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Research Article

Impact of parental ages and other characteristics at childbearing on congenital anomalies: Results for the Czech Republic, 2000-2007

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Abstract

BACKGROUND

While it is widely known that maternal age at childbearing plays a role in the occurrence of Down syndrome, less is known about the effects of maternal age on other major congenital anomalies. Information on the possible effects of other maternal characteristics and of the age of the father is even scarcer.

OBJECTIVE

We present new results on the associations between parental ages and other maternal characteristics on the one hand, and congenital anomalies on the other, using linked data from three Czech registries on mothers, newborns, and malformations, for the period 2000-2007.

METHODS

As the variables are in a categorical format, binary logistic regression is used in order to investigate the relationship between the presence/absence of a congenital anomaly for each of the 11 types of anomalies considered, and for the set of predictors.

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RESULTS

This research confirms that the age of the mother has an impact on the incidence of Down syndrome and other chromosomal anomalies. Paternal age is not associated with chromosomal anomalies, and, in this Czech population, has a rather slight effect on some of the congenital anomalies examined. Another finding of the present study is that various other maternal characteristics may affect the incidence of congenital malformations.

CONCLUSIONS

Based on a large dataset, this study concludes that the ages of both parents can be associated with congenital anomalies of the child, and that maternal characteristics other than age have also to be considered.

COMMENTS

Risk factors can be tentatively proposed if they are based on a plausible and suitably tested explanatory mechanism. Unfortunately, in the majority of individual cases of congenital anomaly, the cause of the condition is unknown, and is suspected to result from an interaction of multiple environmental and genetic factors.

1. Introduction

In recent decades, all developed countries have experienced a considerable decline in fertility, with most now having total fertility rates below two children per woman. In addition, in most developed countries the average age at which both men and women have children has increased significantly (Mathews and Hamilton 2009). While a large number of studies have examined the consequences of low fertility levels, much less has been written about the possible effects of late childbearing. Various studies in epidemiology and in demography have, however, shown that late childbearing could have deleterious effects on infant survival and health, and that late parenthood likely increases the frequency of congenital anomalies (see, e.g., Gourbin 2005; EUROCAT 2009). The literature also suggests that various other characteristics of the mother may have effects on the incidence of congenital anomalies.

While the role played by maternal age at childbearing in the occurrence of Down syndrome has been widely recognised since the 1930s, less is known about the effects

of the mother's age on other major congenital anomalies. Even less information is available about children born to older fathers. In Section 2 of this paper, we present some evidence—partly based on our own past research—that links parental ages at childbearing,[5] of both the mother and the father, to the congenital anomalies of the child. In the following sections, we present new results on the associations between parental ages and other maternal characteristics on the one hand, and congenital anomalies on the other, using linked data from three Czech registries on mothers, newborns, and malformations. We end with a discussion and a conclusion.

2. Background

Our previous research has shown that late parental ages at childbearing are associated with infant mortality, especially neonatal and early neonatal mortality (Wunsch and Gourbin 2002), and with late foetal mortality (Rychtaříková 2001, Rychtaříková, Gourbin, and Wunsch 2004). Several studies have also linked late childbearing to congenital anomalies. The association between maternal age and congenital anomalies is well-known, especially for Down syndrome (Šípek et al. 2001; Dobson 2006), but also for neural tube defects (Šípek et al. 2002a) and abdominal wall defects (Šípek et al. 2002b). These and other chromosomal anomalies are generally attributed to the ageing of women's ova.[6] Maternal ageing is much less relevant for non-chromosomal anomalies, which seem more dependent upon external factors, such as smoking or alcohol and drug consumption (Loane et al. 2009).

The possible impact of paternal age on congenital anomalies is less clear (Yang et al. 2007). A few studies have pointed out that sperm may decline in quality and quantity as men age, which might have an impact on congenital anomalies (Plaset al. 2000, Auger and Jouannet 2005; Sartorius and Nieschlag 2010). For spontaneous abortions, it has been shown that autosomal trisomies and monosomy X can have a paternal origin as a consequence of an increasing frequency of chromosomal anomalies in the spermatozoa with male age (Slama et al. 2005), but no clear impact of paternal age on chromosomal anomalies has been detected for live births.

According to the literature[7] (see, e.g., Hall and Solehdin 1998; Inzucchi 1999; Khalil and O'Brien 2010; Mastroiacovo et al. 1999; Morales-Suarez Varela et al. 2009, Nørgaard et al. 2010, Olesen et al. 2009; Wax 2009; Zhu et al. 2006), a number of

[5] Childbearing concerns the mother, of course, but, for the sake of brevity, we will extend the term to the father as well.

[6] An introduction to chromosomal abnormalities can be found, for example, on the website of the National Human Genome Research Institute, U.S. National Institutes of Health, www.genome.gov.

[7] Including a Medline search (January 2005 up to June 2011) on the causes of congenital anomalies.

factors in addition to the ages of the parents at the birth of the child may contribute to congenital anomalies, including multiplicity of birth, and, for the mother, having had a previous live birth, a previous perinatal[8] death of a child, or a previous miscarriage. Other factors include the mother's education, socio-economic status, and marital status; as well as whether the mother is obese, suffers from diabetes or rheumatoid arthritis, smokes, drinks alcohol, lacks folic acid, has used assisted reproductive technologies (ART[9]) to become pregnant, or has other genetic factors. These characteristics should be taken into account, when possible, in the analysis of the putative risk factors of congenital anomalies. They may also have confounding effects on the relationship between parental ages and congenital anomalies.

In a case-control surveillance of congenital anomalies using the *Hungarian Congenital Abnormalities Register*, Vandresse et al. (2008) have shown that, after controlling for a series of other parental characteristics, both maternal age and paternal age have independent effects on the risk of congenital anomalies. Parents older than age 40 have an increased risk of giving birth to a child with a congenital anomaly. An analysis of some specific congenital anomalies indicates that maternal age (35 and older) is a well-known risk factor in the incidence of Down syndrome, and that paternal age (40 and older) is a risk factor in the incidence of congenital anomalies of the circulatory system and of oral clefts. The epidemiologic literature dealing with the effects of the ages of both parents on congenital anomalies more or less confirms these results. In one study (Bille et al. 2005), both a high maternal age and a high paternal age were found to be associated with the occurrence of cleft lip with or without cleft palate, while a higher paternal age, but not a higher maternal age, was shown to increase the risk of having a child with cleft palate only. A Norwegian study confirmed the effect of the father's age, but not of the mother's age, on the incidence of cleft palate (Harville et al. 2007). In another study (Materna-Kiryluk et al. 2009), advanced maternal and paternal ages were both shown to be independently associated with congenital heart defects; furthermore, a higher paternal age was found to be positively associated with the incidence of cleft palate and cleft lip. Similar effects of older paternal ages were found by Yang et al. (2007) in the USA.

