*Journal of Developmental Origins of Health and Disease*

**www.cambridge.org/doh**

# Associations of offspring birthweight and placental weight with subsequent parental coronary heart disease: survival regression using the walker cohort

Carlos Sánchez-Soriano[1], Ewan R. Pearson[2] and Rebecca M. Reynolds[1]

[1]Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK and [2]Division of Population Health and Genomics, Ninewells Hospital and School of Medicine, University of Dundee, Dundee, UK

**Original Article**

**Cite this article:** Sánchez-Soriano C, Pearson ER, and Reynolds RM. (2023) Associations of offspring birthweight and placental weight with subsequent parental coronary heart disease: survival regression using the walker cohort. *Journal of Developmental Origins of Health and Disease* **14**: 746–754. doi: 10.1017/S2040174423000430

Received: 13 December 2022
Revised: 9 August 2023
Accepted: 5 December 2023
First published online: 9 January 2024

**Keywords:**
Birth weight; placental weight; coronary heart disease; survival analysis; parental associations

**Corresponding author:**
R. M. Reynolds; Email: r.reynolds@ed.ac.uk

## Abstract

Low birth weight (BW) is consistently correlated with increased parental risk of subsequent cardiovascular disease, but the links with offspring placental weight (PW) are mostly unexplored. We have investigated the associations between parental coronary heart disease (CHD) and offspring BW and PW using the Walker cohort, a collection of 48,000 birth records from Dundee, Scotland, from the 1950s and 1960s. We linked the medical history of 13,866 mothers and 8,092 fathers to their offspring's records and performed Cox survival analyses modelling maternal and paternal CHD risk by their offspring's BW, PW, and the ratio between both measurements. We identified negative associations between offspring BW and both maternal (hazard ratio [HR]: 0.91, 95% confidence interval [CI]: 0.88–0.95) and paternal (HR: 0.96, 95% CI: 0.93–1.00) CHD risk, the stronger maternal correlation being consistent with previous reports. Offspring PW to BW ratio was positively associated with maternal CHD risk (HR: 1.14, 95% CI: 1.08–1.21), but the associations with paternal CHD were not significant. These analyses provide additional evidence for intergenerational associations between early growth and parental disease, identifying directionally opposed correlations of maternal CHD with offspring BW and PW, and highlight the importance of the placenta as a determinant of early development and adult disease.

## Introduction

Following the investigation linking early life development and adult cardiometabolic outcomes,[1,2] multiple epidemiological studies have investigated associations between offspring birth weight (BW) and parental mortality. Strong and consistent inverse associations have been found between offspring BW and maternal cardiovascular disease (CVD) mortality[3–10] and CVD risk factors such as blood pressure or carotid intima media thickness.[11,12] Studies including fathers have also reported inverse associations with paternal CVD mortality,[3,7–10] although generally weaker compared to the maternal association, suggesting the potential effect of the intrauterine environment conditioning this relationship.[10] Similar associations were found linking BW to CVD mortality in aunts, uncles, and grandparents,[13,14] supporting the role of inheritance of genetic variants influencing fetal growth and increasing CVD risk.[3,7,11] It is hypothesised that the associations between parental CVD and offspring BW result from a matrix of genetic, epigenetic, intrauterine, and other shared environmental influences.[9,15,16]

Despite being a vital organ for fetal development, placental weight (PW) is often unavailable for epidemiological studies tying early growth to adult health. Only a few studies have considered the association between placental characteristics and adult disease development,[17–20] and even fewer studies have investigated their association with parental CVD. Davey-Smith *et al.* did not find significant associations between PW or PW to BW ratio and maternal CVD mortality.[5] However, using a larger sample, Yeung *et al.* found positive associations between offspring PW to BW ratio and maternal CVD mortality.[21] Apart from the correlation between placental size and fetal development,[22,23] suggesting similar genetic associations to those seen for BW,[24–26] the role of the placenta in the association between fetal growth restriction and parental health outcomes is not yet understood. A recent causal mediation analysis by Sato and colleagues[27] revealed that while maternal polygenic scores for blood pressure measurements are inversely associated with offspring BW, this effect was greatly mediated by placental weight, further adding to the complexity of the early determination of adult cardiometabolic disease.

The Walker cohort[28] is a collection of birth records from Dundee, Scotland, from 1952 to 1970. Walker includes information for 75% of all births in the area for that timeframe, recording PW measurements and details on the mothers and fathers, making it relevant to study links

between parental cardiometabolic disease and birth outcomes. The inclusion of paternal data in these analyses is vital to attempt to discriminate genetic and intrauterine effects from a phenotypic point of view. Using Walker, we previously investigated the associations between offspring BW and PW and parental type 2 diabetes (T2D) risk,[29] identifying novel links between offspring PW and paternal T2D. We hypothesised that parental CHD incidence would be negatively associated with offspring BW and PW, by effect of the genetic inheritance of variants which might reduce fetal growth while also increasing CHD susceptibility. Survival regression analyses of maternal and paternal CHD risk modelled by their offspring BW and PW were performed to test this hypothesis.

## Methods

### Study population and data sources

All individuals included in the analysis were part of the Walker cohort.[28] Offspring BW, PW, gestational age (GA), and sex were documented directly in the Walker records at the time of birth (1951–1968) by obstetricians. For around 70% of the individuals, GA was inferred from the time between the date of birth (DOB) and the last maternal menstrual period, or from the time between 280 days before the DOB and the recorded estimated delivery date, if last menstrual period records were not available. Parental health information was obtained through data linkage using the NHS Scotland Community Health Index unique identifier. Parental CHD and death information were obtained through the SMR01 (hospital admissions) and the National Records Scotland (death records) datasets. The World Health Organization ICD9 and ICD10 codes and National Health Service OPCS-4 codes used to define CHD for these analyses are included in Supplementary Table 1. The national Community Health Index dataset was used to obtain parental DOB and Health Board specific Scottish Index of Multiple Deprivation (HBSIMD, 2019 v2 release), categorising areas according to their deprivation quintile (five meaning least deprived).

