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Association between number of children and mortality of mothers: results of a 37-year follow-up study

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Abstract

Purpose—To examine the association between parity and long term all-cause mortality and mortality due to specific causes in women.

Methods—This prospective population-based study included 40,454 mothers who gave birth in Western Jerusalem, Israel, to 125,842 children and were followed for an average of 37 years following the birth of their first child. Cox Proportional Hazards Models were used to evaluate long-term total and specific cause mortality of women by their parity.

Results—We found a U-shaped relationship between the number of offspring and risk of all-cause mortality in mothers. After adjustment for sociodemographic characteristics and maternal health and obstetric conditions, higher mortality rates were observed for mothers of 1 child (HR=1.18; 95% CI 1.04–1.4), mothers of 5–9 children (HR=1.21; 95% CI 1.09–1.33), and mothers of 10 children (HR=1.49; 95% CI 1.12–1.99) as compared to mothers of 2–4 children. Mortality risk from specific causes including coronary disease, circulatory disease, and cancer were increased for multiparous women.

Conclusions—In this long-term follow-up study, there was an association between number of children mortality risk of mothers. These findings suggest that maternal pregnancies and post-natal characteristics as reflected by number of children may have consequences for long-term maternal health.

Keywords

parity; mothers' mortality; socioeconomic factors; survival

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Introduction

The reproductive patterns of women have long-term implications for women's health, yet only a few studies have addressed the association between parity, as reflected by number of children, and long-term mortality. Theories from evolutionary biology, such as the "disposable soma" theory, suggest a trade-off between reproductive factors and somatic maintenance (1, 2). These theories are based both on experiments in *Drosophila melanogaster* and on epidemiologic studies that show a positive relationship between fertility and mortality (3, 4). The physiological findings complement the "antagonistic pleiotropy" theory, which suggests that deleterious mutations that accumulate during an organism's lifetime favour reproduction at younger ages but are harmful at later ages (5, 6).

Findings from studies that have investigated historical cohorts as well as contemporary populations have been inconsistent. While most of these studies showed a positive association between parity and mortality (7–11), others found the opposite association (12–14). It may be that this inconsistency can to some extent be attributed to short follow up period, loss of follow up, misclassification of the number of births (especially in historical cohorts), random error due to small numbers at the extremes of family size and to small differences in mortality risk and failure to adjust for important potential confounders such as biological and socioeconomic factors (15).

The purpose of the current study was to examine the associations between number of children and all-cause mortality and mortality due to specific causes in mothers after taking into account maternal health conditions as well as lifestyle and socioeconomic factors as potential confounders.

Methods

The Jerusalem Perinatal Study (JPS), a population-based cohort, recorded data on 44,067 mothers with a total of 92,408 births in all hospitals in Western Jerusalem from 1964 to 1976. Details regarding data collection methods were described previously (16). Briefly, the demographic, socioeconomic, medical, obstetric, and neonatal information for all births was obtained from birth notifications and from maternity ward logbooks. Of the 44,067 mothers in the original JPS, identifiers, such as first and last names, date of birth and gender, of approximately 92% were verified through the Israeli Population Registry, totaling 40,454 mothers of 125,842 children that are included in the current study.

Parity data included (1) live births delivered after the 28th week of pregnancy from 1964 to 1976 (n=86,537); and (2) the number of children who were born prior to the inception of the cohort as reported by the mothers (n=39,305). No information was available regarding births that occurred after the year 1976. The follow-up time was calculated according to the mother's age when she first gave birth. For the 15,439 mothers who gave birth for the first time prior to 1964, this information was missing. Hence, for these mothers we imputed the age at first birth based on the number of children the mother had prior to 1964 and the median birth intervals. Practically all (>99%) deaths in Israel are reported to the National Population Registry (17, 18), through which the mothers were followed until April 30, 2005. The date and cause of death were obtained for the deceased mothers.

For categorical analysis, we used the following parity classification: 1 child, primiparous; 2–4, multiparous; 5–9, grand multiparous; and 10, great grand multiparous. Analyses in the current study used the number of children also as a continuous variable. Results of the categorical models were corroborated using models that tested parity as a continuous variable with linear and quadratic terms.