Congenital anomalies are rather rare at birth. The total occurrence of malformations of the foetus is, of course, much higher, but many affected pregnancies are aborted spontaneously, especially during the first trimester of pregnancy (Simpson and Carson 1993), and voluntary terminations of pregnancy may be performed if an anomaly of the foetus is detected. Excluding the well-known relationship between maternal age and Down syndrome, results regarding the impact of parental ages on congenital anomalies tend to vary from study to study. Some non-significant results

[8] Stillbirth and early neonatal death.
[9] Assisted reproductive technologies.

might simply be due to the small number of cases available in the datasets, while larger sets might show significant correlations. The results could also depend upon which factors are controlled for or whether the occurrence of an anomaly is contrasted with cases without anomalies, as it is the case with odds and odds ratios, or against all cases, as with probabilities or frequencies. In order to check the stability of the results, it is necessary to replicate research concerning the possible impact of parental ages on congenital anomalies using large datasets, and taking other parental characteristics into account, as we are doing in the present study.

The aim of this paper is to test the following assumptions using the unique dataset at our disposal. Based on our background knowledge, we postulate that, in the case of the Czech Republic, both the mother's and the father's ages at childbearing can have independent effects on the incidence of congenital anomalies among live births. We also postulate for live births that the mother's age alone will be associated with chromosomal anomalies, and that both the mother's and the father's ages can be correlated with non-chromosomal anomalies. Finally, we examine to what extent other characteristics of the mother are associated with congenital anomalies, as various maternal characteristics have been shown to be related to birth defects in other studies.

3. Data

To our knowledge, very few large, reliable databases currently exist that are suitable for investigating this topic, as to conduct such studies it is necessary to compare children born with and without a congenital anomaly, and to take into account various parental characteristics. One such dataset is, however, available in the Czech Republic. It was developed at the Institute of Health Information and Statistics of the Czech Republic by linking data from three national registries—namely, the registers on mothers, newborns, and malformations—using the personal national identification number of the mother. The data collection goes beyond the usual vital statistics, as it also provides information on health. However, information concerning the father is limited.

The data are taken from three individual forms: the report on the mother (Zpráva o rodičce), the report on the newborn (Zpráva o novorozenci), and the congenital malformation of a foetus or a child (Vrozená vada plodu nebo dítěte). The first two forms are gathered and processed by the Institute of Health Information and Statistics (ÚZIS). The report on the mother is filled in by the obstetrician immediately after delivery. In case of a delivery outside a hospital, the form must be completed by the medical worker who assisted during or after the delivery. Reporting is mandatory by law. Anamnestic information is copied from the pregnancy file, with the data being established during pregnancy by the attending gynaecologist. The report on the

newborn is completed by the neonatologist just after delivery. Reporting is also mandatory. The content of the third form is reported in the register on congenital malformations. The latter includes all cases detected up to the age of 15, and the data are reported by the medical doctor who diagnosed the malformation. The registration of malformations started on 1 January 1964, and is obligatory. Since1 January 1996, the registration has been based on a new extended form and includes foetuses diagnosed with a congenital malformation, spontaneous abortions weighing more than 500 grams with a diagnosed malformation, stillbirths, live births, and detected cases up to the age of 15. The registration covers all congenital malformations listed in ICD 10-Chapter XVII (Congenital malformations, deformations and chromosomal abnormalities: Q00-Q99). Detailed information concerning congenital malformations can be found in Czech at http://www.uzis.cz/registry-nzis/nrvv.

The maximum number of registered malformations allowed per case is eight. The date of a diagnosis is reported by year, month, and day. When a malformation is diagnosed before delivery (i.e., prenatal diagnosis), the week of gestation is reported in addition to the date. The data are collected and entered into the national registration system (NZIS), which is also operated and supervised by the Institute of Health Information and Statistics. Therefore, all of the statistical information used in this study is processed within the same Institute, following the same technical rules. Children with only one anomaly represented 78.2% of the cases in our dataset, with the rest (21.8%) being children with more than one anomaly. In our analysis, we have used only the first reported malformation in cases of multiple anomalies.[10] For all of the children with one or more anomalies, in 63.4% of the cases the first reported anomaly was detected just after delivery (at zero completed days), in 25.9% of the cases it was detected within one to six completed days after delivery, in 2.1% of the cases it was detected prenatally, and in 8.6% of the cases it was detected later in life. Abortions are not included in our dataset. However, the information related to abortions performed because of a diagnosed malformation is available in a yearbook on abortions (Potraty) published by the Institute of Health Information and Statistics. In the period under study, 2000-2007, only 3.5% abortions (1443) of all the abortions for medical reasons were due to malformations.

The three datasets, which cover the period 2000-2007, were linked using the personal identification number of the mother at the Czech Institute of Health Information and Statistics. From the total number of live births (788434) reported by the Czech Statistical Office for the whole Czech Republic in 2000-2007, only 988 cases, or 0.13%, could not be linked. The dataset used in this study for the same period, 2000-2007, contains individual anonymous information on 670765 live births, of which

[10] We have not pursued the analysis on multiple anomalies as the number of cases is small, especially if the number of anomalies reported and the types of anomalies are taken into account.

25006, or 3.7%, were born with (at least) one congenital anomaly. Our working dataset represents 85.1% of all live births in the Czech Republic for the period 2000-2007. Not all live births were included, primarily because the ages of the fathers were not known in some cases, and partly because we imposed age restrictions of 15 to 69 for men and 12 to 49 for women. The distribution of live births in our dataset according to the ages of both parents is given in Annex Table 1 of the Supplementary Material.

The age of the father was unknown in 92331 cases, and in 1715 cases the father was either younger than age 15 or older than age 69; in total, 94046 cases were deleted. In addition, 296 cases were deleted because the mother's age was unknown or was over 50 (seven cases). However, all groups of fathers (of unknown age, known age, and age outside the interval of 15-69) for whom the mother's age was known displayed almost the same mean age of mothers and incidence of congenital malformations. For fathers with a known age between 15 and 69, the mother's mean age was 27.7, and congenital anomalies were reported in 3.7% of the cases. For the group in which the father's age was unknown, the corresponding values were, respectively, 27.3 years and 3.7%; and for the group in which the father's age was outside the age group 15-69, the values were, respectively, 27.9 years and 3.1%. The relative age distributions of mothers when the father's age was known and when the father's age was unknown are very similar (data not shown).

We have also compared cases in which the father's age was unknown to cases in which the father's age was known to have been between 15 to 69, based on the mother's educational attainment and marital status. There were more cases in which the father's age was unknown among women with a basic education only and among women who were single.[11] However, we found that the percentage of anomalies was very similar between the two groups (unknown and known father's age) when we considered the various educational and marital status categories.

