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Birthweight of Offspring and Mortality of Parents: The Jerusalem Perinatal Study Cohort

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Abstract

Purpose— To examine the association between birthweight in offspring and mortality in their parents. Distinguishing between risks of outcomes in mothers from fathers potentially provides clues as to the relative roles of genetic versus non-genetic mechanisms underlying these associations..

Methods— We studied total and cause-specific mortality in a population-based cohort of 37,718 mothers and 38,002 fathers whose offspring were delivered in West Jerusalem during 1964–76, after an average follow-up of 34.12 years

Results— Hazard models controlling for socio-demographic and lifestyle characteristics indicated a U-shaped relationship between offspring's birthweight and overall mortality, deaths from CHD, circulatory and other non-neoplastic causes in their mothers. Higher CHD mortality rates were observed among mothers who gave birth to babies with low (HR=2.13; 95%CI 1.40–3.25) and high birthweight (HR=1.98; 95%CI 1.36–2.88), as compared to mothers whose offspring weighed 2500–3999 gr at birth. Adjustment for maternal pre-eclampsia, slightly attenuated these results.

Multivariate models indicated a negative linear relationship (HR=0.95, 95%CI 0.91–0.99) between offspring's birthweight and overall mortality in their fathers. Unlike the association in mothers, the relation was noted primarily with deaths from "other causes".

Conclusions— Birthweight of offspring is associated with parental mortality although the relation differs for fathers and mothers. These findings broaden previous observations that intra-uterine events have long-term consequences for adult health and support the need to explore genetic and/or environmental mechanisms underlying these associations.

Keywords

cohort; birthweight; mortality; CHD; offspring; parents

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Disclaimer: Dr Friedlander had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

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Introduction

Growing evidence suggests that chronic diseases in adults, for example coronary heart disease (CHD), are influenced by the intra-uterine environment (1,2). One proposed mechanism is that CHD and related disorders result from physiologic adaptations made by the undernourished fetus and infant (3), with long-term consequences for the development and function of physiological systems, such as glucose-insulin metabolism (4), fat metabolism and homeostasis of hormones related to the hypothalamus-pituitary-adrenal axis (5). In addition, the combination of small size at birth, followed by accelerated weight gain during childhood, has been shown to predict large differences in the cumulative incidence of obesity, type II diabetes, hypertension, and CHD (6,7).

An inherited basis for these associations could also exist if low birthweight, adult obesity, insulin resistance, glucose tolerance, diabetes, hypertension, and CHD are the result of pleiotrophic effects of an overlapping set of genetic factors. (8–10).

To the extent that genetic factors are playing a role, we would predict that offspring birthweight would be associated with cardiovascular disease events and/or mortality in parents, with relationships being stronger for mothers than fathers. Some studies (11,12) but not all (13) have shown that lower birthweight of offspring is associated with higher parental mortality from cardiovascular disease. The Jerusalem Perinatal Study (JPS), a large, population-based research cohort, provides a unique opportunity to explore the relation between birthweight of offspring and mortality in their parents.

Methods

We undertook a prospective study of mortality in parents from 90,355 Jewish offspring born between January 1964 and December 1976. Through the Israeli Population Registry we verified the identities of 40,595 mothers and 39,026 fathers (96.2% and 92.5% respectively) in the original cohort and using unique identity numbers updated vital status including dates of death. Underlying cause of death is available in the Population Registry for deaths occurring since 1979. All death certificates in Israel are coded at the Central Bureau of Statistics by trained nosologists who were unaware of the study hypothesis. We excluded 2,877 mothers (7.1%) and 1,024 fathers (2.6%) of offspring with congenital malformations or unknown birth weight, and those who could not be traced by the Population Registry. Subjects with congenital malformation were excluded from the study population since these conditions may have a profound effect on birth weight through mechanisms which differ from the common pathways which link between fetal development with adult diseases and mortality.

Study variables

Data included demographic and socioeconomic information, medical conditions of the mother during the current and previous pregnancies, and offspring birthweight. The information was abstracted either from birth certificates or maternity ward logbooks. Antenatal and post-partum interviews of a subset of mothers (11,500 + 16,856 mothers, respectively) provided further information on medical conditions and habits.

In Israel, practically (>99%) all deaths are reported. Information on causes of death was available for 80.8% of mothers and 75.6% of fathers. Deaths without coded causes include those which occurred prior to 1979 as well as a proportion from 2004–2005 in which coding has not yet been completed. The underlying cause of death was categorized according to International Classification of Diseases-9, into the following groups: CHD (ICD-9 codes 410–414, 427.4 and 427.5); all circulatory conditions (ICD-9 codes 390–459); all neoplasms (ICD-9 140–239) and deaths due to all “other causes” taken together.

The following independent variables were included: offspring's birthweight (as a continuous variable or sub-grouped into 3 categories; <2500 g (LBW), 2500–3999 g (NBW), ≥4000 g (HBW), (the NBW group was further divided into three 500 gr groups in order to examine whether differences exist between these groups), parents' ages at birth (in 5-year categories (from <20 to 35+ yrs in mothers and from <25 to 40+ yrs in fathers), parent's level of education (grouped into 4 categories; 0–4 yrs, 5–8 yrs, 9–12 yrs, ≥13 yrs) and a social class scale (SES, ranging from 1=highest to 6=lowest) based on father's occupation. Parent's ethnic origin was classified according to their country of birth and for parents born in Israel, that of their father (categorized as: Israel, other West Asia, North Africa and Europe/America and other industrialized countries).

