse pregnancy outcomes would help clinicians identify women at greater risk who present with RFM, enabling them to target interventions appropriately.

Previous individual studies found factors related to fetal growth and placental health are closely linked to poor pregnancy outcomes following maternal perception of RFM.2,5,13 However, these findings drawn from single-population studies might be susceptible to centre-specific biases, effected by patient populations, smaller sample sizes, and unit-specific guidelines. This imbalance can influence the robustness of the comparison and may not provide reliable effect estimates. Therefore, the impact of the factors on adverse pregnancy outcomes is still uncertain. This research primarily aimed to identify the most predictive factors of adverse pregnancy outcomes in women presenting with RFM using individual patient data meta-analysis (IPD-MA).

**Methods**

This Individual Patient Data Meta-Analysis adhered to the applicable section of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis of Individual Patients Data (PRISMA-IPD) guidelines.14

**Identification of studies and eligibility criteria**

We first conducted a hand search to identify eligible individual studies at various sites over the last decade, internationally. Next, title and abstracts were screened, and the full text of the potential eligible articles was reviewed against the following inclusion/exclusion criteria: 1) Singleton pregnancies where RFM was reported for all observations; 2) Involved cases of stillbirth, fetal growth restriction, or newborns admitted to neonatal intensive care units; 3) Participating women were aged between 16-50 years and within a gestational period of 28+0 to 41+0 weeks, and were able to give written informed consent; 4) Fetuses had no congenital anomalies and there was no clinical indication for immediate delivery (e.g. pathological fetal heart rate trace); 5) This was not their first contact with maternal service.

**Data collection process**

Authors of eligible studies were contacted by email and invited to provide the original dataset of their studies. Data from individual studies were collected at an individual participant level through mothers’ notes (maternal demographics, details of the duration of RFM, past obstetric and medical history), fetal heart rate trace (cardiotocograph), and biochemical testing (biomarkers measurement). Variable definitions and data coded instructions were provided by authors.

**Data Items and IPD Integrity**

Available explanatory variables were identified by searching for the same variables in each study. Individual participant data (IPD) were checked by using exploratory data analysis, including identifying missing values and outliers, visualising distribution, correlation analysis, and feature engineering (e.g., encoding, binning, and combination). All IPD were assembled in a single dataset, each observation labelled with a study-specific identifier to denote its original source.

**Risk of bias assessment within individual and across studies**

The Cochrane Collaboration’s Risk of Bias Tool15 was applied to each randomised controlled trial (RCT), and the Newcastle-Ottawa Scale (NOS)16 for each prospective cohort study to assess the risk of bias within individual studies. Egger’s regression test was applied to assess the publication bias across studies.

**Specification of outcomes and effect measures**

Adverse pregnancy outcome (APO) was defined as the occurrence of any of the following criteria: stillbirth, fetal growth restriction (FGR) (individualised birthweight centile≤3rd centile), or admission to neonatal intensive care unit at term (gestation at delivery≥37 weeks) (*Table 2*). While preterm birth and small for gestational age infants (birthweight <10th centile) were included in some individual studies, they were excluded from this analysis to maintain a narrow focus on the most severe complications, which are likely to demonstrate the most pronounced associations with the risk factors under investigation within our study’s framework. The estimated effects of risk factors on the outcome were reported using odds ratios (OR) and 95% confidence intervals (CI), p-values, and heterogeneity level.

**Synthesis methods**

Multiple imputation (MI) was employed to handle missing data after integrating individual datasets. Ten imputed datasets were generated for the combined data and compared by density plots. The subsequent models accounted for the potential bias introduced by the missingness in the original data by including the missing indicators.21 Univariate logistic regression and variable selection process were applied as an initial screening to identify variables with a potential relationship with APO. A stepwise regression approach based on the Akaike Information Criterion (AIC)22 was employed, considering both forward and backward steps to optimise the logistic regression model according to the AIC. The strength of the association for each factor with APO was assessed across the six studies.