Potential confounders were selected based on the literature and on the descriptive analysis and include: mother's age at first birth, mother's origin and socioeconomic status, maternal health characteristics and obstetrical conditions. Maternal origin was based on the woman's country of birth and, for mothers born in Israel, on their father's country of birth. Ethnic origin was categorized into the following major groups: West Asia, Europe and America, North Africa, and Israel. A social class scale (SES), ranging from 1 (highest) to 6 (lowest) was developed based on the woman's husband's occupation using the Central Bureau of Statistics occupational categories. This scale was shown to have predictive validity in subsequent studies (19–21) and has the advantage that it allows classification of occupational groups unique to the Israeli population, such as Rabbis and yeshiva students, in a dimension that differed from education and ethnic group. This scale was also found to be similar and well correlated with other Israeli social class scales (22). Data regarding maternal years of education was available for 97.1% of the cohort. To deal with missing values of maternal education, 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 (23). This approach had a trivial effect on the results.

Dichotomous variables were used to characterize mother's history regarding medical conditions (i.e. diabetes, hypertension, heart disease) and smoking status. Dichotomous variables were also used to characterize mother's obstetrical history regarding the following obstetrical conditions: preeclampsia and gestational diabetes mellitus in one of the pregnancies, multiple pregnancies, and Cesarean sections. The data were almost complete for the demographic and socioeconomic variables, maternal lifestyle, health, and obstetrical characteristics.

Outcome variables were all-cause mortality and cause-specific deaths of the mother that occurred during the 37-year follow-up period due to coronary heart diseases (CHD) (ICD-10: I20.0–I25.9, I46.0–I46.9, I49.0–I49.9); circulatory diseases (ICD-10: I20.0–I25.9, I46.0–I46.9, I49.0–I49.9, I60.0–I69.9, I99); cancer (ICD-10: C00.0–C97); and other causes (ICD-10: A, B, E–S, V, X60, Y36.0–36.9).

Cox proportional hazards models were employed to assess the association between number of children and mortality rate in mothers after controlling for age at first birth, ethnic origin, socioeconomic status, previous maternal health conditions, smoking, and obstetrical conditions. The follow-up period was calculated from first birth until death, or censored at end of follow-up (April 30, 2005). Hazards ratios (HR) and 95% confidence intervals (CI) were calculated from the estimated regression coefficients and standard errors. The proportional hazards assumption was tested graphically using log minus log of survival curves comparing the categories of parity. The multivariate Cox model was also used to examine possible interaction effects between number of children and other covariables on the mortality hazard ratios of mothers. The statistical software package SPSS 20.0 (SPSS Inc., Chicago, IL) was used for all data analyses.

This study was approved by the Institutional Review Board of the Hadassah-Hebrew University Medical Center.

Results

The mean ages of the women at enrolment (age at first birth) and at the end of follow-up were 23.8 and 60.9 years, respectively. There were the following numbers of women in the cohort (n=40,454) who belonged to the different parity groups: 8,826 (21.8%) mothers of 1 child, 23,427 (58%) mothers of 2–4 children, 7850 (19.4%) mothers of 5–9 children, and

351 (0.8%) mothers of 10 or more children. Table 1 presents the characteristics of the women in the study population according to parity group. Of the total study population, 2,766 (6.8%) women had died by April 30, 2005. Mortality rates of mothers increased as the number of children increased. Lower socioeconomic status and lower level of education were more common in the two highest parity groups.

Number of events and all-cause and specific-cause mortality rates are presented in Table 2. As compared to mothers with 2–4 children, the hazard ratios (HRs) for all-cause mortality were lower for mothers with one child (RR=0.77; 99% CI 0.68–0.87) and increased for those with 5–9 (RR=1.95; 95% CI 1.80–2.11) and 10+ (RR=2.05; 95% CI 1.53–2.67) children. Similar trends were observed for cause-specific death rates. Cox proportional hazards models showed a U-shaped association between parity and all-cause mortality after accounting for demographic variables, maternal smoking, socioeconomic status, maternal health characteristics, and obstetric conditions (Table 3). Specifically, compared to women with 2–4 children, the hazard ratio was 1.18 (95% CI 1.04–1.34) for those with one child, 1.21 (95% CI 1.09–1.33) for those with 5–9 children, and 1.49 (95% CI 1.12–1.99) for those with 10+ children. Similar results were observed in models that assessed non-linear relationships between parity as a continuous variable and mortality rates (Figure 1).