### Data exclusions

Individuals with GA under 37 weeks or over 42 weeks, BW under 2,500g or over 4,500g, or PW under 200g or over 1,000g were excluded from the analysis, to select only healthy term pregnancies and exclude extreme BW and PW measurements. Only singleton pregnancies and firstborn were included. Offspring BW and PW were sex-stratified and standardised through Z-transformation, to compare their effects more appropriately and account for any variation due to offspring sex. The analyses included all identifiable parents living in the area who had not been admitted to hospitals due to CHD causes prior to January 1st 1981, when SMR01 data started being collected routinely. This date defined the study start point. The dataset was supplemented with additional CHD events from the death registry from 1989, when causes of death started being recorded as ICD codes. The study endpoint was defined as the date of the last CHD event (September 12th 2019). After the exclusion process, the final datasets included 13,866 mothers and 8,092 fathers, 91.52% and 92.58% of the total identifiable Walker parents, respectively. A subset of this dataset was used for the supplemental Fine-Gray survival regression analysis, setting the study start in January 1st 1989 due to the need of ICD-coded causes of death from the death records. This dataset included 12,094 mothers and 6,677 fathers. Survival analyses were performed using all individuals with complete information for the explanatory variables.

## Statistical analyses

All analyses were conducted using the R statistical software[30] version 3.6.2.

### Summary statistics

All analyses were performed separately for the maternal and paternal datasets. Welch two sample t-tests were used to determine differences in continuous variables by parental CHD status or between the maternal and paternal datasets, using the test of equal proportions for binary variables. Violin plots comparing these differences were built using only offspring whose mother and father could be identified ($n = 7{,}478$).

### Survival analysis study design

Two sets of survival models were built to analyse parental risk of CHD. Cox survival regression[31] was used to investigate the association between offspring BW, PW, and PW:BW ratio and parental CHD risk, defined by CHD-related hospital admission or death by CHD (collected from 1989). The event time was defined as the period between the start of the study (January 1st 1981) and the first CHD event, or until censoring due to death, loss of follow-up, or no event presented. Sex-stratified Z-transformed offspring BW, PW, BW and PW together (BW + PW), and PW to BW ratio (PW:BW) were used as main explanatory variables in different models within each set. The BW and PW models were built to independently assess their contribution to parental CHD risk. The BW + PW models were built to investigate these variables accounting for each other, particularly to provide an estimate for PW accounting for BW. The PW:BW ratio models were built to assess the association such variable as a measure of placental efficiency. Offspring GA, parental age in 1981, and parental HBSIMD were included as additional explanatory variables. Due to the aged population of the study and the lack of follow-up before 1981, supplemental Fine-Gray survival models[32] were built to analyse parental risk of CHD (defined as hospital admission only) accounting for the competing risk of death from causes other than CHD. January 1st 1989 was set as the start of the study for these analyses, as ICD codes for cause of death were not available before then. The Fine-Gray models also included offspring GA, parental age in 1989, and parental HBSIMD as additional variables. The Cox and Fine-Gray regression analyses were performed using the *survival*[33] and *cmprsk*[34] packages, respectively. The effect sizes of the covariates were reported as hazard ratios (HR) for the Cox models, and subdistribution hazard ratios (SHR) for the Fine-Gray models. Scaled Schoenfeld residuals tests[35] were performed to determine violations of the proportional hazards assumption, supported with observational assessment of Schoenfeld residuals against event time plots, performed using the Cox models. In order to account for violations of the proportionality of hazards, any variables with time-dependent effects were adjusted including an interaction term with a logarithmic function of time. Cumulative incidence curves for parental CHD by age and offspring BW, PW, and PW:BW ratio quartiles were built using the *cmprsk* package.[34] The power calculations for the Cox models were performed using the *powerSurvEpi* package.[36]

## Results

### Parental CHD and death summary statistics

Table 1 shows the characteristics of the parents included in the analyses and their offspring. Overall, 23.9% and 36.7% mothers and fathers, respectively, had developed CHD. Fathers had CHD

https://doi.org/10.1017/S2040174423000430 Published online by Cambridge University Press

**Table 1.** Summary statistics for the maternal and paternal datasets

| | Maternal Dataset ($n = 13,866$) | Missing | Paternal Dataset ($n = 8092$) | Missing | $p$ value |
|---|---|---|---|---|---|
| **Offspring** | | | | | |
| BW (g) | 3375.83 ± 412.21 | 0.11% | 3389.45 ± 411.60 | 0.10% | 0.018 |
| PW (g) | 651.53 ± 117.91 | 55.03% | 654.15 ± 120.21 | 48.22% | 0.270 |
| PW:BW Ratio | 0.19 ± 0.03 | 55.20% | 0.19 ± 0.03 | 48.27% | 0.743 |
| GA (weeks) | 39.89 ± 1.29 | 2.54% | 39.89 ± 1.28 | 2.49% | 0.743 |
| Age at Study End (y) | 59.91 ± 4.68 | 0.17% | 59.15 ± 4.51 | 0.14% | <0.001 |
| Sex | F: 6025 (43.45%) M: 7841 (56.55%) | 0% | F: 3300 (40.78%) M: 4792 (59.22%) | 0% | <0.001 |
| **Parent** | | | | | |
| CHD Event | 3308 (23.86%) | – | 2967 (36.67%) | – | <0.001 |
| Age at CHD Event (y) | 69.92 ± 10.70 | 1.51% | 67.68 ± 10.41 | 1.40% | <0.001 |
| Death | 8559 (61.73%) | – | 6035 (74.58%) | – | <0.001 |
| Age at Death (y) | 76.53 ± 10.58 | 1.51% | 75.42 ± 9.79 | 1.40% | <0.001 |
| HBSIMD | 1: 4487 (33.91%) | 4.58% | 1: 2465 (31.46%) | 3.17% | < 0.001 |
| | 2: 2929 (22.14%) | | 2: 1661 (21.20%) | | |
| | 3: 1635 (12.36%) | | 3: 977 (12.47%) | | |
| | 4: 1967 (14.86%) | | 4: 1186 (15.14%) | | |
| | 5: 2213 (16.72%) | | 5: 1546 (19.73%) | | |

The p value for the difference in variables between the maternal and paternal datasets is included. Data are mean ± standard deviation or number (percentage). The *Age at coronary heart disease (CHD) Event* row represents the mean age at the time of CHD event (hospital admission or death). The *HBSIMD* row represents the number of individuals categorised under each quintile of the Scottish Index of Multiple Deprivation (five meaning least deprived). The *Missing* column refers to the percentage of missing records for each measurement in each dataset. The *Missing* values next to the mean ages of CHD development and death represent the percentage of individuals missing date of birth.

events and died at younger ages than mothers, but had lower deprivation levels on average. The paternal dataset included significantly heavier (13.6g on average) offspring than the maternal dataset, likely due to paternal data being less common during the earlier years of the study, and due to a higher percentage of offspring being male.

Ischaemic heart diseases accounted for the majority of CHD events recorded for both mothers and fathers (Supplementary Table 1). CHD-related hospital admissions accounted for 82.65% and 86.98% of the maternal and paternal CHD events recorded in the dataset, respectively. The characteristics of the dataset used for the supplemental Fine-Gray regression analyses were similar to the main dataset, with no significant differences in the main offspring outcomes studied (Supplementary Table 2).