Mother's medical history before and during the pregnancy included data on diabetes, hypertension and heart disease, pre-eclampsia in the current pregnancy and smoking (ever/never) coded as dichotomous variables. Data were virtually complete for all variables except for smoking and hypertension where data were available for 62% and 38.5% of the mothers, respectively. Information on gestational age was available on a subset 7,866 infants whose mothers were interviewed during the final 3 years of the study.

Statistical analysis

Age and birthweight-specific mortality rates were calculated by the person-time method. Time was counted from earliest birth in the cohort until death or study closure (December 2004). The Cox proportional hazards model was used to evaluate the association between birthweight of offspring and parental mortality after controlling for possible confounders. When birthweight was introduced as a continuous variable the fit of linear models was compared with that of non-linear models by adding quadratic and cubic terms. Competing hypotheses were tested by the likelihood ratio test. Four sets of models were fit with offspring birthweight as a main predictor: model 1 included age of parents as a covariate; model 2 additionally adjusted for demographic characteristics of parents and for smoking status of mothers. Model 3 further adjusted for medical conditions in mothers, i.e. diabetes, hypertension and heart disease; and model 4 also adjusted for pre-eclampsia in the current pregnancy. To deal with missing values regarding smoking and hypertension, a sensitivity analysis was carried-out using a valid approach through which missing data were imputed by obtaining the most plausible value from the predictive distribution of the missing values conditional on the observed values (14). This approach had a trivial effect on the results.

Initially, analyses were based on information from the first child in the cohort, in cases when parents had multiple offspring. In addition, analyses were repeated using a regression calibration model that incorporates the estimation of the average birthweight within each family after adjustment for potential covariates (15,16).. The latter method enables retrieving the information from all offspring. Both approaches provided similar findings with respect to both estimated sizes of effect and standard errors and therefore, only the results from the analysis using a single offspring are reported in the tables. This study was approved by the Institutional Review Boards of Hadassah-Hebrew University Medical Center in Jerusalem and of Columbia University in New York.

Results

Table 1 shows the distributions of parental characteristics by birthweight of their first-born offspring in the cohort. There was a graded positive relation between offspring's birthweight and age of mother at birth. While LBW (<2500 gr) offspring tended to aggregate in families characterized by mothers who gave birth before age 25, HBW (≥4000 gr) offspring tended to aggregate in families characterized by mother who gave birth after that age. Lower birthweights

were observed among offspring of mothers originating from Western Asia and higher weights among those with North African mothers. HBW tended to aggregate in families characterized by mother's low education, yet no clear relationship was observed between offspring's birthweight and mother's SES. Smoking mothers and those with heart disease and preeclampsia had a higher proportion of offspring with LBW, while the percentage of offspring with HBW tended to be higher among mothers with diabetes. Hypertension in mothers was associated with both LBW and HBW offspring. Finally, there was a strong relationship between birthweight and gender. The percentage of infant females was greater among those who were born at <2500 g birthweight, and considerably lower among babies with high birth-weight (≥ 4000 gr).

Offspring birthweight was also related to father's age at birth. Birthweight tended to be lower among offspring of fathers originating from Asia and somewhat higher among those born to North African and European fathers.

During the follow-up period (average of 34.74 years for mothers and 33.5 years for fathers), the included 37,718 mothers and 38,002 fathers contributed 1,310,148 and 1,274,443 person-years of observation, respectively, with 2,575 and 6,305 deaths occurring in mothers and fathers, correspondingly. Table 2 showed that the adjusted mortality rate was significantly higher among mothers who gave birth to babies with either LBW (HR=1.33; 95%CI 1.15–1.54) or HBW (HR=1.20; 95%CI 1.04–1.38) as compared to the NBW group. The additional adjustment for socio-demographic variables and smoking status did not result in major differences between models 1 and 2. Further analysis with refinement of birthweight into 5 categories shown in Figure 1, indicated that the U-shaped relation was apparent for mothers and not for fathers.. These findings were also evaluated when birthweight information of all offspring (rather than the first in a family) were taken into consideration. Under model 2, the HR associated with LBW and HBW were similar to the estimates derived from the sample using the first offspring (Table 2) (LBW - HR=1.36; 95%CI 1.17–1.58; and HBW - HR=1.30; 95%CI 1.12–1.51). Mother's death from cancer was not associated with offspring's birthweight.

Higher CHD mortality was observed among mothers who gave birth to babies with LBW (HR=2.13; 95%CI 1.40–3.25) and with HBW (HR=1.98; 95%CI 1.36–2.88), as compared to the NBW group. Further refinement of BW into five categories indicated that only mothers of offspring at the extremes of birthweight were at increased risk of CHD mortality (not shown). A similar association was observed between offspring's birthweight and maternal mortality from circulatory diseases.