A two-stage IPD meta-analysis (IPD-MA)23,24 was then performed across six datasets (*Figure 1*). Stage 1 involved logistic regression on each study within each imputed dataset to obtain effect estimates and variances. At stage 2, we combined the study-specific effects using a random-effects meta-analysis model.23,25,26 The between-study variance in the random-effect model was estimated using Tau-squared (τ²), while theI2 statistic quantified the proportion of total variance in effect estimates that is attributable to heterogeneity rather than chance. Cochran’s Q Test assessed whether there was significant heterogeneity among the effect sizes of the studies.17-20 Forest plots displayed the effect estimates for each study, along with their confidence intervals, allowing for exploration variation across studies and visualisation of the pooled effect.

**Additional analyses**

Sensitivity analyses were conducted to further validate the robustness of the main IPD-MA. In Sensitivity Analysis 1, we added an additional variable, fetal heart rate trace assessment, considered an impactful factor, into the model. We excluded data from Study 3 and Study 5 as they lacked abnormal cases for this variable in their sample populations. In Sensitivity Analyses 2 and 3, we repeated the procedures from the main IPD-MA and Sensitivity Analysis 1 but excluded the intervention arms from the RCTs. Additionally, we conducted another analysis to investigate the impact of MI on the results by comparing it with the complete-case analysis.

**Results**

**Study selection and IPD obtained**

*Figure S1* shows the PRISMA2020 flow diagram for study identification. Hand searches identified six studies from journal articles and two from unpublished research studies. Following requests, one author did not respond, and one was restricted from sharing data due to data protection regulations. This analysis was ultimately confined to IPD derived from six eligible UK studies, including four published (participants = 936) and two unpublished studies (total participants = 239). In total, 1,175 women between 28+0 and 41+0 weeks’ gestation with singleton pregnancies with perceived RFM between 2009 and 2021 were included in this IPD-MA (*Table 1*). A PRISMA-IPD checklist is provided in *Table S1.*

**Study characteristics**

The number of events for individual studies are shown in *Table 2* and *Figure 2*. 90 cases (7.7%) met the criteria for the adverse pregnancy outcome (APO). The most common complication reported (4.6%) was fetal growth restriction (birthweight≤3rd centile). A total of four participants had more than one complication across all studies.

Detailed characteristics across levels of composite and individual outcomes are available in supplementary *Table S2*. The average age of the study population was 28.6 years. The ethnicity of the population was 67.4% White, 18.6% Asian, 9.7% Black, and 3.2% mixed or other. There were no significant differences in maternal age and ethnicity between participants with and without APO. Women with APO were more likely to report significant past medical history (PMH) (p<0.01) and had a higher rate of cigarette use (p=0.04). Additionally, fetal heart rate abnormalities were more prevalent in this group (p<0.01), they also presented with RFM at an earlier stage of gestation (p=0.04) and exhibited lower EFW percentile (p<0.01), compared to those without APO.

**IPD integrity**

Twenty common explanatory variables were identified across the six studies (*Table S3*). In the combined dataset, the level of missingness ranged from 0.09% to 9.96%, with nearly 10% missing data for fetal heart rate assessment, and approximately 7.5% missing for amniotic fluid index (*Table S4 and Figure S4*). Results from the univariate logistic regression are shown in *Table S5*.

**Risk of bias within studies**

*Table 3* shows that two RCTs (Study 5 and 6) may have a high risk of performance bias due to the lack of blinding of participants and personnel, which could influence outcomes. There were uncertainties in allocation concealment and blinding outcome assessment, as there is no explicit information on whether allocation concealment was implemented to prevent foreknowledge of group assignment before enrolling a participant, and whether the outcome assessors were blinded to the intervention groups, which is crucial to prevent detection bias. The risk of other biases, including selection bias, attrition bias, and reporting bias, remains low. The two prospective cohorts were rated as good quality, demonstrating comprehensive strengths across selection, comparability, and outcome domains, indicating a low risk of bias in its results (*Table 3*). For the two unpublished studies (Study 3 and 4), we have limited available information on the methodology to assess the risk of bias across domains. The lack of mothers who consumed alcohol during pregnancy in these two unpublished studies could introduce selection bias within the study (*Figure S2-S3)*.

