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Birthweight of Offspring, Maternal Pre-pregnancy Characteristics and Mortality of Mothers: The Jerusalem Perinatal Study Cohort

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Abstract

Purpose—To explore the association between birthweight in offspring, a marker of the intrauterine environment, and mortality in their mothers taking into account maternal pre-pregnancy characteristics, including maternal BMI, smoking, and socioeconomic status. Distinguishing the effects of offspring's birthweight and pre-pregnancy characteristics on maternal outcome may provide clues regarding mechanisms underlying the association between birth weight and maternal mortality.

Methods—We studied long-term total mortality (average follow-up period 29.1 years) in a population-based cohort of 13,185 mothers, aged 15 to 48 years at their offspring's birth, who delivered in West Jerusalem during 1974–76

Results—Univariate and multivariate Cox-proportional hazard models used to estimate the hazard of overall mortality among mothers indicated a non-linear relationship with birthweight of offspring when introduced into the models as a continuous variable, and a linear positive association with maternal pre-pregnancy BMI. Inclusion of maternal BMI and other pre-pregnancy characteristics in the model did not alter the association between offspring's birthweight and mothers' all-cause mortality.

When birthweight was introduced as a categorical variable, higher mortality was observed among mothers who gave birth to babies with birthweight < 2500 gr (HR=1.90; 95%CI 1.23–2.94) as compared to mothers whose offspring had birthweight between 3000 and 3499 gr. The hazard ratio for mothers who gave birth to babies with birth weight ≥ 4000 gr was 1.30 (95%CI 0.88–1.91).

Conclusions—Independent of pre-pregnancy maternal BMI and other characteristics, birthweight of offspring was associated with mortality in their mothers, suggesting that intra-uterine metabolic

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events reflected by birth weight and not explained by maternal obesity, smoking, and SES have remote consequences for maternal health. These findings underline the need to explore specific genetic and/or environmental mechanisms that account for these associations.

Introduction

There is mounting evidence that chronic diseases in adults, such as coronary heart disease (CHD), are influenced by events occurring in fetal life [1]. We have previously found a negative relationship between birthweight (BW) and total mortality, in a population-based cohort of 80,936 offspring born in Jerusalem with an average follow-up of 28.8-years [2]. Recently, we have shown a U-shaped relationship between birthweight of offspring and long-term overall mortality rates in their mothers; both low and high birth weight were associated with total mortality rates in the mothers, especially deaths from CHD and circulatory causes [3]. The latter findings suggest that a genetic pathway may explain, at least in part, the association between fetal development and chronic diseases later in life. However, maternal obesity (MO), smoking, SES and maternal health characteristics during pregnancy may confound this association. Each of these characteristics are associated with neonatal BW and these characteristics also influence adult atherosclerotic metabolic risk and mortality due to obesity-related metabolic diseases [4–9]. The present study extends our previous analysis and examines whether the association between offspring's BW and maternal mortality is independent of maternal obesity, smoking, SES and maternal health characteristics or whether this association is explained by the dual effects of one or more of these characteristics on BW and on the risk of maternal mortality (i.e. confounding).

Methods

The JPS prospective study includes 42,209 Jewish mothers who gave birth to 90,355 offspring over a 13-year period (January 1964 through December 1976). In the present investigation, we undertook an analysis of mortality in a sub-cohort of mothers who gave birth during 1974–76. Data included demographic and socioeconomic information, medical conditions of the mother during the current and previous deliveries and birthweight of her offspring. This information was abstracted either from birth certificates or from the maternity ward logbooks. In addition, mothers included in this sub-cohort were interviewed in hospital on the first or second day post-partum by nurse-midwives. Data were gathered on date of last menstrual period, mother's smoking, maternal weight and height prior to pregnancy and weight gain during pregnancy, gynecological history, and other characteristics.

We verified 96.2% of the identities of mothers in the original sub-cohort through the Israeli Population Registry. Records were linked via identity number and death notifications were obtained including dates of death. A small proportion of mothers (n=1441, 10.9%) gave birth twice during this period and the first child in the sub-cohort was selected for the analysis to avoid violation of the independence assumption.