“Other causes” of death in mothers were attributed to injuries and other external causes (19.0%), endocrine diseases (19.2%), respiratory diseases (13.4%), digestive (7.9%), nervous system (7.6%), genitourinary (8.1%), mental disorders (1.3%), and miscellaneous causes (23.5%). Higher mortality rates from “other causes” were observed among mothers of LBW infants (HR=1.61; 95%CI 1.22–2.11), as compared to the reference group. Offspring's low birthweight was specifically associated with increased risk of mother's death from respiratory (HR=2.67; 95% CI = 1.4, 4.9) and genitourinary causes (HR=2.43; 95% CI = 1.0, 5.8) and high birthweight was associated with increased risk of mother's death from endocrine diseases (HR=2.0; 95% CI = 1.2, 3.3).

Adjustment for maternal hypertension, diabetes and heart disease to the baseline multivariate model, slightly attenuated the association between birthweight and CHD mortality in mothers (Table 3, Model 1). When pre-eclampsia was also introduced into the multivariate model the coefficients for both LBW and HBW variables were somewhat reduced, yet remained

significant (Model 2). Similar findings were observed for mothers' mortality from circulatory causes (data not shown).

The addition of hypertension, diabetes and heart disease to the baseline multivariate model did not change the strength of the association between birthweight and maternal mortality from "other causes" (Table 3, Model 3). With further adjustment for pre-eclampsia, the coefficient for LBW was somewhat reduced, yet remained significant (Model 4). Similar results were observed in relation to all-cause mortality.

With respect to fathers, the adjusted mortality rates were not significantly higher among fathers whose wives gave birth to babies with either LBW or HBW as compared to the NBW reference group. However, a multivariate model with adjustment for socio-demographic characteristics of fathers, indicated that offspring's birthweight measured as a continuous variable was negatively and linearly associated with the hazard of all-cause mortality in fathers [HR=0.95, 95%CI=0.91,0.99; Table 4, Model 2]. When the analysis was repeated using the available birthweight of all offspring, a stronger negative association with all-cause mortality in fathers was observed [HR=0.87, 95%CI=0.78, 0.96]. However there was no evidence of an association between offspring's birthweight (as a categorical or linear term) and fathers' mortality from cancer, CHD and from circulatory disorders.

In a multivariate Cox proportional hazard model a negative linear relationship was observed [HR=0.89, 95%CI=0.82,0.98], between offspring's birthweight and father's mortality due to "other causes", which included injuries and external causes (19.8%), respiratory diseases (15.4%), digestive disorders (10.7%), endocrine disorders (12.7%), genitourinary causes (8.8%), nervous system disorders (6.9%), mental disorders (3.7%) and miscellaneous causes (22.1%). Specifically, offspring's low birthweight was positively associated with increased risk of father's death from digestive disorders (HR=1.89; 95% CI = 1.2, 3.1) and from genitourinary causes (HR=1.93; 95% CI = 1.1, 3.3) and negatively associated with fathers' death from injuries and external causes (HR=0.43; 95% CI = 0.2, 0.8).

Discussion

We observed a U-shaped association between offspring birthweight and CHD, circulatory and all-cause mortality among their mothers. Among fathers, there was a negative linear relationship between birthweight of offspring and overall mortality, however, the association was mostly due to deaths from "other causes".

The association between LBW and mothers' death is in accordance with a variety of studies (11,17–20).

Few studies have investigated these associations with respect to both parents. In a small prospective birth cohort study, birthweight of offspring was inversely associated with maternal stroke, and no significant association with risk of paternal diseases was shown (13). In a large Swedish study, birthweights were inversely associated with parental diabetes mortality (21). In a third study, similar associations were observed between offspring's birthweight and all-cause and cardiovascular mortality for mothers and fathers, with stronger associations found in mothers (19). Finally, results from a recent study have also shown weaker inverse associations between offspring birthweight with all-cause mortality and cardiovascular mortality in fathers as compared to mothers (12).

Numerous studies also suggest that birthweight in offspring is related to parental birth weight (22,23). It has been shown that the association with mother's birthweight is stronger than that of fathers' (24), and this could contribute to the differential strength of associations between offspring's birth weight and parental mortality.

The most commonly cited hypothesis explaining the association of LBW and occurrence of CHD in adults (1,25) is that adaptations made during fetal life in response to fetal “malnutrition” affect vascular structure and metabolic functions (4). The association between offspring’s birthweight and parental mortality could be attributed to socio-demographic and environmental factors which may influence both the birthweight of offspring and mortality of the parents. Under such circumstances, however, similar associations between offspring’s birthweight and mortality for both mothers and fathers would be expected. Furthermore, the relatively modest degree of attenuation of the association following adjustment for the available socio-demographic variables indicates that these factors are unlikely to be the sole explanation for the differential patterns. However, any other characteristics of the parents, especially those developed since the birth of the child, remains a concern, since they may account for intergenerational health effects tied to birthweight. It is also possible that the intra-uterine environment reflects specific maternal characteristics (e.g. smoking and pre-pregnancy weight). Such maternal exposure before and during pregnancy could generate stronger associations between offspring’s birthweight and mothers’ mortality than with fathers’ mortality, as seen in this study for most associations.