When maternal education was introduced into the multivariate model instead of SES the coefficients for both high and low fertility groups were somewhat reduced, yet remained significant.

These findings were also evaluated when age of mother at censoring (death or end of follow up) rather than at first birth was taken into consideration. The HRs associated with parity groups of 5 children or more were similar to the estimates derived from the model using the maternal age at first birth, yet, mother of one child did not show higher risk of mortality. The associations between number of children and maternal cause-specific mortality hazards are presented in Table 4. While no significant U-shaped association was observed, there was a clear increase in mortality risk for mothers of 5–9 and 10 children as compared to mothers of 2–4 children. Notably, these women had considerably higher cardiovascular mortality risks, i.e. the coronary heart disease (CHD) hazard ratios for mothers of 5–9 and 10 children were 2.73 (95%CI 1.9–3.9) and 6.70 (95%CI 2.9–15.6), respectively, as compared to the reference group of mothers with 2–4 children. Notably, adding intervals between births to the models did not change the trends for our results (not shown).

Kaplan-Meier curves provide initial evidence of an interaction between number of children and mother's age at first birth on mortality of mothers, showing a positive association between parity and mortality in the 'young-age at first birth' groups but not in the older age groups (not shown). A significant interaction was shown ($p<0.0001$) using the Cox model (Table 5). Specifically, compared to the reference group (i.e. young mothers <25 years old with 1–4 children) the additional risk associated with older age at first birth was HR=2.25 ($p<0.0001$), and the risk associated with grandmultiparity (5+ children) was HR=1.28 ($p<0.0001$). If there were no interaction, the expected mortality risk for older mothers with 5+ children would be $HR=2.25 \times 1.28=2.88$. Yet the joint association derived from the Cox model was HR=1.95 ($p_{\text{interaction}}<0.0001$), suggesting an antagonistic interaction. In an exploratory analysis, interaction between number of children and mother's age at first birth was found also on mortality from cancer ($p=0.017$) and circulatory diseases ($p=0.011$). Sensitivity analysis was carried-out to assess potential bias in our findings due to unavailable information on births that occurred after the year 1976. For this purpose, we examined the association between number of children and mortality of mothers in women with a follow-up period longer than 37 years (mean follow-up, $n=18,602$). This limited group reflects mainly women who gave birth during the sixties and therefore were less likely

to have had more children after 1976. Cox proportional hazards regression models repeated on this sub-sample of women yielded similar HR estimates (and standard errors) to those obtained from the total women sample (data not shown).

Discussion

The main finding of this prospective study was that parity was positively associated with risk of all-cause mortality in mothers. In addition, high parity was associated with an increased risk of mortality from cancer, CHD, circulatory diseases, and other diseases. We found an 18% increase in the total mortality risk for mothers of one child, and 21% and 49% increases in total mortality risk for mothers having 5–9 and 10 children, respectively, as compared with mothers of 2–4 children.

This U-shape association between number of children and mortality risk is in accordance with findings from a large prospective Norwegian study (24), a Finnish prospective study of 12,055 mothers (25), and a recent census-based longitudinal Israeli study that has shown a similar non-linear relationship between parity and mortality (26). However, several of these studies failed to adjust for potential confounding factors such as health conditions of the mother and lifestyle variables (e.g. maternal smoking). Our findings support the ‘antagonistic pleiotropy’ and the ‘disposable soma’ theories proposed by Kirkwood & Westendorp that suggest a trade-off between reproductive factors and somatic maintenance (1, 2). Others, however, reported findings that were the opposite of ours. For example, a genealogical study in the Amish community (13), and a relatively small sample of Afro-American & Caucasian women in the United States (14), found a negative association between fertility and mortality i.e. that increased parity was associated with decreased mortality. The differences in findings among studies could be explained by social factors, as proposed by Grundy (27). However, the relatively modest degree of attenuation of the association following adjustment for the available sociodemographic variables in our study suggests that these factors are unlikely to be major determinants of the different women’s risk of mortality by parity.