The following independent variables were included: offspring's birthweight (sub-grouped into 5 categories; <2500 g (LBW), 2500–2999g, 3000–3499g, 3500–3999g, ≥4000 g (HBW)), mother's pre-pregnancy BMI (as a continuous variable and sub-grouped into 4 categories; <25.0, 25.0–26.9, 27.0–29.9, ≥30), mother's age at birth and mother's level of education (grouped into 4 categories; 0–4 yrs, 5–8 yrs, 9–12 yrs, ≥13 yrs). Mother's ethnic origin was classified according to country of birth and for mothers born in Israel, that of their father. Ethnic origin was categorized as follows: Israel, Asia, North Africa and Europe/America and other industrialized countries. A social class scale (SES, ranging from 1=highest to 6=lowest) relating to the father's occupation was developed using the Central Bureau of Statistics occupational categories [10].

Dichotomous variables were used to characterize mother's history regarding the following medical conditions: diabetes, hypertension and heart disease, pre-eclampsia in the current pregnancy and current smoking during the pregnancy and ever/never. Data were almost complete for the demographic and socioeconomic variables, maternal lifestyle and health characteristics and for information on gestational age.

Statistical analysis

The Cox proportional hazard model was used to assess differences in mortality according to birthweight after controlling for possible confounders. Four sets of models were fit: model 1 included offspring birthweight as a main predictor; model 2 additionally adjusted for maternal demographic and lifestyle characteristics and for perinatal information. Model 3 further adjusted for pre-pregnancy maternal BMI; and finally model 4 additionaly adjusted for maternal health characteristics (e.g. pre-eclampsia, gestational diabetes).

Due to the relative modest sample size and the number of deaths during the follow-up period in the subset of mothers included in this analysis, we examined the association only with all-cause mortality and did not examine the possible associations with specific causes of mortality.

This study was approved by the Institutional Review Boards in Jerusalem (Hebrew University) and New York (Columbia University)

Results

During the follow-up period (average of 29.1 years), the 13,185 mothers contributed 383,872 person-years of observation and there were 451 deaths. Only 6.6% of the maternal deaths were due to unnatural causes.

Table 1 shows the characteristics of the study sample by maternal life status. Mothers who died were older at birth of their offspring, less educated and exhibited higher prevalences of smoking, heart disease, diabetes and preeclampsia as compared to mothers who did not die. In addition, mother who died tended to weigh more given their height, and had a higher proportion of offspring with LBW and HBW.

When birthweight was examined as a continuous variable in a univariate analysis, there was a non-linear relationship between birthweight of offspring and overall mortality rates among their mothers (b=−1.63; p=≤0.0001; b^2=0.29; p=≤0.0001; $\chi^2_{(2)}$= 20.01; p=≤0.0001; Data not shown). The fit of the non-linear model was significantly better than that of a linear model. A model using offspring's birthweight as a categorical variable indicated that the mortality rate was significantly higher among mothers who gave birth to babies with birth weight <2500 g (LBW:HR=1.71; 95%CI 1.17–2.51) and for mothers of offspring with a birth weight of >4000 g (HBW: HR=1.52; 95%CI 1.04–2.21) as compared to offspring with a birth weight of 3000–3499 g, the reference group in Table 2. Both the linear and the categorical models also indicated a significant direct association between pre-pregnancy BMI and maternal overall mortality (b=0.093; p=≤0.0001; data from the linear model). Additional adjustment for pre-pregnancy maternal characteristics, including maternal obesity, maternal smoking, and maternal SES, altered the association of offspring's birthweight treated as a continuous variable and mother's mortality only slighty (b=−1.47; p=≤0.0008; b^2=0.23; p=≤0.0009; data not shown). Further adjustment for maternal health conditions, including pre-eclampsia, hypertension, diabetes and heart disease, attenuated the strength of the association between birthweight and maternal mortality (b=−1.20; p=≤0.01; b^2=0.18; p=≤0.017), and pre-pregnancy maternal BMI and mortality (b=0.0478; p=≤0.0046), but both associations remained statistically significant (data not shown in Table 2). The multivariate analysis with birthweight categorized into 5 groups, indicated a higher risk for mothers who gave birth to LBW babies (HR=1.90; 95%CI 1.23–

2.94) as compared to the reference group (Table 2). This association was independent of the associations of maternal pre-pregnancy characteristics with mortality of mothers (Table 2, Models 2 and 3). Further adjustment for maternal medical conditions did not change the strength of the association between low birthweight and maternal mortality (Mothers of LBW babies (HR=1.90; 95%CI 1.22–2.98). The association with HBW babies was somewhat attenuated (HR=1.24; 95%CI 0.82–1.86). When maternal medical conditions during pregnancy were introduced into the multivariate model the coefficients for pre-pregnancy maternal BMI were reduced slightly, (hazard ratios 1.31, 1.46, and 1.77, in those mothers belonging to BMI group of 25.0–26.9, 27.0–29.9, and ≥30.0, respectively (p value for trend = 0.03) (data not shown).