An alternative hypothesis is that genetic variation accounts for the association between LBW and parental mortality. Maternal, paternal, and offspring genotypes may directly or indirectly influence birthweight and adult diseases (8–10). Maternal genotypes which influence the intrauterine environment as well as epigenetic effects may also account for the differential association observed. For example, an animal study has shown that pregnant mice that received dietary supplements with vitamin B12 and folic acid gave birth to babies predominantly with brown coats while the group of pregnant mice that did not receive the nutritional supplements gave birth predominantly to mice with yellow coats (26). A cellular investigation of the differences between the two groups of baby mice indicated that the extra nutrients altered the expression of a specific gene without mutating the gene itself. In mammals, the imprinted genes are particularly implicated in the regulation of fetal growth and development, cancer, and aging. The DNA modification for imprinting includes DNA methylation, histone modifications, and differences in chromatin structure. Maternal dietary methionine is another example of a dietary supplement that changes gene methylation status and the methylation status of epigenetic marks may be transmitted from one generation to the next. An animal controlled dietary trial has shown that methyl supplements before and during pregnancy increased the level of DNA methylation in the A^{vy} IAP element that causes coat colour variegation by its methylation state (27). Others have confirmed that methyl supplements affected A^{vy} IAP methylation status in various organs and that IAP methylation status can be transmitted from one generation to the next (28,29). Recent animal experiments have also indicated that a parental high-fat diet before intrauterine developmental stage may increase body-fat accumulation in their offspring (30). The authors raised the intriguing possibility that parental diet may influence the lifelong health of offspring and epigenetic inheritance may be occurred. In human, epigenetic mechanisms such as parental imprinting may also contribute to common metabolic disorders, such as diabetes (31). Kaati et al (32) reported that the grandchildren of well-fed adolescents had a greater risk of mortality from diabetes, whereas those descended from famine survivors were less likely to have fatal CHD. A possible explanation may be related to epigenetics since changes in diet could activate certain pathways that then leave an imprint that is passed on to the next generation. In such a biological scenario, the risk occurs regardless of which parent transmits the “variant” alleles.

We observed that having an offspring with HBW was also associated with higher risk of mothers’ death from CHD. 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 (33). In a recent study, offspring's HBW was associated with maternal insulin resistance 8 years after delivery (34). In the present investigation, maternal CHD mortality associated with LBW and HBW was not explained by diabetes, hypertension or CHD of mothers. It is possible that the variables we used to assess these mechanisms were inadequate to capture the disease process; with the use of more sensitive markers such as insulin sensitivity, a greater contribution of these established CHD mechanisms might be discernible. Our results indicated that the excess CHD mortality in mothers attributed to offspring's LBW was explained in part by maternal pre-eclampsia. This suggests the involvement of mechanisms separate from the traditional pathways. Recent studies have shown that women with a history of pre-eclampsia have higher concentrations of fasting insulin, lipids, coagulation factors and ICAMP-1 post-partum (35), and higher rates of defects in endothelial vascular function (36), as well as death due to cardiovascular disease (37–39), compared to women without such a history.

With respect to mortality from “other causes” an association was observed between LBW in offspring and both maternal and paternal genitourinary deaths, namely deaths due to renal failure. Several studies support the hypothesis that renal impairment can be a consequence of intrauterine growth retardation (40–41). This could be explained by the well known inverse association of birthweight with later development of type II diabetes (3). Diabetes duration and severeness of the disease that lead to glomerular injury and loss of renal function may be accelerated in people with LBW and lead to higher mortality from renal failure.

There are several limitations to this study. First, the information on parents' cause of death is incomplete. However, when sociodemographic characteristics, age at delivery and offspring birthweight and smoking (in mothers) in the subsets of parents with and without recorded cause of death were compared, the subgroups were similar. Furthermore, hazard ratios for total mortality on the subsamples of mothers and fathers with and without available information on their cause of death were similar. .

Another potential drawback of these data is the lack of information on gestational age. We compared characteristics of mothers with (n=7,866) and without these data (n=29,852), and found few differences between the two groups with regard to mother's ethnic origin and offspring's birthweight. Mothers with low levels of education and who gave birth at younger ages were somewhat less likely to have information on gestational age. Due to the relative short follow-up and the small number of deaths in the subset of mothers with gestational age information we did not examine the possible impact of missing data on the estimates of the birthweight effect. However when the missing gestational age information was introduced into the model as a separate category, the HR of parental all-cause mortality associated with offspring's birthweight remained unchanged (e.g. for mothers' mortality HR=1.33 associated with LBW and HR=1.20 associated with HBW).

We used the combination of uniquely detailed obstetric records with linkage to the Israeli Population Registry (95.9% successful) over 35 years of follow-up in this report. Obstetric information in this study is thought to be of high quality; it was abstracted from labor ward logs at the time of the birth and was thus independent of either maternal interviews or registration in the birth certificate (42). This minimizes the potential problem of selection bias or differential loss of follow-up. Confounding by socioeconomic status remains a concern in studies of the relationship of birthweight and adult diseases. Unlike many studies, we had information which allowed us to characterize the socioeconomic environment at birth, permitting control for these important factors. All of the demographic and social data were derived from birth certificates and have been shown to be highly reproducible; most of the items used were also recorded on identity cards. It is possible however, that some of the more rare causes of death are confounded by parental characteristics that have not been measured.