### Difference in offspring BW and PW by parental CHD status

Table 2 shows the difference in offspring BW, PW, and PW:BW ratio according to parental CHD status. Offspring from mothers who subsequently developed CHD were, on average, 30.7g lighter ($p < 0.001$) than offspring from mothers who did not develop CHD. Mothers who developed CHD also had offspring with higher PW:BW ratios, representing higher PW for a given BW ($p < 0.001$), although PW did not differ. Mothers who developed CHD had shorter pregnancies than those without CHD by around 10 hours ($p = 0.021$). We found no significant differences in mean offspring BW, PW, PW:BW ratio, or GA between fathers who developed CHD and those who did not.

Fig. 1 shows the difference in offspring BW, PW, and PW:BW ratio by the individual CHD status of each parent. Offspring were born lighter when both parents ($p = 0.019$) or only the mother ($p = 0.011$) subsequently developed CHD. In contrast, offspring from parents who both developed CHD had significantly higher PW:BW ratios than offspring from parents who did not develop CHD ($p = 0.016$) or when only the father did ($p = 0.005$).

### Parental CHD cumulative incidence by offspring BW and PW quartiles

Fig. 2 shows the cumulative incidence curves for maternal and paternal CHD by offspring BW, PW, and PW:BW ratio quartiles. In mothers, incidence of CHD was significantly higher for those whose offspring was in the lowest BW quartile (Q1), compared to the highest quartile ($p < 0.001$). Maternal CHD incidence appeared higher for those whose offspring was in the highest PW quartile, but the interquartile differences were not significant. Maternal CHD incidence was significantly higher in those whose offspring PW:BW ratio was in the highest quartile (Q4), compared to the lowest quartile ($p < 0.001$). The patterns for paternal CHD incidence were similar, but interquartile differences were not significant.

### Cox survival analyses of parental CHD risk

The results from the maternal and paternal survival analyses of CHD risk are shown in Tables 3 and 4, respectively. Parents at the highest risk of developing CHD were those who had offspring born smaller (mothers HR: 0.91, CI: 0.88–0.95, $p < 0.001$; fathers HR: 0.96, CI: 0.93–1.00, $p = 0.048$). A decrease of 1 SD in the offspring BW Z-score was associated with a 8.6% and 3.8% increase in the HR for CHD risk in mothers and fathers, respectively. Mothers at higher risk of developing CHD also had higher offspring PW when accounted for BW (HR: 1.14. CI: 1.07–1.22, $p < 0.001$), and PW:

**Table 2.** Summary of variables of interest and their difference between parents who developed coronary heart disease and those who did not

| | CHD Mothers ($n = 3308$) | Undiagnosed Mothers ($n = 10,558$) | $p$ value | CHD Fathers ($n = 2967$) | Undiagnosed Fathers ($n = 5125$) | $p$ value |
|---|---|---|---|---|---|---|
| **Offspring** | | | | | | |
| BW (g) | 3352.43 ± 411.65 | 3383.17 ± 412.13 | <0.001 | 3384.93 ± 406.90 | 3392.07 ± 414.31 | 0.450 |
| PW (g) | 654.51 ± 114.26 | 650.81 ± 118.77 | 0.315 | 652.15 ± 117.11 | 655.21 ± 121.82 | 0.428 |
| PW:BW Ratio | 0.20 ± 0.03 | 0.19 ± 0.03 | <0.001 | 0.19 ± 0.03 | 0.19 ± 0.03 | 0.878 |
| GA (weeks) | 39.84 ± 1.33 | 39.90 ± 1.28 | 0.021 | 39.91 ± 1.28 | 39.88 ± 1.27 | 0.394 |
| Age at Study End (y) | 60.83 ± 4.56 | 59.62 ± 4.69 | <0.001 | 59.49 ± 4.48 | 58.95 ± 4.51 | <0.001 |
| Sex | F: 43.44 % | F: 43.45% | 0.988 | F: 39.94 % | F: 41.27% | 0.240 |
| **Parent** | | | | | | |
| HBSIMD | 2.40 ± 1.42 | 2.64 ± 1.51 | <0.001 | 2.61 ± 1.52 | 2.76 ± 1.53 | <0.001 |

The $p$ value for the difference in variables is included. Data are mean ± standard deviation. The *HBSIMD* row represents the number of individuals categorised under each quintile of the Scottish Index of Multiple Deprivation (higher meaning less deprived).

https://doi.org/10.1017/S2040174423000430 Published online by Cambridge University Press

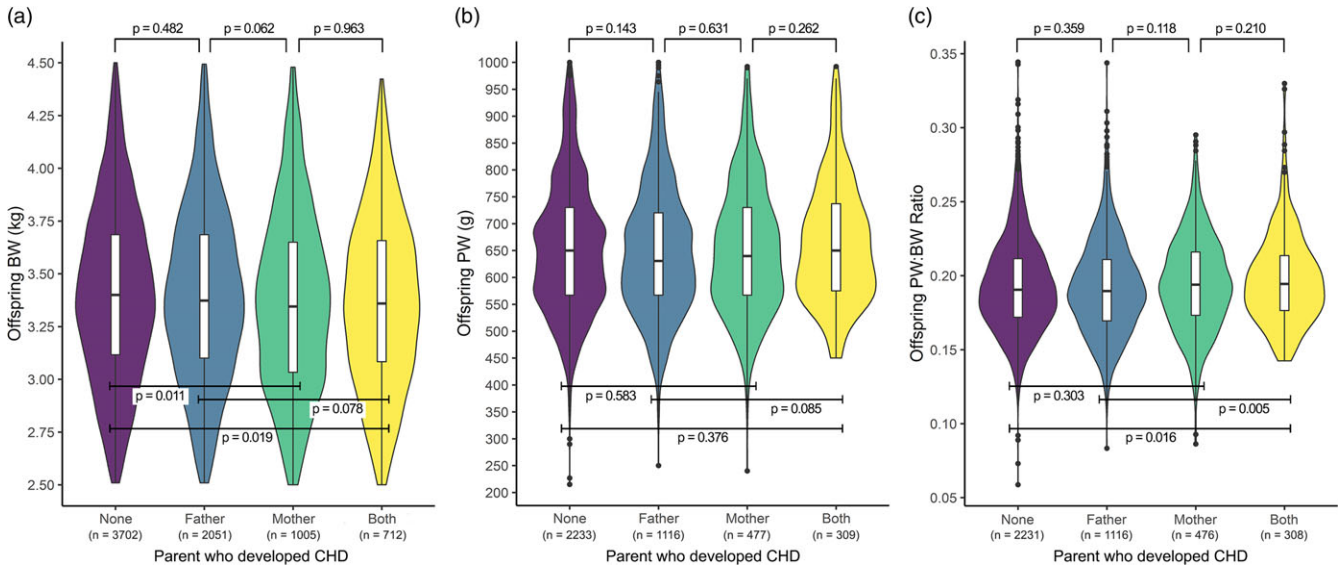


**Figure 1.** Violin plots of offspring birth weight (A) and placental weight (B) by post-birth development of parental coronary heart disease. Vertical box-and-whiskers plots are included. The p values for the difference in means between each pair of samples (identified by the black lines) was calculated through Welch two sample t-tests.