Mother's education and mother's marital status were also not reported in some cases. The mother's education was unknown in 20386 cases, her marital status was unknown in 1595 cases, and there were 988 unlinked records due to other incomplete observations. The occurrence of a congenital anomaly was reported twice in the linked file, from the newborn register and from the congenital malformation register. The 365 cases in which the anomaly was reported at birth but not later in the congenital malformation register were deleted. In addition, one case was deleted because the child's sex was unknown. In total, 117669 cases were deleted from the original dataset of 788434 live births. However, the frequency of congenital anomalies remained at 3.7% when the original dataset (29166/788434) was compared with our working dataset

[11] For women with basic education, the shares were 23% (unknown father's age) versus 77% (known father's age). For university graduates, the shares were 11% (unknown father's age) versus 89% (known father's age). For single mothers, the shares were 22% (unknown father's age) versus 78% (known father's age).

(25006/670765). The mean mother's age was 27.7 (standard deviation 4.6) and the mean father's age was 31.2 (standard deviation 5.9) in our final dataset.

The total group of congenital anomalies for the period considered has been subdivided into 11 groups of anomalies coded according to ICD 10 (WHO, 1992), taking into account the type of anomaly. The groups of congenital anomalies, ranked according to their frequency, are shown in Table 1. We can see that, as expected, the number of anomalies was rather small for most groups. Only live births with an anomaly of the circulatory system exceeded 1% of all live births.

Table 1: Number of live births by groups of anomalies according to ICD 10, their respective percentages, and their proportions among all live births

		Percentage	
	numbers	**anomalies**	**live births**
Anomalies of the circulatory system (Q20.0-Q28.9)	7144	28.57	1.065
Anomalies of the musculoskeletal system (Q65.0-Q79.9)	5629	22.51	0.839
Anomalies of the genital organs (Q50.0-Q56.4)	3698	14.79	0.551
Anomalies of the urinary system (Q60.0-Q64.9)	2462	9.85	0.367
Anomalies of eyelid, lacrimal apparatus and orbit (Q10.0-Q18.9)	1164	4.65	0.174
Congenital non-neoplastic naevus (Q82.5)	987	3.95	0.147
Anomalies of cleft lip and cleft palate (Q35.0-Q37.9)	897	3.59	0.134
Anomalies of the nervous system (Q00.0-Q07.9)	442	1.77	0.066
Down syndrome (Q90.0-Q90.9)	285	1.14	0.042
Other chromosomal abnormalities (Q91.0-Q99.0)	223	0.89	0.033
Other anomalies (Q30.0-Q34.9, Q38.0-Q39.9, Q40.0-Q45.9, Q80.0-Q82.4, Q82.8-Q89.9, Q99.1-Q99.9)	2075	8.30	0.309
Total anomalies	25006	100	3.728
No anomaly	645759		96.272
Total	670765		100

In the present study, we examined only the possible predictors (presented in Section 2) that were available in the dataset, and the characteristics that were sufficiently frequent. For example, alcohol intake was poorly reported, and therefore was not included in the analysis. We took into account the following parental characteristics: the ages of both of the parents at the birth of the child, multiplicity of birth, and, for the mother, having had a previous live birth, having had a previous perinatal death of a child, having had a miscarriage, education[12], marital status, having diabetes[13], and being a smoker[14]. The frequency distributions of live births with and without anomalies over all categories of the covariates are given in Annex Table 2 of the Supplementary Material.

4. Methods

We have specified all of the covariates as categorical variables as follows (reference category in bold): mother's age (12-19, 20-24, **25-29**, 30-34, 35-39, 40-44, 45-49), father's age (15-19, 20-24, 25-29, **30-34**, 35-39, 40-44, 45-69), mother's education (basic, vocational, **secondary**, university), mother's marital status (single, **married**, divorced and widowed), multiple birth (**1**, 2+), previous miscarriage (**0,** 1, 2+), previous perinatal death (**no**, yes), previous live birth (0, **1**, 2+), mother's diabetes (**none**, gestational, pre-existent), and mother's smoking (**no**, yes). We have contrasted other modalities as well, but as the global picture does not change, the results will not be presented. The age groupings considered are in five-year intervals over the fertile period, except for young mothers (12 to 19) and older fathers (45 to 69). The latter grouping was chosen because of the small number of births that occur at these ages, and the former grouping was chosen because female fertility is not observed before 12 years of age.

Binary logistic regression[15] analysis was used in a main effects model in order to investigate the relationship between the presence/absence of a congenital anomaly, for each type of anomaly considered, and for the set of explanatory variables listed above.

[12] Basic (ISCED 1, 2), vocational (ISCED 3C), secondary (ISCED 3A), university (ISCED 5, 6)

[13] Each pregnant woman is tested for diabetes (laboratory tests). In a normal pregnancy, she is tested during the 24-28 weeks of gestation. In a pregnancy at risk, she is tested during the first trimester (risks are: being obese, previous children weighing more than 4000 grams, previous pregnancy with preeclampsia, glycosuria in urine, diabetes in family, older than 30 years). In case of a positive result, the woman is sent to the special consulting service for diabetes and is supervised by a diabetologist.

[14] Smoking is self-reported. The thresholds are: more than five cigarettes a day, any time during pregnancy, or less than five cigarettes a day repeatedly.

[15] The dependent (response) variable is the presence/absence of a congenital anomaly. SAS 9.3 and procedure logistic were used for the estimations.

The evaluation of the overall model (in which the proposed logistic model was compared to an intercept-only model) was conducted using three inferential statistical tests: the likelihood ratio, the score, and Wald tests. The three tests showed that all of the logistic models are more effective than the null model (intercept-only model), as might be expected given that such a large dataset is bound to contain some bogus correlations. More interestingly, the goodness of fit of the logistic models against actual outcomes was tested using the Hosmer–Lemeshow (H–L) inferential goodness-of-fit test (Hosmer and Lemeshow 2000). The tests showed that the hypothesis that the model is a good fit for the data is tenable, although it should be remembered that models are schematic representations of the unknown relationships between the data, and that these actual relationships may differ from their model representation. Finally, the statistical significance of individual regression coefficients, transformed into odds ratios (OR), has been tested using the Wald chi-square statistic, and is reported for each variable in Annex Tables 3a to 3k published as Supplementary Material in the columns headed Pr>ChiSq.