We observed an overall association between offspring's birthweight and mortality in their parents. Specifically an association was identified for mothers' deaths from CHD and circulatory causes and for both parents who died from "other causes". Further research exploring the genetic pathways to both extremes of birthweight and to specific causes of death, will provide clues for the understanding and prevention of premature death among susceptible mothers of infants with low and high birthweights.

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References

1. Barker DJP, Winter PD, Osmond C, Margetts B. Weight in infancy and death from ischaemic heart disease. *Lancet* 1989;2:577–80. [PubMed: 2570282]
2. Friedlander Y, Paltiel O, Deutsch L, Knaanie A, Masalha S, Tiram E, et al. Birthweight and Mortality in the Jerusalem Perinatal Study. *Paediatric Perinatal Epidemiology* 2003;17:398–406.
3. Barker, DJP. Mothers, babies and health in later life. Edinburgh: Churchill Livingstone; 1988.
4. Hales CN, Barker DJ. The thrifty phenotype hypothesis. *Br Med Bull* 2001;60:5–20. [PubMed: 11809615]
5. Lucas A. Programming by early nutrition in man. *Ciba Found Symp* 1991;156:38–50. [PubMed: 1855415]
6. Curhan G, Willett W, Rimm E, Spiegelman D, Ascherio A, Stampfer M. Birth weight and adult hypertension, diabetes mellitus and obesity in US men. *Circulation* 1996;94:3246–50. [PubMed: 8989136]
7. Barker DJ, Eriksson JG, Forsen T, Osmond C. Fetal origins of adult disease: strength of effects and biological basis. *Int J Epidemiol* 2002 Dec;31(6):1235–1239. [PubMed: 12540728]
8. Hattersley AT, Tooke JE. The fetal insulin hypothesis: an alternative explanation of the association of low birth weight with diabetes and vascular disease. *Lancet* 1999;353:1789–1792. [PubMed: 10348008]
9. Ijzerman RG, Stehouwer CD, van Weissenbruch MM, de Geus EJ, Boomsma DI. Evidence for genetic factors explaining the association between birth weight and low density lipoprotein cholesterol and possible intrauterine factors influencing the association between birthweight and high density lipoprotein cholesterol: analysis of twins. *J Clin Endocrinol Metab* 2001;86:5479–5484. [PubMed: 11701725]
10. Ijzerman RG, Stehouwer CD, Boomsma DI. Evidence for genetic factors explaining the birth weight - blood pressure relation: analysis in twins. *Hypertension* 2000;36:1008–1012. [PubMed: 11116116]
11. Smith GD, Harding S, Rosato M. Relation between infants' birth weight and mothers' mortality: prospective observational study. *BMJ* 2000;320:839–40. [PubMed: 10731177]
12. Smith GD, Sterne J, Tynelius P, Lawlor DA, Rasmussen F. Birth weight of offspring and subsequent cardiovascular mortality in parents. *Epidemiology* 2005;16:563–9. [PubMed: 15951676]
13. Adams J, Pearce MS, White M, Unwin NC, Parker L. No consistent association between birthweight and parental risk of diabetes and cardiovascular disease. *Diabet Med* 2005;22:950–3. [PubMed: 15975114]
14. Raghunathan TE. What do we do with missing data? Some options for analysis of incomplete data. *Annu Rev Public Health* 2004;25:99–117. [PubMed: 15015914]
15. Carroll RJ, Stefanski LA. Approximate quasilikelihood estimation in models with surrogate predictors. *J Am Stat Assoc* 1990;85:652–663.
16. Rosner B, Spiegelman D, Willett WC. Correction of logistic regression relative risk estimates and confidence intervals for measurement error: the case of multiple covariates measured with error. *Am J Epidemiol* 1990;132:734–45. [PubMed: 2403114]