Discussion

We observed a significant non-linear association between offspring birthweight and long-term overall mortality among their mothers. In a previous investigation using the total JPS population, similar associations were observed between offspring birthweight and maternal total mortality, and the associations were due to the associations of birthweight with CHD and circulatory mortality [3]. A potential drawback of our previous analysis was the lack of complete information on characteristics such as gestational age, maternal obesity, maternal smoking, maternal SES, and maternal health conditions. Mothers with these data tended to differ from those with missing data in characteristics related to the mother's ethnic origin, education and SES, and offspring's birthweight. For example, mothers with low levels of education and those who gave birth at younger ages were somewhat less likely to have information on gestational age. Our data, in accordance with variety of studies have documented the relationships between SES, maternal smoking and maternal health conditions such as preeclampsia and gestational diabetes with offspring birth weight [4–5] as well as with maternal long-term health outcomes [9,11]. However, the association between offspring birthweight and long-term overall mortality in their mothers persisted after adjustment for these possible confounders.

In addition, the short and long-term consequences of maternal obesity have been examined in a series of studies [12–14]. Over the past 20 years, studies have demonstrated an increase in the prevalence of neonatal obesity, defined using either BW or fat mass; and, the increase in BW during this period has occurred concurrently with the increase in MO [6]. Other studies showed that maternal pre-pregnancy BMI and weight gain during pregnancy are associated with neonatal weight and adiposity and were predictors of overweight/obesity in early adolescence [15,16]. For example, among infants of normoglycemic mothers, increased pre-pregnancy BMI was a strong predictor of neonatal percent body fat and fat mass at delivery [17]. In addition, maternal pre-pregnancy BMI was the strongest predictor of higher adolescent mean BMI and the risk of overweight or obesity [18]. These effects remained largely unchanged after adjustment for maternal education and parity. Further adjustment for birth weight and gestational age at birth did not alter this association. In the present study population, pre-pregnancy BMI in mothers was positively and significantly associated with offsprings' birthweight.

In addition, there is mounting evidence to suggest that the long-term consequences of MO on the woman's own health is of particular concern. Therefore, it is unclear whether the previously described associations between birthweight of offspring and their mothers' mortality in the total JPS cohort are causal or whether they reflect confounding due to the associations of maternal obesity with both BW and maternal mortality.

In the sub-cohort of mothers who gave birth during 1974–76 included in this report, data on date of last menstrual period, smoking history and on maternal weight and height prior to

pregnancy and weight gain during pregnancy were available in addition to demographic, socioeconomic and medical information. A non-linear association between BW and maternal mortality was again demonstrated independent of the associations with maternal pre-pregnancy characteristics.

Few studies have investigated the association between offspring's birthweight and maternal mortality after taking into consideration maternal characteristics that could confound this association, such as maternal obesity, smoking, SES, and health conditions [19–22]. In a recent investigation from the 1958 British birth cohort the birthweight of offspring was inversely associated with all-cause and cardiovascular mortality for mothers after the adjustment for height and BMI in 1969 and smoking during pregnancy [19]. In a small study of 794 married couples in western Scotland, a strong association was found between birthweight and maternal mortality from all causes and from cardiovascular disease [20]. Adjusting for other risk factors including maternal BMI had only modest effect on relative risks. In another large prospective birth cohort study, birthweight of offspring in the lowest quintile for gestational age was associated with increased risk in mothers for mortality from all-causes and from ischemic heart disease, after adjustment for maternal age, SES, hypertension and maternal height [21].

These findings are consistent with the hypothesis that genetic variation accounts, at least in part, for the independent associations of birthweight and maternal obesity with maternal mortality. Inherited maternal genotypes that may directly influence birthweight and non-inherited maternal genotypes which may influence the intrauterine environment as well as epigenetic effects may account for the observed association [23,24].

Several pathways are linked with the intrauterine environment and may have adverse effects on the metabolic status of obese mothers, and thus influence the risk of death from metabolic-related diseases. For example, based upon animal-experimental data, leptin both alters placental gene transcription and cell proliferation and has a trophic effect on hypothalamic neurons and pathways involved in feeding regulation [25,26]. In addition, neural pathways regulating food intake, body weight, and cardiovascular disease risk may be influenced by elevated leptin in mothers, through direct effects on the central nervous system. It has also been suggested that leptin's effect on the central nervous system can affect the sympathetic nervous system and lead to hypertension, cardiovascular disease and mortality from these causes.