The possible presence of interactions between the two parental ages has also been examined, although the interactions are particularly difficult to interpret in the case of logistic models and other non-linear models (Ai and Norton, 2003). Following de la Rochebrochard and Thonneau (2002), we have also constructed a single variable, "couple age," with couples composed of a woman and a man, both aged 20-29, forming the reference group. As in the paper by de la Rochebrochard and Thonneau, the ages of the mother and father are cross-classified according to the following age classes: 20-29, 30-34, 35-44 for the mother; and 20-29, 30-34, 35-39, 40-64 for the father. In a similar vein, we considered the age difference between parents (by five-year age groups) instead of paternal age, and in addition to the mother's age. In this latter model, we were able to avoid the high correlation between parental ages. The covariates other than parental ages were simultaneously included in all of these models. These approaches took into account to a large extent the age homogamy between spouses and the co-linearity between the father's and the mother's ages.

5. Results

The model with the maternal age and the age difference between the parents gave almost the same results as the model that took into account the ages of both the mother and the father. The same was true of the model combining the mother's and the father's ages at childbearing. We therefore decided to focus primarily on the results of the main effects model that deals with both parental ages for each of the anomalies considered.

As the effects of parental ages have been highlighted in the literature, we first examined their possible impact on congenital anomalies, controlling for the other covariates (Table 2). We then focused the analysis on the associations between each group of congenital anomalies and the other characteristics of the mother, controlling for parental ages (Table 3). The impact of each variable on a group of congenital anomalies, which can be seen in Tables 2 and 3, is shown only for statistically significant odds ratios (taken here as $p \leq 0.050$[16]; 95% Wald confidence intervals included). It is important to note that "significant" is not the same as "meaningful", for example, an odds ratio (OR) of 1.1 might be statistically significant, but it is not very meaningful, as the odds ratio is close to one. The results presented in the Supplementary Material Tables 3a to 3k show the logistic regression outputs for all age categories, regardless of the significance level.

We observed that, controlling for the father's age and for the other covariates, the mother's age had an effect on circulatory system anomalies, with the risk (i.e., OR) increasing slightly with age. In the case of musculoskeletal anomalies, the opposite trend was observed; i.e., the risk decreased as the mother's age increased; the ORs were, however, close to one. A higher risk was also seen for younger fathers (aged 20-24). The occurrence of congenital non-neoplastic naevus was lower among older mothers, but the confidence interval was wide. For cleft lip and cleft palate, higher odds were seen among younger mothers and among fathers aged 35-39 years. The odds ratios were particularly high for Down syndrome and for other chromosomal anomalies in the case of older mothers, primarily after the age of 40, and especially after age 45. However, for the age group 35-39, the odds were three times higher than for mothers aged 25-29. We found no evidence that the father's age had an impact on either group of chromosomal anomalies (Down syndrome and other chromosomal anomalies), but it appears to have been the only age factor for the group "all other congenital anomalies." All of the ORs relating to the father's age were, however, rather low (i.e., < 1.4). These results were obtained regardless of whether all live births or only singletons were taken into account (results not shown).

[16] OR : odds ratio. Taking $p \leq 0.050$ means that we accept up to 5% type-I errors or false positives with a null hypothesis of OR equal to one. Three-digit p-values are used throughout this paper.

Table 2: Impact of parental ages on congenital anomalies (live births) controlling for other covariates

Anomaly	Modalities	OR	95% Wald C.I.
Circulatory system	Mother's age		
	30-34 versus 25-29	1.10	1.04 - 1.18
	35-39 versus 25-29	1.14	1.03 - 1.27
Musculoskeletal system	Mother's age		
	20-24 versus 25-29	1.09	1.01 - 1.18
	30-34 versus 25-29	0.91	0.85 - 0.98
	Father's age		
	20-24 versus 30-34	1.13	1.02 - 1.26
Congenital non-neoplastic naevus	Mother's age		
	40-44 versus 25-29	0.25	0.08 - 0.78
Cleft lip and cleft palate	Mother's age		
	12-19 versus 25-29	1.65	1.15 - 2.38
	20-24 versus 25-29	1.38	1.15 - 1.66
	Father's age		
	35-39 versus 30-34	1.23	1.01 - 1.52
Down syndrome	Mother's age		
	30-34 versus 25-29	1.52	1.09 - 2.11
	35-39 versus 25-29	2.73	1.75 - 4.28
	40-44 versus 25-29	9.13	5.11 - 16.30
	45-49 versus 25-29	25.33	5.88 - 109.22
Other chromosomal anomalies	Mother's age		
	35-39 versus 25-29	3.41	2.11 - 5.52
	40-44 versus 25-29	6.80	3.31 - 13.96
	45-49 versus 25-29	43.78	12.53 - 152.95
All other congenital anomalies	Father's age		
	20-24 versus 30-34	1.22	1.02 - 1.45
	45-69 versus 30-34	1.35	1.05 - 1.74

Note: The dependent variable is the presence of a congenital anomaly. OR: odds ratio. Only statistically significant results at p≤0.05 level are presented. CI: confidence interval. Logistic regression is computed for each anomaly separately. Controls: mother's education, mother's marital status, multiple birth, previous miscarriage, previous perinatal death, previous live birth, mother's diabetes, mother's smoking.

The potential interactions between parental ages were generally not found to be statistically significant (results not shown). An interaction effect was, however, found between very young mothers aged 12-19 and much older fathers (aged 35 and older) for musculoskeletal, genital, and urinary anomalies. In each of these cases, the odds ratios were significantly greater than one.

We also examined the effect of the other maternal characteristics, controlling for parental ages (Table 3, significant contrasts only: $p \leq 0.050$). Congenital non-neoplastic naevus and other chromosomal anomalies (excluding Down syndrome) were not included in Table 3, as only the age of the parents had an impact on these anomalies. Once again, almost the same results were obtained regardless of whether all live births or only singletons were taken into account (results not shown).

Women with lower levels of education were shown to be more likely than those with higher levels of education to deliver a child with Down syndrome (the odds were 1.9 times higher for women with a basic level of education than for those with secondary education), or with an anomaly of the nervous system (1.7), of the lip and palate (cleft) (1.5), and of the eye (1.3). In addition, lower education of the mother was shown to be statistically significant in the case of all other congenital anomalies, and of those of the circulatory and musculoskeletal systems. The mother's marital status had a slight impact on the occurrence of all other congenital anomalies (the odds were 1.2 higher for divorced and widowed women than for married women) and of the musculoskeletal system (1.1). However, being divorced or widowed was associated with a lower risk of giving birth to a child with Down syndrome than being married (0.6).