**Results of individual studies and syntheses**

**Past medical history**

PMH encompasses a broad range of conditions including asthma, deep vein thrombosis (DVT), epilepsy, hypertension, hypothyroidism, obesity, polycystic ovary syndrome (PCOS), infertility, and depression, among others (*Table S6*). Individual studies reported varied estimated effects of PMH on APO, from adjusted odds ratio (aOR) of 1.37 (0.56, 3.36) in Study 1 to 7.13 (2.36, 21.54) in Study 6. The random-effects model in the meta-analysis confirmed PMH as a significant risk factor of APO, with an adjusted odds ratio (aOR) of 2.28 (1.08, 4.83) (*Table 4, Figure 4*).

**Estimated fetal weight centile (EFW centile)**

Studies reported small individual effects with aORs very closed to 1.00. The synthesised result from six studies yielded a pooled aOR of 0.97 (0.96, 0.99) (*Table 4, Figure 4*), reflecting a slight but significant reduction of 3% in the risk of APO with every unit increase in EFW percentile. The highest percentages of adverse outcome were seen in groups characterised by EFW < 30th centile with PMH presence (40.0%), and those consisting of cigarette smokers with EFW < 30th centile (45.0%) (*Figure 3).*

**Maternal age**

The estimated effect of maternal age on APO showed minimal variability across studies, with aORs ranging from a non-significant impact in Study 3 (aOR 0.95 [0.83, 1.09]) to a modest, significant impact in Study 4 (aOR 1.14 [1.01, 1.28]). The meta-analysis concluded an overall aOR of 1.05 (1.01, 1.09), which reflects a slight but statistically significant increase in APO with advancing maternal age (*Table 4, Figure 4*).

**Smoking Status**

The effect size – aOR – for the impact of cigarette smoking status on APO varied across six studies, ranging from 0.69 to 7.77. A pooled result from the meta-analysis revealed a significant association, with smokers having a higher risk of experiencing APO compared to non-smokers (aOR 2.52 [1.20, 5.29]) (*Table 4, Figure 4*).

**Heterogeneity**

A high heterogeneity in EFW percentile (I2 = 75.46%, Tau2 = 0.0004, Q-statistic p-value = 0.0012) was observed. The significant Q-statistic p-value (<0.05) suggested the observed variability in the effect sizes was the true differences between studies and not attributed to chance alone. In contrast, smoking status, PMH, and maternal age did not demonstrate significant heterogeneity in their effects on APO across six studies (*Table 4*).

**Risk of bias across studies**

Egger’s regression tests yielded no p-values less than 0.05, indicating no significant evidence of publication bias across the studies incorporated in this IPD-MA.

**Additional analyses**

The results for EFW centile and maternal age were consistent across all analyses, showing significant associations with APO. PMH was also significantly associated with APO in all analyses, except for Sensitivity Analysis 2, where it approached significance with a p-value of 0.07. Cigarette smoking was significantly associated with APO, but this association became non-significant when intervention arms were excluded (*Table S10, Figure S5*).

Variable selection results (*Table S8*) suggested that fetal heart rate trace might be another impactful factor for APO. Results from Sensitivity Analysis 2 and 4 further confirmed that fetal heart rate assessment (aOR 2.92 [1.39, 6.14]) as significant risk factors for APO, alongside with the gestation of RFM presentation (aOR 0.91 [0.84, 0.98]) (*Table S10*). Results from the complete-case analyses closely aligned with those obtained from the imputed data (*Table S7 and Table S9*).

All sensitivity analyses and the main IPD-MA consistently showed that the effect of EFW centile on the outcome has significant heterogeneity across individual studies (*Table S10*).