17. Smith GD, Hart C, Ferrell C, Upton M, Hole D, Hawthorne V, Watt G. Birth weight of offspring and mortality in the Renfrew and Paisley study: prospective observational study. *BMJ* 1997;315:1189–93. [PubMed: 9393220]
18. Smith GD, Whitley E, Gissler M, Hemminki E. Birth dimensions of offspring, premature birth, and the mortality of mothers. *Lancet* 2000;356:2066–8. [PubMed: 11145495]
19. 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;357:2002–6. [PubMed: 11438131]
20. Lawlor DA, Smith GD, Whincup P, Wannamethee G, Papacosta O, Dhanjil S, et al. Association between offspring birth weight and atherosclerosis in middle aged men and women: British Regional Heart Study. *J Epidemiol Comm Health* 2003;57:462–3.
21. Smith GD, Sterne JAC, Tynelius P, Rasmussen F. Birth characteristics of offspring and parental diabetes: evidence for the fetal insulin hypothesis. *Journal of Epidemiology and Community Health* 2004;58:126–128. [PubMed: 14729891]
22. Johnstone F, Inglis L. Familial trends in low birth weight. *BMJ* 1974;14:659–61. [PubMed: 4425792]
23. Emanuel I, Leisenring W, Williams MA, et al. The Washington State Intergenerational Study of Birth Outcomes: methodology and some comparisons of maternal birthweight and infant birthweight and gestation in four ethnic groups. *Paediatr Perinat Epidemiol* 1999;13:352–369. [PubMed: 10440054]
24. Klebanoff MA, Schulsinger C, Mednick BR, Secher NJ. Preterm and small-for-gestational-age birth across generations. *Am J Obstet Gynecol* 1997;176:521–526. [PubMed: 9077599]
25. Barker DJ, Hales CN, Fall CH, Osmond C, Phipps K, Clark PM. Type II (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidemia (syndrome X): relation to reduced fetal growth. *Diabetologia* 1993;36:62–7. [PubMed: 8436255]
26. Waterland RA, Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. *Mol Cell Biol* 2003;23:5293–300. [PubMed: 12861015]
27. Cooney CA, Dave AA, Wolff GL. Maternal methyl supplements in mice affect epigenetic variation and DNA methylation of offspring. *J Nutr* 2002;132:2393S–400S. [PubMed: 12163699]
28. Waterland RA, Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. *Mol Cell Biol* 2003;23:5293–300. [PubMed: 12861015]
29. Morgan HD, Sutherland HG, Martin DI, Whitelaw E. Epigenetic inheritance at the agouti locus in the mouse. *Nat Genet* 1999;23:314–18. [PubMed: 10545949]
30. Wu Q, Suzuki M. Parental obesity and overweight affect the body-fat accumulation in the offspring: the possible effect of a high-fat diet through epigenetic inheritance. *Obesity Reviews* 2006;7:201–8. [PubMed: 16629875]
31. Maier S, Olek A. Diabetes: a candidate disease for efficient DNA methylation profiling. *J Nutr Sci* 2002;132:2440–3.
32. Kaati G, Bygren LO, Edvinsson S. Cardiovascular and diabetes mortality determined by nutrition during parents' and grandparents' slow growth periods. *Eur J Hum Genet* 2002;10:682–8. [PubMed: 12404098]
33. Silverman BL, Metzger BE, Cho NH, Loeb CA. Impaired glucose tolerance in adolescent offspring of diabetic mothers: relationship to fetal hyperinsulinism. *Diabetes Care* 1995;18:611–7. [PubMed: 8585997]
34. Yajnik CS, Joglekar CV, Pandit AN, Bavdekar AR, Bapat SA, Bhave SA, et al. Higher offspring birth weight predicts the metabolic syndrome in mothers but not fathers 8 Years after delivery. The Pune Children's Study. *Diabetes* 2003;52:2090–6. [PubMed: 12882927]
35. Sattar N, Ramsay J, Crawford L, Cheyne H, Greer IA. Classic and novel risk factor parameters in women with a history of preeclampsia. *Hypertension* 2003;42:39–42. [PubMed: 12743016]
36. Chambers C, Fusi L, Malik IS, et al. Association of maternal endothelial dysfunction with preeclampsia. *J Am Med Assoc* 2001;285:1607–12.
37. Funai EF, Friedlander Y, Paltiel O, Tiram E, Xue X, Deutsch L, et al. Long-term mortality after preeclampsia. *Epidemiology* 2005;16:206–15. [PubMed: 15703535]
38. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia. Population based cohort study. *BMJ* 2001;323:1213–17. [PubMed: 11719411]

39. Haukkamaa L, Salminen M, Laivuori H, Leinonen H, Hiilesmaa V, Kaaja R. Risk for subsequent coronary artery disease after preeclampsia. *Am J Cardiol* 2004;93:805–8. [PubMed: 15019902]
40. Nelson RG, Morgenstem H, Bennett PH. Birth Weight and Renal Disease in Pima Indians with Type 2 Diabetes Mellitus. *Am J Epidemiol* 1998;148:650–6. [PubMed: 9778171]
41. Lackland DT, Bendall HE, Osmond C, Egan BM, Barker DJP. Low Birth Weights Contribute to the High Rates of Early-Onset Chronic Renal Failure in the Southeastern United States. *Archives of Internal Medicine* 2000;160:1472–6. [PubMed: 10826460]
42. Davies AM, Prywes R, Tzur B, Weiskopf P, Sterk VV. The Jerusalem perinatal study. 1. Design and organization of a continuing, community-based, record-linked survey. *Isr J Med Sci* 1969;5:1095–106. [PubMed: 5365594]