An association between parity and mortality or morbidity from cardiovascular disease has been investigated by others over the years (28). The first evidence for an association between parity and women’s mortality from cardiovascular disease was found in the early 1990s, when different patterns of fertility were found to be related to changes in blood lipids and blood pressure levels (29, 30). These findings prompted other investigators to examine the association between number of pregnancies and the subsequent risk of cardiovascular disease. The Framingham Heart Study and the National Health and Nutrition Examination Survey National Epidemiologic Follow-up Study (NHEFS) found that having six or more pregnancies is related to an increased risk of CHD and cardiovascular disease (31). These findings were confirmed by other studies (26, 32, 33). This association can be explained in part by lifestyle risk factors associated with childbearing and by adverse effects related to the biological responses to pregnancy (33). For example, one possible biologic response to pregnancy is insulin resistance: pregnancy itself is a state of insulin resistance, which is a known potent cardiovascular risk factor (34). Weight gain is also common after pregnancies, and recurrent pregnancies may have an additive effect with later insulin resistance, leading to higher CHD morbidity risk. Our findings of increased risk of cardiovascular mortality in mothers of 5 children, after adjusting for socioeconomic, health, and lifestyle factors, supports this idea in that it indicates that there is an association between the cumulative effects of multiple pregnancies and cardiovascular morbidity.

Our study showed a positive association between number of children and the risk of cancer mortality. Specifically, the hazard ratios for mothers of 5–9 and 10+ children were 1.25

(95% CI 1.04–1.50) and 2.72 (95% CI 1.60–4.67), respectively, compared to the reference group of mothers with 2–4 children. The studies involving Finnish and Israeli cohorts mentioned above found no such association (25, 32). Differences in length of follow-up and adjustment for different confounders may partly explain the different findings. Although only few studies looked at the relationship between parity and total cancer mortality, associations between fertility patterns and the risk of specific types of cancer have been investigated (35–38). For example, childlessness was shown to be associated with breast cancer (39). We were unable to assess the associations of number of children with mortality from specific cancers since this information is unavailable in the National Population Registry. It is noteworthy, however, that mortality from breast cancer has been shown to be associated with both nulliparity and high parity (40).

Interestingly, in the current study we found an antagonistic interaction between the mother's age at first birth and number of children on mortality risk. The disposable soma theory, which suggests a trade off between somatic and reproductive resources, provides a possible explanation for this interaction. According to this theory, a young woman who chooses to allocate her biologic resources towards reproduction may reduce the resources available for future somatic maintenance.

This work has several strengths. Our prospective study is based on the Jerusalem Perinatal Study (JPS) birth cohort. The JPS is a large population-based cohort of unselected individuals living in the Jerusalem area during 1964–1976. On the one hand, the Israeli population in general and the population in Jerusalem in particular, have a relatively high percentage of families with 5 or more children (41). This allows comprehensive evaluation of the association between parity and all-cause mortality and cause-specific deaths in mothers. On the other hand, the urban geographic setting of this cohort and the equal accessibility to the Israeli public health system makes the JPS a representative study of most western population to date. Notably, the similar findings of a recent census-based study of parity and mortality suggest that the JPS cohort is indeed representative of the Israeli population (26). Relevant here is the fact that most studies that have examined the associations between parity and health of mothers were historical cohorts from before the 20th century, not reflecting today's modern way of living, especially in terms of quality of health care and its accessibility. The JPS prospective cohort is also unique in its combination of both high-quality detailed records as well as very long follow-up data. The availability of socioeconomic characteristics, as well as medical and obstetric conditions improved the characterization of the environment before and after pregnancies permitting control for these important factors. Additionally, associations of early pregnancy-related attributes, such as birth weight, maternal pre-pregnancy body size, gestational weight gain and gestational diabetes with long term clinical outcomes in both mothers and offspring were described previously in this cohort (42–46) and are compatible with studies conducted in other populations (47–51), lending support to the validity of the data.

Our study has several limitations. First, no information was available regarding births after 1976. However, the use of categories to define number of children would likely reduce the impact of this source of misclassification. Nevertheless, a sensitivity analysis including only women that were less likely to give birth after 1976 yielded similar results compared to those obtained when all women were included. Moreover, additional support for the validity of our parity data and findings is provided by using a sub-sample of 1220 mothers who gave birth between 1974–1976 and for whom we have recently obtained complete information on total number of children and measurements of cardio-metabolic outcomes. Within this sub-sample, a significant positive correlation between number of children as reported at birth and at follow-up was found. Importantly, a positive and significant association was also observed between number of children at follow-up and clinical cardio-metabolic outcomes

in the mothers. For example, the odds ratios associated with each additional child were 1.15 for obesity ($p < 0.001$) and 1.11 for diabetes ($p = 0.027$) (unpublished data).