Table 3: Impact of other maternal characteristics on congenital anomalies (live births) controlling for parental ages

Anomaly	Predictor	Modalities	OR	95% Wald C.I.		
Circulatory system	mother's education	basic vs secondary	1.18	1.08	-	1.29
	multiple birth	2+ vs 1	2.00	1.82	-	2.20
	previous miscarriage	1vs 0	1.11	1.03	-	1.19
	previous perinatal death	Yes vs. no	1.51	1.20	-	1.90
	previous live birth	0 vs 1	1.10	1.04	-	1.16
	diabetes	pre-existent vs none	2.44	1.71	-	3.47
	smoking	yes vs no	1.19	1.08	-	1.32
Musculoskeletal system	mother's education	vocational vs secondary	1.08	1.02	-	1.15
		university vs secondary	0.86	0.79	-	0.95
	mother's marital status	divorced+widowed vs married	1.14	1.02	-	1.29
	previous miscarriage	2+ vs 0	1.20	1.02	-	1.42
	previous live birth	0 vs 1	1.15	1.09	-	1.23
	diabetes	gestational vs none	0.72	0.58	-	0.90
Genital organs	mother's education	basic vs secondary	1.16	1.03	-	1.31
	multiple birth	2+ vs 1	1.22	1.04	-	1.44
	previous live birth	0 vs 1	1.22	1.13	-	1.31
Urinary system	multiple birth	2+ vs 1	1.92	1.63	-	2.26
	diabetes	pre-existent vs none	2.72	1.54	-	4.82
Eyelid, lacrimal apparatus and orbit	mother's education	basic vs secondary	1.27	1.03	-	1.56
		university vs secondary	0.75	0.61	-	0.93
	previous miscarriage	2+ vs 0	1.80	1.35	-	2.40
Cleft lip and cleft palate	mother's education	basic vs secondary	1.46	1.15	-	1.84
		vocational vs secondary	1.52	1.30	-	1.77
Nervous system	mother's education	basic vs secondary	1.70	1.25	-	2.33
	multiple birth	2+ vs 1	1.89	1.28	-	2.80
Down syndrome	mother's education	basic vs secondary	1.89	1.28	-	2.80
	mother's marital status	divorced+widowed vs married	0.58	0.34	-	0.99
Other	mother's education	vocational vs secondary	1.23	1.11	-	1.37
	mother's marital status	divorced+widowed vs married	1.21	1.01	-	1.45
	multiple birth	2+ vs 1	1.33	1.08	-	1.64
	previous miscarriage	1 vs 0	1.23	1.08	-	1.40

Note: The dependent variable is the presence of a congenital anomaly. OR: odds ratio. Only statistically significant results at p≤0.05 level are presented. CI: confidence interval. Logistic regression is computed for each anomaly separately. The impact of parental ages is presented in Table 2. Controls: age of mother at childbearing, age of father at childbearing.

The fact that a birth was multiple had an important effect on the incidence of anomalies of the circulatory system (the odds were 2.0 times higher than for a singleton birth), urinary (1.9), and nervous (1.9) systems. A weaker but statistically significant effect was seen in the case of all other congenital anomalies (1.3) and of the genital organs (1.2). The likely influence of the mother's previous reproductive history was shown by the impact of previous miscarriage, perinatal death, or previous live birth. Experiencing two or more previous miscarriages was associated with particularly high odds of delivering a child with an anomaly of the eye (1.8) and—to a lesser degree—of the musculoskeletal system (1.2). Experiencing only one previous miscarriage had a statistically significant but rather weak impact on all of the other congenital anomalies (1.2) and of those of the circulatory system (1.1). The occurrence of a previous perinatal death was associated with a rather high OR (1.5) in the case of circulatory system anomalies. By contrast, having had a previous live birth might be considered a rather good predictor for a successful subsequent pregnancy, even though we lack information about anomalies in the previous child. This hypothesis was supported for anomalies of the genital organs (the odds ratio was 1.2 when nulliparous women were compared to primiparous women), of the musculoskeletal system (1.2), and of the circulatory system (1.1). Pre-existent diabetes was an important risk factor for anomalies of the urinary system (2.7), and circulatory system (2.4), but gestational diabetes appears to have been a (rather slight) protective factor for musculoskeletal anomalies (0.7). The impact of the mother's smoking was detected only in the case of anomalies of the circulatory system (the odds ratio was 1.2 higher for smokers).

6. Discussion and conclusion

The findings on the impact of parental ages at childbearing on the incidence of congenital anomalies vary somewhat from study to study; for example, while most studies have found no effect of the father's age on Down syndrome, a few studies have shown an effect (e.g., Stene et al. 1977; Stene et al.1981). This is probably because the number of children born with a congenital anomaly is small compared to the number of children born without such abnormalities, and because the ages of the mother and the father tend to be strongly correlated.

Concerning chromosomal anomalies, our analysis confirmed our assumption that the mother's age, but not the father's, has an effect on the incidence of Down syndrome. The impact of a higher mother's age on other chromosomal anomalies was also found to be strong, as we initially hypothesised. It is possible that the relationship found in some other studies between the father's age and Down syndrome was spurious, due to a residual correlation between parental ages, even when the mother's age is controlled for

(Slama and Werwatz, 2005). Paternal age was also not shown to be associated with other chromosomal anomalies, which confirmed our initial hypothesis as well. However, a study published recently in *Nature*, which looked at autosomal chromosomes only, showed that the diversity in the mutation rate of single nucleotide polymorphisms is dominated by the age of the father at the conception of the child (Kong et al. 2012). Thus, the study found that men transmit a much higher number of mutations to their children than women. Furthermore, the age of the father was identified as the dominant factor in determining the number of *de novo* mutations in the child. The relationship between paternal age at childbearing and chromosomal anomalies thus remains an open question.

Children born of younger mothers were, on the other hand, found to be more at risk of having a cleft lip or palate. Other studies have shown that older, rather than younger, mothers are more at risk of having children with cleft (e.g., Bille et al. 2005). However, a higher risk among mothers under age 20 than among those aged 25-29 has been reported in the literature (Croen and Shaw 1995). The minor birth defect related to congenital non-neoplastic naevus is an interesting case. The relative risk of this defect occurring is very low among older mothers (OR = 0.25; p = 0.017). This benign malformation can become a malignant melanoma (Bataille et al. 1996). Because our data come from the congenital anomaly register only, we do not know whether the frequency of the malignant form (melanoma) is higher in children born to older mothers. If so, the low odds ratio for congenital non-neoplastic naevus could derive from a selection effect; i.e., older mothers would be more likely to deliver children with a malignant melanoma, and therefore fewer cases of a congenital non-neoplastic naevus would be observed, as the malignant melanoma cases are not registered in our data source. Congenital non-neoplastic naevus is a relatively frequent anomaly, and it should therefore be compared to the incidence of melanoma from the cancer incidence register.

Turning now to the impact of the other maternal characteristics on congenital anomalies, as presented in Table 3, we note that the effect of maternal education on congenital anomalies has been found elsewhere (Olesen et al. 2009). In particular, an effect on Down syndrome has been observed for California (Dzúrová and Pikhart 2005). The authors of this study attribute this educational gradient to selective impacts of maternity care, prenatal diagnosis, elective termination, and the acceptance of prenatal diagnostic measures. More generally, better educated women are usually more informed on health matters, have better life styles, and have greater access to the health care system and prenatal diagnosis than less educated women.