**Discussion**

**Main findings**

This IPD-MA highlighted maternal smoking status and past medical history were important risk factors for the composite adverse pregnancy outcome in women with RFM in the third trimester. Smokers are approximately 2.5 times more likely to experience APO compared to non-smokers, underscoring the critical need for targeted interventions and continued surveillance of smoking behaviours among pregnant women to effectively reduce this risk. Additionally, women with pre-existing medical conditions have an approximately 2.3 times higher risk of APO. These comorbidities, especially those affecting the cardiovascular and endocrine systems, may impact placental function.27 Other factors, including EFW centile and maternal age, also contribute to the risk, but to a lesser extent. Mlynarczyk et al. reported neonates with sonographic-estimated fetal weight below the 5th percentile experienced a higher rate of neonatal morbidity (31%) compared to those within the 5th to 9th percentile (13%).28 This finding further indicates that lower EFW percentiles correlate with increased risks. Our results also align with the trends observed in a systematic review and meta-analysis,29 which demonstrated an increased risk of stillbirth with advanced maternal age (OR 1.75 [1.62, 1.89]), alongside similar trends in fetal growth restriction, neonatal death, and NICU admission.

**Strengths**

Unlike the traditional meta-analyses that rely on aggregated data, IPD-MA allows for the reanalysis of raw data across studies in a consistent way. This approach enables more precise data management and analysis:

1) Improved data consistency and harmonisation: We tailored outcome definitions to align with our research objectives - e.g., defining fetal growth restriction as birth weight≤3rd percentile, rather than the 10th percentile as in previous studies. Additionally, we applied multiple imputation across the entire IPD to ensure the methodological consistency and reduce bias.

2) Accounted for Between-Study Heterogeneity: The random effects model quantified the heterogeneity and pooled estimates, providing more reliable insights into our clinical question. In this IPD-MA, significant heterogeneity in the association between EFW percentile and APO suggests differences in the effect of EFW centile on the outcome across different settings or populations, rather than chance. Since we have already adjusted for several important variables - maternal age, gestation at RFM presentation, PMH, and smoking status – in our analysis, yet we still observed significant heterogeneity in the effect of EFW centile. This heterogeneity suggests that there might be other unexplored factors contributing to this inconsistency, such as variability in EFW centile measurements and unmeasured confounders (e.g., genetic predispositions, nutritional and socioeconomic status) that are linked to both fetal growth and the risk of APO.

3) Enhanced sensitivity analysis: We conducted multiple sensitivity analyses to explore how different combinations of studies or data influenced the relationships between the risk factors and APO. In the main IPD-MA, cigarette smoking was significantly associated with an increased risk of APO. However, this association was not significant in the sensitivity analysis that excluded the intervention arms from RCTs, leaving only the cohort studies and the control arms. This change implies that the variation in smoking status between two arms may have contributed to the initial significant effect. In the main analysis, the smoking rates varied more widely (from 6.4% to 11.7%), which could have introduced greater variability in the data, making the relationship between smoking and adverse outcomes more detectable. After removing the intervention arms, the remaining sample became more homogeneous in terms of smoking distribution (around 8.5% to 9.4%), which reduced the variability and, consequently, the statistical significance of smoking status as a risk factor for APO.

**Limitations**

**Missing data**

We observed missing data across individual datasets. We utilised multiple imputation, assuming data were either missing at random (MAR) or missing completely at random (MCAR)30. Although complete-case analysis results aligned closely with those from the main analysis, the wider confidence intervals in the complete-case analysis reflect a reduced sample size and potential underlying biases. Further validation through alternative imputation methods or expanded datasets could help ensure the robustness and generalisability of our findings.

**Population – ethnicity and behavioural**

Most participants in our IPD were White (85%), suggesting potential selection bias across within and across studies, as non-White women may be less likely to seek obstetric care for RFM.31,32 Similarly, no participants in Studies 3 and 4 reported alcohol consumption during pregnancy, which is inconsistent with the contemporaneous Midlands and North of England Stillbirth Study, where a 6.1% incidence of alcohol consumption was reported.33 This discrepancy raises concerns about potential selection bias in Studies 3 and 4, where zero alcohol consumption may not accurately reflect broader population behaviours.