BW ratio (HR: 1.14, CI: 1.08–1.21, $p < 0.001$). No significant associations were found between offspring PW or PW:BW ratio and paternal CHD risk.

### *Fine-gray survival analyses of parental CHD risk*

In the supplemental Fine-Gray analyses accounting for the competing risk of death (Supplementary Tables 3 and 4), similar associations were found. Mothers at the highest risk of developing CHD were those who had offspring of lower BW (SHR: 0.93, CI: 0.87–0.97, $p < 0.001$) and higher PW:BW ratio (SHR: 1.26, CI: 1.07–1.49, $p = 0.007$). No significant associations were found between offspring BW, PW, or PW:BW ratio and the paternal risk of developing CHD accounting for the competing risk of death.

## Discussion

In a novel approach using the Walker cohort, this study investigated the association between parental CHD and offspring birth outcomes. This is the first study including PW measurements and a paternal sample, allowing exploration of associations between offspring PW (and its ratio to BW) and paternal CHD development.

Walker babies from mothers who later developed CHD were born nearly 31g lighter, and this association was independent of whether the father also developed CHD or not. This is in agreement with previous reports of maternal CVD mortality being consistently associated with lower offspring BW.[3,4,7,9,10,14,37] Although we found no difference in offspring BW by whether the fathers subsequently developed CHD or not, using Cox regression we found negative associations between offspring BW and both maternal and paternal CHD risk. This is also supported by the cumulative incidence curves, where the trajectories for parents with offspring in the lowest quartile of BW show increased CHD incidence compared to parents in the highest quartile. Although we identified associations between paternal CHD risk and offspring BW, they are notably of a smaller magnitude than those seen for the mothers, and closer to the 0.05 significance level. The paternal associations suggest that offspring BW is partially genetically determined through the inheritance of CVD-susceptibility variants. The maternal results, however, are consistent with the strong influence of the intrauterine environment and the reflection of maternal health (and subsequent disease risk) over offspring fetal growth,[38,39] likely obscuring the effect of the maternal genotype.[40,41] One might argue that the paternal associations result simply from the shared parental environment and familial deprivation, but the associations between offspring BW and CVD spread across the extended family,[13,14] strongly suggesting the transmission of CVD-risk alleles through generations. The determination of BW and adult disease has been characterised as a complex mechanism resulting from the interplay between the environmental influences over maternal health (and therefore over the intrauterine environment), the independent expression of the maternal and fetal genomes, and possibly also epigenetic modifications.[14,16,27,37,42]

The model including offspring BW and PW showed strong and directionally opposed effect estimates for BW (HR: 0.837) and PW (HR: 1.142), identifying a positive association between the latter and maternal CHD development after accounting for BW. We also found associations between maternal CHD risk and increased offspring PW:BW ratio (HR: 1.144), as a rough reflection of placental inefficiency. This is consistent with the study by Yeung *et al.*[21] who identified associations between higher offspring PW:BW ratios and increased maternal mortality from several causes such as CVD. Earlier, Davey-Smith *et al.*[5] failed to find such associations, but their sample size was considerably smaller. These results support a link between placental efficiency, fetal growth, and maternal cardiovascular health. Maternal vascular disorders have been linked to poor placental perfusion, leading to insufficiency, impaired fetal growth, and an enlargement of the placenta.[12,43] Increased PW and PW:BW ratios have been associated with adult CVD risk factors and mortality,[17–20] supporting the role of the placenta as a determinant of fetal outcomes and later disease development. We did not find significant associations between paternal CHD risk and offspring PW or PW:BW ratio, but there are no other studies in the literature

https://doi.org/10.1017/S2040174423000430 Published online by Cambridge University Press