According to our results, marital status was not strongly associated with congenital anomalies, except in the case of Down syndrome. For the latter, children of divorced and widowed women had a lower risk than married women. This could be because women who are divorced or widowed are less likely to be living in a stable partnership,

and are thus less prepared to raise a disabled child. These women might be more likely to have a prenatal diagnosis and an abortion, either because they do not want to have a child at all, or to have a child with Down syndrome. Unfortunately, the Czech published data on induced abortions do not give combined information on marital status and medical reasons for having an abortion, such as a diagnosis of Down syndrome.

In our study, multiplicity of birth was found to be a risk factor for several congenital malformations, such as those of the circulatory, urinary, and nervous systems. These results are in agreement with those of a large international study, which showed that multiplicity of birth has an impact on most congenital malformations (Mastroiacovo et al. 1999). It would be interesting to distinguish between monozygote and heterozygote twins, as has been suggested by some studies (Pharoah et al. 2009).

Looking now at the other covariates, we found that a previous perinatal death was associated with an increased risk of having a child with a malformation of the circulatory system. It would be useful to know the cause of previous perinatal deaths, but this information is unavailable in our dataset. The presence of a pre-existing diabetes is a well-known risk factor of various congenital anomalies (Inzucchi 1999). In the present study, we found an impact on the circulatory system and on the urinary system. Regarding the effect of gestational diabetes (GD), the following issues arose. While GD first occurred during pregnancy among some women, other women might have been suffering from undiagnosed diabetes before pregnancy. These two sub-populations present different risks of congenital malformations, but we cannot distinguish between these two groups here. Furthermore, for true GD, hyperglycemia could have had differing effects according to the duration of pregnancy at which the condition occurred; i.e., at which stage of the organogenesis of the embryo/foetus. Once again, the data are lacking. It would also be helpful to know more about the quality of the prenatal care. We cannot explain the protective effect found here on musculoskeletal anomalies. Could it be spurious?

Several limitations of this study have to be stressed. First, the data refer to live births only. Second, due to missing data, such as the age of the father, a series of cases were dropped from the analysis. It is difficult to know whether this biases the results, although, as was pointed out in Section 3, our tests did not show major differences in the frequency of the incidence of anomalies between, for example, the group in which the father's age was unknown, and the group in which the father's age was known. Third, various possible determinants of congenital anomalies that have been pointed out in the literature—such as folic acid intake, obesity, alcohol consumption, and genetic factors—are either not included in the Czech registers or are poorly reported, and therefore could not be taken into account in this study. For example, although alcohol intake is considered a potential cause of various birth defects, because it was not reported often, this variable was not included in the analysis. There is also no

information on folic acid intake, maternal obesity, or rheumatoid arthritis. Some studies have found that the use of ART may affect the incidence of congenital anomalies, such as malformations of the genital organs after intracytoplasmic sperm injection (ICSI). Some anomalies may also be due to the use of ovulation-inducing drugs (Santos et al. 2010). The use of ART has nevertheless been dropped from our analysis, as the information given by the respondents is too crude (solely yes or no), is less reliable, and is most likely under-estimated. Finally, while a significant percentage of congenital anomalies are of a genetic origin, the possible association between ageing, genetic conditions, and congenital anomalies cannot be examined with the present database. We should, however, note that factors such as alcohol consumption and obesity are often strongly related to education; controlling for the latter, as we have done, might take the former into account to some extent. This correlation between education and various latent behavioural determinants might also explain why education appears to be a possible factor in several groups of congenital anomalies.

In conclusion, this research has confirmed once again, on the basis of a large dataset, that women of higher ages are more likely to have children with Down syndrome or other chromosomal anomalies. Paternal age was not found to be associated with chromosomal anomalies. In this Czech population, paternal age had only a slight effect on some of the congenital anomalies examined. An interesting finding of the present study is that a range of other maternal characteristics may have an impact on congenital malformations, which confirms some results in the literature. In particular, several biological factors—such as having diabetes, multiplicity of birth, having a previous child who died perinatally—were found to be associated with some congenital anomalies. In terms of socio-economic variables, the education of the mother was found to be associated with Down syndrome in our dataset, and also with the risk of cleft and of malformations of the nervous system. Of course, some of our findings might be due to chance.

It should be remembered, however, that statistical analysis detects only correlations between parental characteristics and congenital anomalies, and that correlation is not causation, especially in observational studies. Following the arguments developed by, for example, Mouchart, Russo, and Wunsch (2010), putative risk factors can be tentatively proposed if they are based, to the best of current knowledge, on a plausible and suitably tested explanatory mechanism, and the known confounders, both explicit and latent, are controlled for. Results should also be stable across studies. Unknown confounders may of course still play havoc with the results; this issue is of particular importance when using logistic regression, as odds ratios not only reflect the effects of the variables considered, but also unobserved heterogeneity (Allison 1999; Mood 2010). Unfortunately, as EUROCAT (2009) has stressed, "in the majority of individual cases of congenital anomaly, the cause of the condition is

unknown, but suspected to be an interaction of multiple environmental and genetic factors." Plausible mechanisms of action are still to be discovered for several of the birth defects examined in this paper.

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Supplementary material

Annex Table 1: Distribution of live births with and without anomaly according to the ages of both parents

LB no anomaly	Mother's age							
Father's age	**12-19**	**20-24**	**25-29**	**30-34**	**35-39**	**40-44**	**45-49**	**Total**
15-19	3138	1255	219	53	24	4	0	4693
20-24	10556	35245	10218	1931	349	34	2	58335
25-29	4951	65958	118382	18552	2618	290	8	210759
30-34	1594	22321	109874	76529	7182	717	14	218231
35-39	450	5738	27263	46049	17643	1137	36	98316
40-44	178	1971	7467	12995	11253	2447	49	36360
45-69	140	1208	4035	6235	5235	2068	144	19065
Total	21007	133696	277458	162344	44304	6697	253	645759

LB with anomaly	Mother's age							
Father's age	**12-19**	**20-24**	**25-29**	**30-34**	**35-39**	**40-44**	**45-49**	**Total**
15-19	130	43	11	3	0	0	0	187
20-24	445	1498	401	70	12	2	0	2428
25-29	192	2724	4515	680	103	4	0	8218
30-34	61	857	4095	2839	311	25	2	8190
35-39	25	240	993	1739	698	44	3	3742
40-44	6	82	275	527	451	109	0	1450
45-69	5	61	159	258	201	100	7	791
Total	864	5505	10449	6116	1776	284	12	25006

Annex Table 2: Distribution of live births with and without anomalies over all categories of the covariates