Second, age at first birth was missing for mothers who gave birth before the initiation of the JPS cohort in 1964. To address this limitation, for these mothers, age at first birth was imputed based on the number of children the mother had prior to 1964 and the median birth intervals. To validate our findings, two additional approaches were applied calculating the follow-up period for all mothers from the age of 18 or from the age at first birth documented within the study period (1964–1976). Both approaches yielded similar results to our primary analysis using imputed missing data. Other limitations included unknown reasons for mortality for part of the cohort, lack of information regarding women with no children, pregnancies not resulting in live births and quality of life.

In summary, this study has shown that (1) the relationship between parity and all-cause mortality is u-shaped even after accounting for demographic, lifestyle and reproductive factors; (2) women with five or more children had higher CHD and cancer mortality risks than those with fewer children; and (3) age at first birth may modify the parity-mortality association. Further research exploring the pathways (biological, social and environmental) underlying these relationships will provide clues for the understanding and prevention of premature death among women in general, and among susceptible highly parous women in particular.

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Figure 1. Association between number of children (N) and total mortality in mothers: a continuous model*

*Adjusted for mother's age at first birth, mother's origin, socioeconomic status, diabetes mellitus, gestational diabetes mellitus, toxemia, hypertension, smoking, multiple pregnancies, Cesarean sections.

Table 1

Characteristics[§] of mothers by number of children

Characteristic	1 (N=8,826)	2-4 (N=23,427)	5-9 (N=7,850)	10+ (N=351)
All-cause mortality	Alive	96.3	94.3	86.5
	Deceased	3.7	5.7	13.6
Specific-cause mortality	Cancer	1.1	1.8	2.6
	CHD	0.2	0.3	1.4
	Circulatory	0.1	0.3	1.2
	Other	0.5	0.8	2.3
	Not known	1.8	2.5	6.1
	Israel	14.1	14.5	10.5
Mother's origin	West Asia	21.1	27.2	38.6
	North Africa	18.3	18.7	31.8
	Europe/America	46.5	39.6	19.1
	0	0.5	1.2	19.6
Education	1-8	9.7	20.2	45.9
	9-12	43.0	42.1	21.23
	>12	46.8	36.6	13.2
	Low	16.0	25.1	54.9
Socioeconomic status	Intermediate	37.5	42.7	24.7
	High	46.6	32.2	20.5
	<20	10.9	13.6	32.6
Mother's age at first birth	20-24.99	55.4	49.6	43.6
	25-29.99	26.1	27.0	20.1
	30-34.99	5.3	8.1	3.2
	>35	2.4	1.7	0.4
	>45	—	0.1	1.8
		0.2	0.4	0.9
Diabetes mellitus		0.1	1.4	3.5
Hypertension		8.0	11.3	11.9
Cancer				12.0

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Characteristic		1 (N=8,826)	2-4 (N=23,427)	5-9 (N=7,850)	10+ (N=351)
Smoking		21.3	19.2	7.3	3.3
Gestational diabetes mellitus		0.6	1.2	1.4	1.7
Toxemia		2.4	3.1	4.9	9.1

\$Data reported as %

Table 2
Number of deaths, mortality rates, and hazard ratios for exposed* and not exposed** mothers