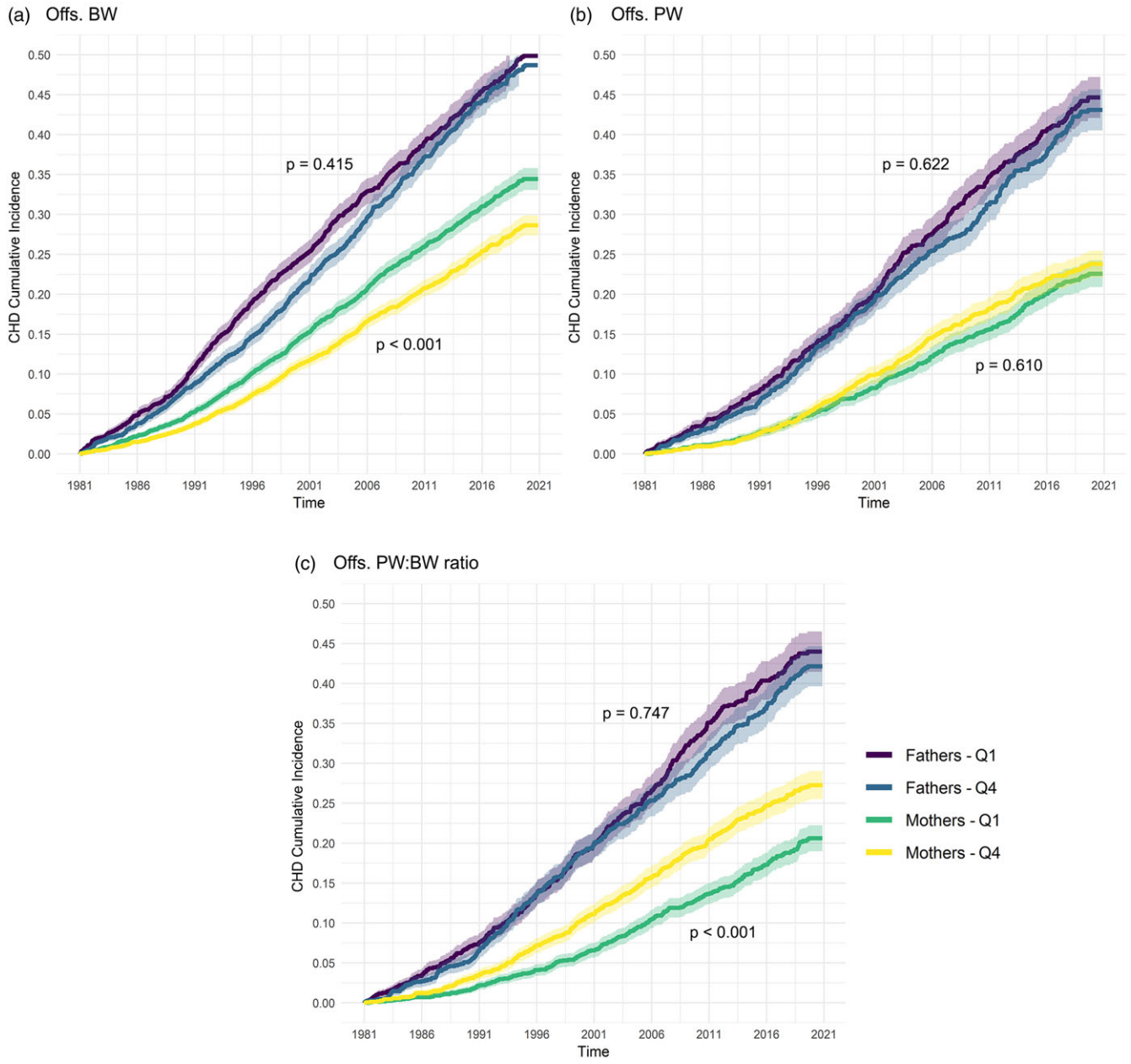


**Figure 2.** Cumulative incidence curves for parental coronary heart disease by time and offspring (a) birth weight (BW), (b) placental weight (PW), and (c) PW:BW ratio quartiles. Only quartiles 1 and 4 are plotted for clarity. Maternal curves are depicted in green (Q1, lowest quartile) and yellow (Q4, highest quartile). Paternal curves are depicted in purple (Q1) and blue (Q4). The p values for the interquartile difference in trajectories were calculated using Gray's test of equality.

for comparison. In contrast to our previous investigation on parental T2D,[29] we failed to identify paternal associations with offspring PW which could be explained by the fetal inheritance of a disease susceptibility genotype, leading to adult cardiometabolic disorders. Nonetheless, offspring from fathers who later developed CHD had slightly lighter placentas. Alternatively, fetal CVD-susceptibility variants might not be expressed in the placenta,[44] they might be subject to parent-of-origin differential expression,[45] or their action might be outweighed by direct maternal effects.

Our capacity to find a significant negative association between paternal CHD and offspring PW might have been restricted by our late study start point or by the reduced sample with PW available, limiting the statistical power. Through power calculations, we estimated that we had around 50% probability of finding real associations between PW adjusted for BW or PW:BW ratio and paternal CHD of a magnitude similar to those seen in the maternal analyses with the same confidence level (0.001), but around 90% probability of finding them under a 0.05 confidence level. However, these calculations[36] did not incorporate the adjustments performed to comply with the proportional hazards assumption. Recent studies have shown that the association between low BW and the adult development of cardiometabolic disease is governed by a fetal-only effect, being confounded by the maternal effect on the intrauterine environment.[26,46,47] Following this logic and due to the additional evidence hinting at an effect similar to BW, it is likely that our restricted power among other study limitations described below prevented us from finding associations between paternal CHD and offspring PW.

https://doi.org/10.1017/S2040174423000430 Published online by Cambridge University Press

**Table 3.** Cox survival analysis of maternal coronary heart disease (CHD) risk

| Cox survival regression of maternal CHD risk (CHD hospitalisation + death) | | | | |
|---|---|---|---|---|
| | H. R. | C. I. ($\alpha = 0.05$) | S. E. | *P* value |
| **Analysis including only Offs. BW ($n = 12,863$)** | | | | |
| Offs. BW | 0.914 | (0.881–0.948) | 0.019 | <0.001 |
| Offs. GA | 0.988 | (0.961–1.016) | 0.014 | 0.386 |
| Age '81 | 1.068 | (1.063–1.073) | 0.002 | <0.001 |
| HBSIMD | 0.759 | (0.688–0.837) | 0.050 | <0.001 |
| HBSIMD * log(t) | 1.048 | (1.013–1.083) | 0.017 | 0.006 |
| **Analysis including only Offs. PW ($n = 5821$)** | | | | |
| Offs. PW | 1.048 | (0.990–1.110) | 0.029 | 0.107 |
| Offs. GA | 0.736 | (0.606–0.894) | 0.099 | 0.002 |
| Age '81 | 1.113 | (1.073–1.154) | 0.018 | <0.001 |
| HBSIMD | 0.781 | (0.652–0.936) | 0.092 | 0.007 |
| Offs. GA * log(t) | 1.094 | (1.025–1.169) | 0.033 | 0.007 |
| Age '81 * log(t) | 0.984 | (0.972–0.996) | 0.006 | 0.012 |
| HBSIMD * log(t) | 1.031 | (0.971–1.095) | 0.031 | 0.312 |
| **Analysis including Offs. BW and PW ($n = 5815$)** | | | | |
| Offs. BW | 0.837 | (0.780–0.899) | 0.036 | <0.001 |
| Offs. PW | 1.142 | (1.068–1.220) | 0.034 | <0.001 |
| Offs. GA | 0.753 | (0.620–0.914) | 0.099 | 0.004 |
| Age '81 | 1.113 | (1.074–1.154) | 0.018 | <0.001 |
| HBSIMD | 0.789 | (0.659–0.945) | 0.092 | 0.010 |
| Offs. GA * log(t) | 1.096 | (1.027–1.170) | 0.033 | 0.006 |
| Age '81 * log(t) | 0.985 | (0.972–0.997) | 0.006 | 0.014 |
| HBSIMD * log(t) | 1.031 | (0.971–1.095) | 0.031 | 0.318 |
| **Analysis including Offs. PW to BW Ratio ($n = 5815$)** | | | | |
| Offs. PW:BW Ratio | 1.144 | (1.081–1.210) | 0.029 | <0.001 |
| Offs. GA | 0.742 | (0.611–0.901) | 0.099 | 0.003 |
| Age '81 | 1.113 | (1.074–1.154) | 0.018 | <0.001 |
| HBSIMD | 0.783 | (0.654–0.938) | 0.092 | 0.008 |
| Offs. GA * log(t) | 1.096 | (1.027–1.171) | 0.033 | 0.006 |
| Age '81 * log(t) | 0.984 | (0.972–0.997) | 0.006 | 0.013 |
| HBSIMD * log(t) | 1.032 | (0.972–1.096) | 0.031 | 0.305 |

CHD was defined as hospitalisation or death due to CHD. The *H.R.* column represents the hazard ratio for the covariate. The *C.I.* column represents the 95% Confidence Interval for the coefficient. The *S.E.* column represents the regression standard error. *Age '81* refers to the individual 'age in 1981' variable. *HBSIMD* refers to the Scottish Index of Multiple Deprivation (higher meaning less deprived).