Mother's age by mother's education

Without anomaly					With anomaly				
	Education					Education			
Age	basic	vocational	secondary	university	Age	basic	vocational	secondary	university
12-19	12870	6437	1693	7	12-19	536	258	70	0
20-24	22216	55814	53435	2231	20-24	974	2327	2114	90
25-29	19280	88979	133009	36190	25-29	771	3504	4879	1295
30-34	9989	46428	70685	35242	30-34	461	1845	2545	1265
35-39	4151	12852	17672	9629	35-39	213	525	680	358
40-44	868	1908	2507	1414	40-44	43	97	98	46
45-49	36	70	93	54	45-49	2	3	6	1
Total	69410	212488	279094	84767	Total	3000	8559	10392	3055

Mother's age by mother's marital status

Without anomaly				With anomaly			
	Marital status				Marital status		
Age	single	divorced+widowed	married	Age	single	divorced+widowed	married
12-19	14972	27	6008	12-19	624	3	237
20-24	43948	1801	87947	20-24	1768	94	3643
25-29	43619	9708	224131	25-29	1748	385	8316
30-34	18936	13456	129952	30-34	778	531	4807
35-39	3460	7567	33277	35-39	159	324	1293
40-44	382	1543	4772	40-44	15	59	210
45-49	11	56	186	45-49	0	0	12
Total	125328	34158	486273	Total	5092	1396	18518

Annex Table 2: (Continued)

Mother's age by multiple birth

Without anomaly			With anomaly		
	Multiple birth			Multiple birth	
Age	1	2+	Age	1	2+
12-19	20735	272	12-19	850	14
20-24	130978	2718	20-24	5341	164
25-29	268108	9350	25-29	9929	520
30-34	154995	7349	30-34	5704	412
35-39	42172	2132	35-39	1651	125
40-44	6473	224	40-44	273	11
45-49	242	11	45-49	11	1
Total	623703	22056	Total	23759	1247

Mother's age by previous miscarriage

Without anomaly				With anomaly			
	Previous miscarriage				Previous miscarriage		
Age	0	1	2+	Age	0	1	2+
12-19	20094	857	56	12-19	818	43	3
20-24	121961	10436	1299	20-24	4978	460	67
25-29	243354	28983	5121	25-29	9041	1194	214
30-34	133628	22863	5853	30-34	4987	868	261
35-39	33385	8105	2814	35-39	1312	334	130
40-44	4604	1494	599	40-44	193	58	33
45-49	162	59	32	45-49	3	6	3
Total	557188	72797	15774	Total	21332	2963	711

Annex Table 2: (Continued)

Mother's age by previous perinatal death

Without anomaly			With anomaly		
	Previous perinatal death			Previous perinatal death	
Age	no	yes	Age	no	yes
12-19	20979	28	12-19	862	2
20-24	133225	471	20-24	5484	21
25-29	275951	1507	25-29	10385	64
30-34	160892	1452	30-34	6050	66
35-39	43636	668	35-39	1741	35
40-44	6553	144	40-44	281	3
45-49	247	6	45-49	12	0
Total	641483	4276	Total	24815	191

Mother's age by previous live birth

Without anomaly				With anomaly			
	Previous live birth				Previous live birth		
Age	0	1	2+	Age	0	1	2+
12-19	18095	2606	306	12-19	750	97	17
20-24	92460	34382	6854	20-24	3856	1341	308
25-29	143451	107262	26745	25-29	5568	3847	1034
30-34	53328	72460	36556	30-34	2109	2624	1383
35-39	8778	14397	21129	35-39	397	542	837
40-44	1101	1303	4293	40-44	54	52	178
45-49	46	35	172	45-49	1	2	9
Total	317259	232445	96055	Total	12735	8505	3766

Annex Table 2: (Continued)

Mother's age by mother's diabetes

Without anomaly				With anomaly			
	Mother's diabetes				Mother's diabetes		
Age	gestational	none	pre-existent	Age	gestational	none	pre-existent
12-19	178	20807	22	12-19	5	856	3
20-24	1667	131867	162	20-24	57	5435	13
25-29	5047	271977	434	25-29	161	10275	13
30-34	3929	158091	324	30-34	156	5932	28
35-39	1593	42565	146	35-39	59	1704	13
40-44	308	6355	34	40-44	15	266	3
45-49	11	240	2	45-49	2	10	0
Total	12733	631902	1124	Total	455	24478	73

Mother's age by mother's smoking

Without anomaly			With anomaly		
	Mother's smoking			Mother's smoking	
Age	no	yes	Age	no	yes
12-19	16868	4139	12-19	700	164
20-24	122342	11354	20-24	4947	558
25-29	266705	10753	25-29	10021	428
30-34	156746	5598	30-34	5856	260
35-39	42027	2277	35-39	1659	117
40-44	6284	413	40-44	266	18
45-49	245	8	45-49	12	0
Total	611217	34542	Total	23461	1545

Annex Table 3a: Impact of all characteristics on anomalies of the circulatory system

Variable	Modalities	Pr>ChiSq	OR
mother's age		*0.011*	
	12-19 vs 25-29	0.334	0.93
	20-24 vs 25-29	0.175	1.05
	30-34 vs 25-29	0.003	1.10
	35-39 vs 25-29	0.012	1.14
	40-44 vs 25-29	0.259	1.14
	45-49 vs 25-29	0.071	2.12
father's age		*0.991*	
	15-19 vs 30-34	0.830	1.03
	20-24 vs 30-34	0.785	1.01
	25-29 vs 30-34	0.681	0.99
	35-39 vs 30-34	0.693	0.99
	40-44 vs 30-34	0.709	1.02
	45-69 vs 30-34	0.902	0.99
mother's education		*0.002*	
	basic vs secondary	0.000	1.18
	vocational vs secondary	0.372	1.03
	university vs secondary	0.765	1.01
mother's marital status		*0.456*	
	single vs married	0.249	1.04
	divorced+widowed vs married	0.546	1.03
multiple birth		*0.000*	
	2+ vs 1	0.000	2.00
previous miscarriage		*0.006*	
	1 vs 0	0.005	1.11
	2+ vs 0	0.087	1.13
previous perinatal death		*0.000*	
	yes vs no	0.000	1.51
previous live birth		*0.003*	
	0 vs 1	0.001	1.10
	2+ vs 1	0.199	1.05
mother's diabetes		*0.000*	
	gestational vs none	0.362	1.08
	pre-existent vs none	0.000	2.44
mother's smoking		*0.001*	
	yes vs no	0.001	1.19

Note: The dependent variable is the presence of an anomaly of the circulatory system. OR: odds ratio.