	Exposed (1) vs. not exposed			Exposed (5-9) vs. not exposed			Exposed (10+) vs. not exposed		
	Number of events	Rate (/1000)	HR (95% CI)	Number of events	Rate (/1000)	HR (95% CI)	Number of events	Rate (/1000)	HR (95% CI)
All-cause mortality	325/1,324	1.19/1.55	0.77 (0.68-0.87)	1,063/1,324	3.02/1.55	1.95 (1.80-2.11)	54/1,324	3.17/1.55	2.05 (1.53-2.67)
Cancer	93/419	0.34/0.49	0.69 (0.55-0.87)	206/419	0.59/0.49	1.20 (1.00-1.42)	15/419	0.88/0.49	1.80 (0.99-2.99)
Circulatory	29/136	0.11/0.16	0.67 (0.43-1.00)	199/136	0.56/0.16	3.56 (2.85-4.46)	12/136	0.70/0.16	4.43 (2.23-7.99)
CHD	16/69	0.058/0.08	0.73 (0.39-1.26)	106/69	0.30/0.08	3.73 (2.73-5.14)	7/69	0.41/0.08	5.09 (1.97-11.09)
Other	45/183	0.16/0.21	0.77 (0.54-1.07)	182/183	0.52/0.21	2.42 (1.96-2.99)	8/183	0.47/0.21	2.19 (0.93-4.42)
Unknown	158/586	0.58/0.68	0.84 (0.70-1.00)	476/586	1.35/0.68	1.98 (1.75-2.23)	19/586	1.11/0.68	1.63 (0.97-2.57)

* Exposed= 1, 5-9, 10+ children

** Not Exposed= 2-4 children

Table 3

Associations between number of children and other maternal characteristics and total mortality in mothers: hazard ratio estimates derived from the COX proportional hazard multivariate model

Characteristic		HR	95% CI
Children, N	1	1.18	1.04–1.34
	2–4 (reference)	1	---
	5–9	1.21	1.09–1.33
	10+	1.49	1.12–1.99
Mother's origin	Israel (reference)	1	---
	West Asia	0.90	0.79–1.02
	North Africa	1.00	0.87–1.14
	Europe/America	0.95	0.83–1.07
Socioeconomic Status	High (reference)	1	---
	Intermediate	1.08	0.97–1.20
	Low	1.37	1.23–1.54
Mother's age at first birth, years		1.09	1.08–1.10
Gestational diabetes mellitus	No (reference)	1	---
	Yes	1.25	0.94–1.67
	Unknown	0.92	0.76–1.12
Toxaemia	No (reference)	1	---
	Yes	1.74	1.49–2.04
Diabetes mellitus	No (reference)	1	---
	Yes	2.33	1.76–3.09
Hypertension	No (reference)	1	---
	Yes	1.61	1.15–2.26
	Unknown	0.76	0.64–0.90
Smoking	No (reference)	1	---
	Yes	1.31	1.06–1.63
	Unknown	1.76	1.46–2.13
Multiple pregnancy	No (reference)	1	---
	Yes	1.04	0.83–1.29
Caesarean section	No (reference)	1	---
	Yes	1.19	1.05–1.35

* Adjusted for mother's age at first birth, mother's origin, socioeconomic status, diabetes mellitus, gestational diabetes mellitus, toxaemia, hypertension, smoking, multiple pregnancies, Cesarean sections.

Table 4

Association between number of children and cause-specific mortality of mothers: hazard ratio estimates derived from COX proportional hazard multivariate models^{*}

Cause of death	N of children	HR	95% CI
Cancer	1	0.86	0.68–1.08
	2–4	---	---
	5–9	1.25	1.04–1.50
	10+	2.72	1.60–4.67
Heart disease	1	1.24	0.70–2.18
	2–4	---	---
	5–9	2.73	1.91–3.88
	10+	6.70	2.88–15.58
Circulatory disease	1	1.13	0.75–1.71
	2–4	---	---
	5–9	2.41	1.88–3.11
	10+	4.48	2.38–8.44
Other	1	1.17	0.84–1.64
	2–4	---	---
	5–9	1.71	1.35–2.17
	10+	2.09	1.00–4.37

--- Reference category

^{*} Adjusted for mother's age at first birth, mother's origin, socioeconomic status, diabetes mellitus, gestational diabetes mellitus, toxemia, hypertension, smoking, multiple pregnancies, Cesarean sections.

Table 5

Joint association between mother's age at first birth and number of children ^{*\$}

characteristic		b	HR	95% CI
N of children	Mothers age at first birth			
1–4	<25	Reference	1	Reference
1–4	25	0.81	2.25	2.03–2.49
5+	<25	0.24	1.28	1.14–1.44
5+	25	0.67	1.95	1.69–2.24

* HR estimates derived from a multivariate Cox proportional hazards model

^{\$} Adjusted for mother's age at first birth, mother's origin, socio-economic status, diabetes mellitus, gestational diabetes mellitus, toxemia, hypertension, smoking, multiple pregnancies, Cesarean sections.