**Table 4.** Cox survival analysis of paternal coronary heart disease (CHD) risk

| Cox Survival Regression of Paternal CHD Risk (CHD hospitalisation + death) | | | | |
|---|---|---|---|---|
| | H. R. | C. I. ($\alpha = 0.05$) | S. E. | *P* value |
| **Analysis including only Offs. BW ($n = 7619$)** | | | | |
| Offs. BW | 0.962 | (0.926–1.000) | 0.020 | 0.048 |
| Offs. GA | 1.022 | (0.992–1.053) | 0.015 | 0.146 |
| Age '81 | 1.049 | (1.044–1.055) | 0.003 | <0.001 |
| HBSIMD | 0.802 | (0.742–0.866) | 0.039 | <0.001 |
| HBSIMD * log(t) | 1.044 | (1.016–1.073) | 0.014 | 0.002 |
| **Analysis including only Offs. PW ($n = 3966$)** | | | | |
| Offs. PW | 0.972 | (0.922–1.025) | 0.027 | 0.295 |
| Offs. GA | 1.032 | (0.989–1.076) | 0.022 | 0.150 |
| Age '81 | 1.072 | (1.049–1.096) | 0.011 | <0.001 |
| HBSIMD | 0.797 | (0.709–0.895) | 0.059 | <0.001 |
| Age '81 * log(t) | 0.992 | (0.984–1.001) | 0.004 | 0.068 |
| HBSIMD * log(t) | 1.042 | (1.001–1.086) | 0.021 | 0.047 |
| **Analysis including Offs. BW and PW ($n = 3962$)** | | | | |
| Offs. BW | 0.960 | (0.900–1.024) | 0.033 | 0.220 |
| Offs. PW | 0.991 | (0.932–1.054) | 0.031 | 0.773 |
| Offs. GA | 1.038 | (0.994–1.084) | 0.022 | 0.092 |
| Age '81 | 1.073 | (1.049–1.097) | 0.011 | <0.001 |
| HBSIMD | 0.798 | (0.710–0.896) | 0.059 | <0.001 |
| Age '81 * log(t) | 0.992 | (0.984–1.001) | 0.004 | 0.068 |
| HBSIMD * log(t) | 1.042 | (1.001–1.086) | 0.021 | 0.046 |
| **Analysis including Offs. PW to BW Ratio ($n = 3962$)** | | | | |
| Offs. PW:BW Ratio | 1.003 | (0.950–1.057) | 0.027 | 0.926 |
| Offs. GA | 1.030 | (0.987–1.075) | 0.022 | 0.170 |
| Age '81 | 1.072 | (1.049–1.096) | 0.011 | <0.001 |
| HBSIMD | 0.795 | (0.708–0.894) | 0.059 | <0.001 |
| Age '81 * log(t) | 0.992 | (0.984–1.000) | 0.004 | 0.063 |
| HBSIMD * log(t) | 1.043 | (1.001–1.086) | 0.021 | 0.045 |

CHD was defined as hospitalisation or death due to CHD. The *H.R.* column represents the hazard ratio for the covariate. The *C.I.* column represents the 95% confidence interval for the coefficient. The *S.E.* column represents the regression standard error. *Age '81* refers to the individual 'age in 1981' variable. *HBSIMD* refers to the Scottish Index of Multiple Deprivation (higher meaning less deprived).

For this investigation we have used the Walker cohort,[28] which includes accurate records for three quarters of the total births in the region during its time, and enabling linkage to health records from the parents, which by now have experienced remarkable disease morbidity. However, there are inevitable limitations of such an epidemiological cohort that need to be considered when interpreting our results. In contrast with other reports using a wider cardiovascular mortality outcome definition including a more variable array of conditions, which might be diversely associated with offspring growth, we have focused on CHD hospitalisations and mortality, for which over 90% were categorised as ischaemic heart diseases. Focusing on CHD only might have limited our sample size. In addition, the hospital admissions data only started being collected after 1980, thirty years after the delivery of the oldest children in the cohort. This carries the possibility of some CHD cases being introduced into the model with a delay or being missed completely due to death or no subsequent admissions during the observable period. This is especially problematic for the paternal analyses due to their earlier onset of CHD. Additionally, the possibility of death before developing CHD should also be considered. The Fine-Gray regression was performed to investigate the associations for CHD

https://doi.org/10.1017/S2040174423000430 Published online by Cambridge University Press

risk accounting for the competing risk of death, but the death records lacked cause of death until 1989, which pushed the study start point further back, increasing the CHD cases missed and therefore being relegated to supplementary material. Any explanatory variables violating the proportional hazards assumption for the Cox and Fine-Gray models were adjusted by adding an interaction term of said covariates with the logarithm of follow-up time. This was considered necessary to prevent proportional hazards violations, albeit increasing the risk of overfitting the model and complicating the interpretation of the results, since the estimated effect of these variables should also consider the time-dependent effect as quantified by the interaction term. The survival regression analyses could not be adjusted for parental weight, height, or smoking and alcohol consumption since these were mostly unavailable for Walker, variables which might act as confounders for offspring outcomes and parental CHD risk. The analyses were adjusted by deprivation index (HBSIMD) from 2019 as a proxy for socio-economic class, which was also missing from Walker. This data resulted highly correlated with a social class categorisation[48] of the parental occupation data available from Walker (analyses not shown). We did not adjust for multiple testing as our separate analyses for BW, PW, and BW:PW as predictors of parental CHD each offered different perspectives on the analyses and were conducted in different subsets of the dataset. Finally, since PW measurements were only collected for the latter half of the cohort, our ability to identify significant associations with offspring PW might have been limited by the analyses being restricted to a younger and smaller parental sample, with lower CHD morbidity. The differences between the entire parental datasets and the subset of individuals for which offspring PW was available are described in Supplementary Table 5.