In our univariate analysis, we observed that having an offspring with HBW was also associated with higher risk of mothers' death. In recent years there has been a growing recognition that offspring birthweight could be used as a surrogate for maternal metabolism in pregnancy and that the pregnant mother's metabolic state may provide a window into her future risk of disease and death. For example, it has been shown that both mothers with gestational diabetes mellitus and their large babies have an increased risk of diabetes [2527]. In a recent study, offspring's HBW was associated with maternal insulin resistance 8 years after delivery [2628]. Maternal insulin resistance due to obesity was found to be associated with increased fetal fat mass [27 29] and genes involved in Insulin sensitivity and insulin signaling related molecules may account, in part, for the associations of HBW, MO and maternal mortality. It is possible that variables included in the present investigation (e.g. MO and maternal diabetes) accounted for the association between offspring's HBW and maternal mortality in the multivariate models.

In summary, we observed a non-linear, association between offspring's birthweight and overall mortality in their mothers independent of the relationship with pre-pregnancy maternal obesity, smoking, SES, and health conditions, These findings are consistent with the hypothesis that inherited or non-inherited maternal genetic variation in candidate genes from distinct molecular pathways have effects on both phenotypes.

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Table 1

Characteristics of Mothers and Offspring by Maternal Vital Status

	Alive		Dead	
	12734	**(96.6%)**	**451**	**(3.4%)**
Characteristics	N	%	N	%
Origin				
Israel	1941	15.2	77	17.1
West Asia	3239	25.4	106	23.5
North Africa	2688	21.1	109	24.2
Europe/America	4866	38.2	159	35.2
SES				
1–2	5549	43.6	182	40.3
3–4	4428	34.8	153	33.9
5–6	2757	21.6	116	25.7
Smoking				
Non-smoker	10482	82.3	356	78.9
Smoker	2252	17.7	95	21.1
Heart disease				
No	12685	99.6	444	98.4
Yes	49	0.4	7	4.6
Hypertension				
No	12247	98.9	423	99.1
Yes	131	1.1	4	0.9
Diabetes				
No	12682	0.1	446	1.1
Yes	13	99.9	5	98.9
Preeclampsia				
No	12503	98.5	437	96.9
Yes	192	1.51	14	3.1
Gender of offspring				
Female	6337	49.8	214	47.5
Male	6397	50.2	237	52.5
Birth Weight (gr)[a]	3250 500		3300 600	
<2500	679	5.3	32	7.1
2500–3999	11284	88.6	375	83.1
≥4000	771	6.0	44	9.8
Maternal age (yr)[a]	27.4 5.3		30.6 6.3	
Maternal education (yr)[a]	11.8 3.5		10.9 4.0	
Pre-pregnancy maternal BMI (kg/m^2)[a]	22.0 3.0		23.0 3.8	

[a] Presented as mean and standard deviation

Table 2

Association between Offspring Birthweight, Pre-pregnancy Maternal BMI and Mortality in Mothers

Variables	Model		Model 1[a]		Model 2[b]		Model 3[c]	
			HR	95% CI	HR	95% CI	HR	95% CI
Birth Weight	Categorical	<2500	1.71	1.17–2.51	1.75	1.15–2.66	1.90	1.23–2.94
		2500–2999	1.16	0.87–1.54	1.13	0.86–1.49	1.14	0.85–1.53
		3000–3499	1	-	1	-	1	-
		3500–3999	1.29	1.01–1.66	1.20	0.94–1.53	1.19	0.92–1.54
		≥4000	1.52	1.04–2.21	1.36	0.95–1.95	1.30	0.88–1.91
Maternal Pre-pregnancy BMI	Categorical	<25.0	1	-	-	-	1	-
		25.0–26.9	1.52	1.10–2.12	-	-	1.24	0.88–1.76
		27.0–29.9	1.96	1.35–2.85	-	-	1.55	1.06–2.28
		≥30.0	2.91	1.84–4.59	-	-	2.02	1.24–3.28

[a] HR - hazard ratio and CI - confidence interval estimates from two separate univariate models.

[b] Maternal age, origin and SES, maternal smoking, weight-gain during pregnancy, gestational age and gender of offspring were included in the model in addition to birthweight.

[c] Pre-pregnancy maternal BMI was added to variables included in Model - 2.