Figure 1.
Parents' Overall Mortality by Offspring's Birth-weight

Table 1

Characteristics of Parents by Birth Weight of their Offspring

Mothers	<2500		2500–3999		≥4000	
	N	(6.5%)	N	(88.0%)	N	(5.5%)
Characteristics						
Age						
<19	299	12.2	3,262	9.8	115	5.5
20–24	960	39.2	13,829	41.7	638	30.6
25–29	634	25.9	8,690	26.2	567	27.2
30–34	304	12.4	4,512	13.6	422	20.2
35+	249	10.2	2,893	8.7	344	16.5
Origin						
Israel	343	14.0	4,584	13.8	288	13.81
West Asia	769	31.4	9,596	28.8	441	21.14
North Africa	460	18.8	7,021	21.2	600	28.76
Europe/America	874	35.7	12,035	36.3	757	36.29
Education						
0–4	167	7.1	2,368	7.3	239	11.8
5–8	566	23.9	6,619	20.5	467	23.1
9–12	877	37.1	12,431	38.5	691	34.2
13+	754	31.9	10,900	33.7	621	30.8
SES						
Low	629	25.7	7,711	23.2	548	26.3
Middle	948	38.8	12,968	39.1	785	37.6
High	869	35.5	12,507	37.7	753	36.1
Smoking						
Missing	1,033	42.2	13,821	41.6	948	45.5
Non-smoker	812	33.2	11,772	35.5	783	37.5
Smoker	901	24.6	7,593	22.9	355	17.0
Heart disease						
No	2,420	98.9	32,930	99.2	2,074	99.4
Yes	26	1.1	255	0.8	12	0.6
Hypertension						
Missing	1,143	59.0	20,316	61.2	1,421	68.1
No	987	40.0	12,698	38.3	648	31.1
Yes	25	1.0	172	0.5	17	0.8
Diabetes						
No	2,435	99.5	33,068	99.6	2,040	97.8
Yes	11	0.5	118	0.4	46	2.2
Preeclampsia						
No	2,292	93.7	32,695	98.5	2,020	96.8
Yes	154	6.3	488	1.5	66	3.2
Gender of offspring						
Female	1,305	53.4	16,448	49.6	710	34.1
Male	1,138	46.6	16,738	50.4	1,375	65.9
Fathers	2,302	(6.1)	33,602	(88.4)	2098	(5.5)
Characteristics						
Age						
<24	633	27.5	8,713	25.9	337	16.1
25–29	770	33.5	11,645	34.7	603	28.7
30–34	436	18.9	6,409	19.1	425	20.3
35–39	240	10.4	3,686	11.0	351	16.7
40+	223	9.7	3,149	9.4	382	18.2
Origin						

Mothers	<2500		2500–3999		≥4000	
	2,446	(6.5%)	33,186	(88.0%)	2,086	(5.5%)
Israel	327	14.2	4,842	14.4	288	13.7
West Asia	784	34.1	10,105	30.1	488	23.3
North Africa	417	18.1	6,731	20.0	536	25.6
Europe/America	774	33.6	11,924	35.5	786	37.5
Education						
0–4	93	4.2	1,304	4.0	122	6.0
5–8	492	22.2	6,157	18.8	385	19.1
9–12	807	36.4	12,375	37.9	759	37.6
13+	824	37.2	12,847	39.3	754	37.3
SES						
Low	573	24.9	7,672	22.8	558	26.6
Middle	926	40.2	13,313	39.6	784	37.4
High	803	34.9	12,617	37.6	756	36.0
Gender of offspring						
Female	1,206	52.4	16,653	49.6	713	34.0
Male	1,096	47.6	16,949	50.4	1,385	66.0

Table 2

Mortality Rates in Mothers by Offspring Birth Weight

Cause of death	Model	Birth Weight ^a	Person -years	N. of events	Rate ^b	HR (95% CI)	
All cause mortality	Categorical	<2500	83,502	202	2.42	Model - 1 ^c	Model - 2 ^d
		2500-3999	1,153,656	2153	1.87	1.33 (1.15 – 1.54)	1.33 (1.15 – 1.54)
		>4000	72,990	220	3.01	1.26 (1.10 – 1.45)	1.20 (1.04 – 1.38)
Cancer	Linear	M=3,225; SD=0.52	1,310,148	2,575	1.96	0.99 (0.92 – 1.06)	0.97 (0.90 – 1.04)
		<2500	83,502	56	0.67	0.91 (0.70 – 1.20)	0.91 (0.69 – 1.19)
		2500-3999	1,153,656	866	0.75	1	1
CHD	Linear	M=3,225; SD=0.52	72,990	70	0.96	1.06 (0.83 – 1.35)	1.05 (0.82 – 1.35)
		<2500	1,310,148	992	0.76	1.10 (0.97 – 1.23)	1.10 (0.97 – 1.23)
		2500-3999	83,502	25	0.30	2.11 (1.38 – 3.21)	2.13 (1.40 – 3.25)
Circulatory Disorders	Categorical	<2500	1,153,656	165	0.14	1	1
		2500-3999	72,990	34	0.47	2.20 (1.52 – 3.20)	1.98 (1.36 – 2.88)
		>4000	1,310,148	224	0.17	1.05 (0.83 – 1.33)	0.98 (0.78 – 1.24)
Other causes	Linear	M=3,225; SD=0.52	83,502	42	0.50	1.61 (1.17 – 2.22)	1.61 (1.17 – 2.22)
		<2500	1,153,656	366	0.32	1	1
		2500-3999	72,990	61	0.84	1.86 (1.42 – 2.44)	1.73 (1.32 – 2.28)
	Categorical	<2500	1,310,148	469	0.36	1.04 (0.88 – 1.22)	1.00 (0.85 – 1.18)
		2500-3999	83,502	57	0.68	1.60 (1.22 – 2.10)	1.61 (1.22 – 2.11)
		>4000	1,153,656	507	0.44	1	1
	Linear	M=3,225; SD=0.52	72,990	56	0.77	1.32 (1.01 – 1.75)	1.21 (0.91 – 1.60)
		<2500	1,310,148	620	0.47	0.95 (0.82 – 1.10)	0.91 (0.79 – 1.05)
		2500-3999	83,502	42	0.50	1.61 (1.17 – 2.22)	1.61 (1.17 – 2.22)