**Adverse Events**

Stillbirth is less common in the UK, with a recorded rate of 0.35% in 2021, compared to a global average of 1.39% in the same year.34,35 This lower incidence may influence the detection of associations between certain conditions and adverse pregnancy outcomes in our study. Future research should include more geographically diverse data. For instance, an IPD-MA by Thompson et al. incorporated data from New Zealand, Australia, the UK, and an internet-based study based out of the USA.1 Including data from regions with higher APO rates, such as low-income and developing countries, would ensure a more representative number of events. This diversification will increase the sample size and enhance the statistical power of future analyses, yielding more widely applicable results.

**Past Medical History**

This IPD-MA did not delve into the impact of specific prior health conditions - such as significant mental health problems, cardiovascular diseases, reproductive health issues, or other diseases on severe pregnancy outcomes. This oversight highlights a critical area for future research that could provide more comprehensive insights into the impact of different past medical history on adverse outcomes.

**Inclusion of diverse study designs**

Including both cohorts and RCTs could introduce methodological heterogeneity, complicating result interpretation. For example, the discrepancy of smoking’s effect when included and excluded RCTs highlights the critical role of study design and confounding control. In Study 6,36 a blood test measuring the sFlt-1/PLGF ratio, a biomarker indicative of placental function, informed clinical decisions about early delivery or levels of care. The outcomes modelled in RCTs occur post-intervention, which could influence results differently than observational studies where no interventions are applied. Future meta-analysis should consider focusing on similar designs, such as exclusively RCTs or cohort studies, to help ensure comparability in the meta-analysis.

**Interpretation**

Clinicians should emphasise the importance of considering maternal past medical history and smoking during pregnancy, especially if the estimated fetal weight less than 30th centile, when targeting the highest-risk women with subjectively perceived reduced fetal activity and determine the most appropriate intervention.

**Conclusion**

Maternal past medical history and cigarette smoking were the most strongly associated with the adverse pregnancy outcomes following RFM, including stillbirth, fetal growth restriction (≤3rd centile), and neonatal intensive unit admission at term (≥37 weeks). Estimated fetal weight percentile and maternal age also demonstrated a significant association with the outcome. EFW percentile showed clear heterogeneity in this analysis, which might be due to the difference in quality and potential recording biases in the individual studies. Optimising data collection procedures is crucial to avoid missingness in data, and more studies from various regions are needed to enhance the robustness and minimise the impact of rare outcomes in future IPD meta-analyses.

**List of abbreviations**

IPD-MA Individual Participant Data Meta-Analysis

RFM Reduced Fetal Movement

APO Adverse Pregnancy Outcome

NICU Neonatal Intensive Care Unit

EFW Estimated Fetal Weight

FGR Fetal Growth Restriction

SBP Systolic Blood Pressure

DBP Diastolic Blood Pressure

AFM Absent Fetal Movements

AFI Amniotic Fluid Index

CTG Cardiotocography

MAR Missing at Random

MCAR Missing Completely at Random

MI Multiple Imputation

RCT Randomised Controlled Trial

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**Disclosure of Interests**

None of the authors have any financial, personal, or professional interests that could be construed as influencing the research.

**Contributions to Authorship**

Conceived the IPD-MA: VP AH. Provided raw data: AH. Pre-processed and analysed the data: YL. Wrote the draft manuscript: YL. Provided comments: VP AH. Refined the paper: VP AH.

**Ethics approval**

Individual studies were approved by the Human Research Authority (FEMINA1 - 08/H1011/83; FEMINA2 - 11/NW/0650; FEMINA3 - 16/NW/0481; ReMIT - 11/NW/0664, ReMIT-2 - 17/NW/0014)

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