In conclusion, we have provided additional evidence for independent and directionally opposed effects of maternal CHD risk on offspring BW and PW. Maternal CHD risk was also positively associated with offspring PW to BW ratio, highlighting the importance of placental development and efficiency for fetal growth and its relationship with adult disease. Further analyses with a more comprehensive cohort are required to provide additional insights regarding any association of paternal CHD with offspring PW, and future efforts should focus on unravelling how fetal CVD-susceptibility variants might be influencing not just BW, but placental growth and function.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S2040174423000430.

**Acknowledgments.** We thank K. F. Bedair and A. T. N. Nair from the Division of Population Health and Genomics at the University of Dundee for their assistance on performing Fine-Gray regression.

**Financial support.** CSS is supported by a PhD studentship award from the Medical Research Council and the University of Edinburgh College of Medicine and Veterinary Medicine (MR/N013166/1). RMR acknowledges the support of the British Heart Foundation (RE/18/5/34216).

**Competing interests.** None.

**Ethical standards.** Ethical approval for this study was approved through the Health Informatics Centre at the University of Dundee and this study conforms to all recognised standards.

## References

1. Alambert RP, de Gusmão Correia ML. Effects of fetal programming on metabolic syndrome. In *Diet Nutr. Fetal Program* (eds. Rajendram R, Preedy VR, Patel VB), 2017; pp. 439–451. Springer International Publishing, Cham. DOI: 10.1007/978-3-319-60289-9_32
2. Hoffman DJ, Reynolds RM, Hardy DB. Developmental origins of health and disease: current knowledge and potential mechanisms. *Nutr Rev*. 2017; 75(12), 951–970. DOI: 10.1093/nutrit/nux053.
3. Davey Smith G, Hart C, Ferrell C, *et al.* Birth weight of offspring and mortality in the Renfrew and paisley study: prospective observational study. *BMJ*. 1997; 315(7117), 1189–1193. DOI: 10.1136/bmj.315.7117.1189.
4. Davey Smith G. Relation between infants' birth weight and mothers' mortality: prospective observational study. *BMJ*. 2000; 320(7238), 839–840. DOI: 10.1136/bmj.320.7238.839.
5. Davey Smith G, Whitley E, Gissler M, Hemminki E. Birth dimensions of offspring, premature birth, and the mortality of mothers. *Lancet*. 2000; 356(9247), 2066–2067. DOI: 10.1016/S0140-6736(00)03406-1.
6. Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129 290 births. *Lancet*. 2001; 357(9273), 2002–2006. DOI: 10.1016/S0140-6736(00)05112-6.
7. Davey Smith G, Sterne J, Tynelius P, Lawlor DA, Rasmussen F. Birth weight of offspring and subsequent cardiovascular mortality of the parents. *Epidemiology*. 2005; 16(4), 563–569. DOI: 10.1097/01.ede.0000164790.96316.c0.
8. Davey Smith G, Hypponen E, Power C, Lawlor DA. Offspring birth weight and parental mortality: prospective observational study and meta-analysis. *Am J Epidemiol*. 2007; 166(2), 160–169. DOI: 10.1093/aje/kwm054.
9. Li C-Y, Chen H-F, Sung F-C, *et al.* Offspring birth weight and parental cardiovascular mortality. *Int J Epidemiol*. 2010; 39(4), 1082–1090. DOI: 10.1093/ije/dyq045.
10. Shaikh F, Kjøllesdal MK, Naess Ø. Offspring birth weight and cardiovascular mortality among parents: the role of cardiovascular risk factors. *J Dev Orig Health Dis*. 2018; 9(3), 351–357. DOI: 10.1017/S2040174418000065.
11. Lawlor DA, Davey Smith G, Whincup PH, *et al.* Association between offspring birth weight and atherosclerosis in middle aged men and women: British regional heart study. *J Epidemiol Community Health*. 2003; 57(6), 462–463. DOI: 10.1136/jech.57.6.462.
12. Catov JM, Newman AB, Roberts JM, *et al.* Association between infant birth weight and maternal cardiovascular risk factors in the health, aging, and body composition study. *Ann Epidemiol*. 2007; 17(1), 36–43. DOI: 10.1016/j.annepidem.2006.02.007.
13. Naess O, Stoltenberg C, Hoff DA, *et al.* Cardiovascular mortality in relation to birth weight of children and grandchildren in 500 000 Norwegian families. *Eur Heart J*. 2013; 34(44), 3427–3436. DOI: 10.1093/eurheartj/ehs298.
14. Shaikh F, Kjølllesdal MK, Carslake D, Stoltenberg C, Davey Smith G, Næss Ø. Birthweight in offspring and cardiovascular mortality in their parents, aunts and uncles: a family-based cohort study of 1.35 million births. *Int J Epidemiol*. 2020; 49(1), 205–215. DOI: 10.1093/ije/dyz156.
15. Drake A, Walker B. The intergenerational effects of fetal programming: non-genomic mechanisms for the inheritance of low birth weight and cardiovascular risk. *J Endocrinol*. 2004; 180(1), 1–16. DOI: 10.1677/joe.0.1800001.
16. Gluckman PD, Hanson MA, Beedle AS. Non-genomic transgenerational inheritance of disease risk. *BioEssays*. 2007; 29(2), 145–154. DOI: 10.1002/bies.20522.
17. Barker DJ, Bull AR, Osmond C, Simmonds SJ. Fetal and placental size and risk of hypertension in adult life. *BMJ*. 1990; 301(6746), 259–262. DOI: 10.1136/bmj.301.6746.259.
18. Risnes KR, Romundstad PR, Nilsen TIL, Eskild A, Vatten LJ. Placental weight relative to birth weight and long-term cardiovascular mortality: findings from a cohort of 31,307 men and women. *Am J Epidemiol*. 2009; 170(5), 622–631. DOI: 10.1093/aje/kwp182.