^aMean and SD are presented for the linear model;
^bPer 1000 person years
^cHR - hazard ratio and CI - confidence interval adjusted for age of mother,
^dHR and CI adjusted for age, origin, education, SES and smoking status of mother and gender of offspring

Table 3 Association between Offspring Birthweight and Mortality in Mothers Adjusted for Various Covariates

Cause of death	Model	Birth Weight	Model 3 ^a		Model 4 ^b	
			HR	95% CI	HR	95% CI
All cause mortality	Categorical	<2500	1.30	1.13–1.50	1.23	1.06–1.42
		2500–3999	1		1	
		≥4000	1.19	1.03–1.37	1.17	1.01–1.34
Cancer	Overall birthweight association	<2500	$\chi^2=16.059$;df=2;p=0.0003			
		2500–3999	0.91	0.70–1.19	0.90	0.69–1.18
		≥4000	1		1	
CHD	Overall birthweight association	<2500	$\chi^2=0.753$;df=2;p=0.686			
		2500–3999	2.03	1.33–3.10	1.85	1.20–2.84
		≥4000	1.82	1.25–2.66	1.73	1.18–2.54
Other causes	Overall birthweight association	<2500	$\chi^2=16.03$;df=2;p=0.0003			
		2500–3999	1.57	1.19–2.06	1.45	1.10–1.91
		≥4000	1.20	0.91–1.59	1.17	0.88–1.55
	Overall birthweight association		$\chi^2=10.212$;df=2;p=0.006			

^aHR - hazard ratio and CI - confidence interval adjusted for age, origin, level of education, smoking status, hypertension, diabetes and CHD of mother and gender of offspring
^bModel 4 additionally adjusted for preeclampsia

Table 4

Mortality Rates in Fathers by Offspring Birth Weight

Cause of death	Model	Birth Weight ^a	Person -years	N. of events	Rate ^b	HR (95% CI)	Model - 1 ^c	Model - 2 ^d
All cause mortality	Categorical	<2500	76,152	378	4.96	1.09 (0.98 – 1.21)	1	1.10 (0.98 – 1.22)
		2500–3999	1,128,528	5,434	4.81			
		>4000	69,763	493	7.07	1.08 (0.98 – 1.19)		1.06 (0.96 – 1.16)
Cancer	Linear	M=3,225; SD=0.52	1,274,443	6,305	4.95	0.96 (0.91 – 1.01)		0.95 (0.91 – 0.99)
		<2500	76,152	76	1.00	1.02 (0.80 – 1.28)		1.02 (0.81 – 1.28)
		2500–3999	1,128,528	1,156	1.02	1		1
CHD	Linear	M=3,225; SD=0.52	1,274,443	84	1.20	0.90 (0.72 – 1.13)		0.88 (0.71 – 1.11)
		<2500	76,152	1,316	1.03	0.95 (0.85 – 1.05)		0.94 (0.85 – 1.04)
		2500–3999	1,128,528	993	0.88	0.96 (0.75 – 1.25)		0.96 (0.74 – 1.24)
Circulatory Disorders	Linear	M=3,225; SD=0.52	1,274,443	101	1.45	1.16 (0.95 – 1.43)		1.15 (0.94 – 1.42)
		<2500	76,152	1,156	0.91	0.99 (0.89 – 1.10)		0.98 (0.88 – 1.10)
		2500–3999	1,128,528	1,496	1.33	0.98 (0.79 – 1.20)		0.98 (0.80 – 1.21)
Other causes	Linear	M=3,225; SD=0.52	1,274,443	150	2.15	1.13 (0.96 – 1.34)		1.11 (0.94 – 1.32)
		<2500	76,152	1,740	1.37	1.02 (0.93 – 1.11)		1.00 (0.91 – 1.10)
		2500–3999	1,128,528	1,477	1.47	1.18 (0.98 – 1.43)		1.19 (0.98 – 1.44)
	Linear	M=3,225; SD=0.52	1,274,443	123	1.76	1.00 (0.83 – 1.20)		0.97 (0.80 – 1.17)
		<2500	76,152	1,712	1.34	0.91 (0.83 – 1.00)		0.89 (0.82 – 0.98)
		2500–3999	1,128,528	1,477	1.31	1		1

^aMean and SD are presented for the linear model;

^bPer 1000 person years

^cHR - hazard ratio and CI - confidence interval adjusted for age of father,

^dHR and CI adjusted for age, origin, education and SES of father and gender of offspring.