19. Barker DJP, Thornburg KL, Osmond C, Kajantie E, Eriksson JG. The surface area of the placenta and hypertension in the offspring in later life. *Int J Dev Biol*. 2010; 54(2-3), 525–530. DOI: 10.1387/ijdb.082760db.
20. Barker DJ, Larsen G, Osmond C, Thornburg KL, Kajantie E, Eriksson JG. The placental origins of sudden cardiac death. *Int J Epidemiol*. 2012; 41(5), 1394–1399. DOI: 10.1093/ije/dys116.
21. Yeung EH, Saha A, Zhu C, *et al.* Placental characteristics and risks of maternal mortality 50 years after delivery. *Placenta*. 2022; 117, 194–199. DOI: 10.1016/j.placenta.2021.12.014.
22. Salafia CM, Zhang J, Charles AK, *et al.* Placental characteristics and birthweight. *Paediatr Perinat Epidemiol*. 2008; 22(3), 229–239. DOI: 10.1111/j.1365-3016.2008.00935.x.
23. Roland MCP, Friis CM, Voldner N, *et al.* Fetal growth versus birthweight: the role of placenta versus other determinants. *PLoS ONE*. 2012; 7(6), e39324. DOI: 10.1371/journal.pone.0039324.
24. Horikoshi M, Beaumont RN, Day FR, CHARGE Consortium Hematology Working Group, Early Growth Genetics (EGG) Consortium, *et al.* Genome-wide associations for birth weight and correlations with adult disease. *Nature*. 2016; 538(7624), 248–252. DOI: 10.1038/nature19806.
25. Beaumont RN, Warrington NM, Cavadino A, *et al.* Genome-wide association study of offspring birth weight in 86 577 women identifies five novel loci and highlights maternal genetic effects that are independent of fetal genetics. *Hum Mol Genet*. 2018; 27(4), 742–756. DOI: 10.1093/hmg/ddx429.
26. Warrington NM, Beaumont RN, Horikoshi M, EGG Consortium. Maternal and fetal genetic effects on birth weight and their relevance to cardio-metabolic risk factors. *Nat Genet*. 2019; 51(5), 804–814. DOI: 10.1038/s41588-019-0403-1.
27. Sato N, Fudono A, Imai C, *et al.* Placenta mediates the effect of maternal hypertension polygenic score on offspring birth weight: a study of birth cohort with fetal growth velocity data. *BMC Med*. 2021; 19(1), 260. DOI: 10.1186/s12916-021-02131-0.
28. Libby G, Smith A, McEwan NF, *et al.* The walker project: a longitudinal study of 48 000 children born 1952-1966 (aged 36-50 years in 2002) and their families. *Paediatr Perinat Epidemiol*. 2004; 18(4), 302–312. DOI: 10.1111/j.1365-3016.2004.00575.x.
29. Sánchez-Soriano C, Pearson ER, Reynolds RM. Associations between parental type 2 diabetes risk and offspring birthweight and placental weight: a survival analysis using the Walker cohort. *Diabetologia*. 2022; 65(12), 2084–2097. DOI: 10.1007/s00125-022-05776-5.
30. R Core Team. *R: A Language and Environment for Statistical Computing*, 2020. Vienna, Austria: R Foundation for Statistical Computing.
31. Cox DR. Regression models and life-tables. *J R Stat Soc Series B*. 1972; 34(2), 187–220.
32. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999; 94(446), 496–509. DOI: 10.1080/01621459.1999.10474144.
33. Therneau T. *Survival. A Package for Survival Analysis in R*, 2021. R Package Version 3.2-13. https://CRAN.R-project.org/package=survival.
34. Gray B. *cmprsk: Subdistribution Analysis of Competing Risks*, 2020. R Package Version 2.2-10. https://CRAN.R-project.org/package=cmprsk.
35. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994; 81(3), 515–526.
36. Qiu W, Chavarro J, Lazarus R, Rosner B, Ma J. *powerSurvEpi: Power and Sample Size Calculation for Survival Analysis of Epidemiological Studies*, 2021. R Package Version 0.1.3. https://CRAN.R-project.org/package=powerSurvEpi.
37. Vik KL, Romundstad P, Carslake D, Davey Smith G, Nilsen TI. Comparison of father-offspring and mother-offspring associations of cardiovascular risk factors: family linkage within the population-based HUNT study, Norway. *Int J Epidemiol*. 2014; 43(3), 760–771. DOI: 10.1093/ije/dyt250.
38. Heaman M, Kingston D, Chalmers B, Sauve R, Lee L, Young D. Risk factors for preterm birth and small-for-gestational-age births among Canadian women: risk factors for PTB and SGA births. *Paediatr Perinat Epidemiol*. 2013; 27(1), 54–61. DOI: 10.1111/ppe.12016.
39. Bai G, Korfage IJ, Mautner E, Raat H. Associations between maternal health-related quality of life during pregnancy and birth outcomes: the generation R study. *Int J Environ Res Public Health*. 2019; 16(21), 4243. DOI: 10.3390/ijerph16214243.
40. Catov JM, Wu CS, Olsen J, Sutton-Tyrrell K, Li J, Nohr EA. Early or recurrent preterm birth and maternal cardiovascular disease risk. *Ann Epidemiol*. 2010; 20(8), 604–609. DOI: 10.1016/j.annepidem.2010.05.007.
41. Cirillo PM, Cohn BA. Pregnancy complications and cardiovascular disease death: 50-year follow-up of the child health and development studies pregnancy cohort. *Circulation*. 2015; 132(13), 1234–1242. DOI: 10.1161/CIRCULATIONAHA.113.003901.
42. Agha G, Hajj H, Rifas-Shiman SL, *et al.* Birth weight-for-gestational age is associated with DNA methylation at birth and in childhood. *Clin Epigenetics*. 2016; 8(1), 118. DOI: 10.1186/s13148-016-0285-3.
43. Benagiano M, Mancuso S, Brosens JJ, Benagiano G. Long-term consequences of placental vascular pathology on the maternal and offspring cardiovascular systems. *Biomolecules*. 2021; 11(11), 1625. DOI: 10.3390/biom11111625.
44. Herzog EM, Eggink AJ, Willemsen SP, *et al.* The tissue-specific aspect of genome-wide DNA methylation in newborn and placental tissues: implications for epigenetic epidemiologic studies. *J Dev Orig Health Dis*. 2020; 12(1), 1–11. DOI: 10.1017/S2040174420000136.
45. Reik W, Constancia M, Fowden A, *et al.* Regulation of supply and demand for maternal nutrients in mammals by imprinted genes. *J Physiol*. 2003; 547(1), 35–44. DOI: 10.1113/jphysiol.2002.033274.
46. Moen G-H, Brumpton B, Willer C, *et al.* Mendelian randomization study of maternal influences on birthweight and future cardiometabolic risk in the HUNT cohort. *Nat Commun*. 2020; 11(1), 5404. DOI: 10.1038/s41467-020-19257-z.
47. Chen J, Bacelis J, Sole-Navais P, *et al.* Dissecting maternal and fetal genetic effects underlying the associations between maternal phenotypes, birth outcomes, and adult phenotypes: a mendelian-randomization and haplotype-based genetic score analysis in 10,734 mother-infant pairs. *PLOS Med*. 2020; 17(8), e1003305. DOI: 10.1371/journal.pmed.1003305.
48. General Register Office. *The Classification of Occupations, 1960*, 1960. H.M. Stationery Office, London.


https://doi.org/10.1017/S2040174423000430 Published online by Cambridge University Press