Annex Table 3b: Impact of all characteristics on anomalies of the musculoskeletal system

Variable	Modalities	Pr>ChiSq	OR
mother's age		*0.018*	
	12-19 vs 25-29	0.936	1.01
	20-24 vs 25-29	0.020	1.09
	30-34 vs 25-29	0.017	0.91
	35-39 vs 25-29	0.884	0.99
	40-44 vs 25-29	0.415	0.88
	45-49 vs 25-29	0.496	0.51
father's age		*0.219*	
	15-19 vs 30-34	0.987	1.00
	20-24 vs 30-34	0.022	1.13
	25-29 vs 30-34	0.053	1.07
	35-39 vs 30-34	0.322	1.05
	40-44 vs 30-34	0.926	1.01
	45-69 vs 30-34	0.451	0.93
mother's education		*0.000*	
	basic vs secondary	0.245	1.06
	vocational vs secondary	0.015	1.08
	university vs secondary	0.002	0.86
mother's marital status		*0.045*	
	single vs married	0.345	0.97
	divorced+widowed vs married	0.028	1.14
multiple birth		*0.105*	
	2+ vs 1	0.105	1.12
previous miscarriage		*0.084*	
	1 vs 0	0.762	1.01
	2+ vs 0	0.026	1.20
previous perinatal death		*0.281*	
	yes vs no	0.281	0.82
previous livebirth		*0.000*	
	0 vs 1	0.000	1.15
	2+ vs 1	0.337	0.96
mother's diabetes		*0.013*	
	gestational vs none	0.004	0.72
	pre-existent vs none	0.486	1.23
mother's smoking		*0.110*	
	yes vs no	0.114	1.10

Note: The dependent variable is the presence of an anomaly of the musculoskeletal system. OR: odds ratio.

Annex Table 3c: Impact of all characteristics on anomalies of the genital organs

Variable	Modalities	Pr>ChiSq	OR
mother's age		*0.829*	
	12-19 vs 25-29	0.152	0.85
	20-24 vs 25-29	0.447	0.96
	30-34 vs 25-29	0.374	0.96
	35-39 vs 25-29	0.605	0.96
	40-44 vs 25-29	0.889	0.98
	45-49 vs 25-29	.	.
father's age		*0.483*	
	15-19 vs 30-34	0.969	0.99
	20-24 vs 30-34	0.205	0.91
	25-29 vs 30-34	0.757	0.99
	35-39 vs 30-34	0.131	0.92
	40-44 vs 30-34	0.572	0.96
	45-69 vs 30-34	0.340	1.10
mother's education		*0.046*	
	basic vs secondary	0.017	1.16
	vocational vs secondary	0.100	1.07
	university vs secondary	0.520	0.97
mother's marital status		*0.848*	
	single vs married	0.648	0.98
	divorced+widowed vs married	0.763	1.02
multiple birth		*0.016*	
	2+ vs 1	0.016	1.22
previous miscarriage		*0.620*	
	1 vs 0	0.401	1.05
	2+ vs 0	0.573	1.06
previous perinatal death		*0.118*	
	yes vs no	0.118	0.68
previous live birth		*0.000*	
	0 vs 1	0.000	1.22
	2+ vs 1	0.337	1.00
mother's diabetes		*0.174*	
	gestational vs none	0.193	0.85
	pre-existent vs none	0.178	0.46
mother's smoking		*0.542*	
	yes vs no	0.542	0.95

Note: The dependent variable is the presence of an anomaly of the genital organs. OR: odds ratio.

Annex Table 3d: Impact of all characteristics on anomalies of the urinary system

Variable	Modalities	Pr>ChiSq	OR
mother's age		*0.791*	
	12-19 vs 25-29	0.838	1.03
	20-24 vs 25-29	0.730	1.02
	30-34 vs 25-29	0.562	1.03
	35-39 vs 25-29	0.305	0.91
	40-44 vs 25-29	0.371	1.18
	45-49 vs 25-29	.	.
father's age		*0.386*	
	15-19 vs 30-34	0.274	0.74
	20-24 vs 30-34	0.079	0.86
	25-29 vs 30-34	0.178	0.93
	35-39 vs 30-34	0.644	0.97
	40-44 vs 30-34	0.572	1.05
	45-69 vs 30-34	0.372	1.11
mother's education		*0.518*	
	basic vs secondary	0.566	1.05
	vocational vs secondary	0.675	0.98
	university vs secondary	0.272	1.07
mother's marital status		*0.189*	
	single vs married	0.172	1.08
	divorced+widowed vs married	0.282	0.90
multiple birth		*0.000*	
	2+ vs 1	0.000	1.92
previous miscarriage		*0.904*	
	1 vs 0	0.729	1.02
	2+ vs 0	0.754	1.04
previous perinatal death		*0.464*	
	yes vs no	0.464	1.18
previous live birth		*0.644*	
	0 vs 1	0.684	1.02
	2+ vs 1	0.352	1.06
mother's diabetes		*0.003*	
	gestational vs none	0.686	0.94
	pre-existent vs none	0.001	2.72
mother's smoking		*0.126*	
	yes vs no	0.126	1.15

Note: The dependent variable is the presence of an anomaly of the urinary system. OR: odds ratio.

Annex Table 3e: Impact of all characteristics on anomalies of the eyelid, lacrimal apparatus and orbit

Variable	Modalities	Pr>ChiSq	OR
mother's age		*0.815*	
	12-19 vs 25-29	0.663	1.08
	20-24 vs 25-29	0.846	1.02
	30-34 vs 25-29	0.573	0.95
	35-39 vs 25-29	0.266	1.16
	40-44 vs 25-29	0.454	1.23
	45-49 vs 25-29	.	.
father's age		*0.612*	
	15-19 vs 30-34	0.188	0.57
	20-24 vs 30-34	0.453	1.09
	25-29 vs 30-34	0.434	1.06
	35-39 vs 30-34	0.435	0.93
	40-44 vs 30-34	0.709	1.05
	45-69 vs 30-34	0.969	1.01
mother's education		*0.002*	
	basic vs secondary	0.023	1.27
	vocational vs secondary	0.443	1.05
	university vs secondary	0.008	0.75
mother's marital status		*0.338*	
	single vs married	0.764	1.02
	divorced+widowed vs married	0.159	0.82
multiple birth		*0.233*	
	2+ vs 1	0.233	1.20
previous miscarriage		*0.000*	
	1 vs 0	0.768	0.97
	2+ vs 0	0.000	1.80
previous perinatal death		*0.835*	
	yes vs no	0.835	1.07
previous live birth		*0.732*	
	0 vs 1	0.868	1.01
	2+ vs 1	0.432	1.08
mother's diabetes		*0.144*	
	gestational vs none	0.130	0.68
	pre-existent vs none	0.214	1.87
mother's smoking		*0.290*	
	yes vs no	0.290	1.14

Note: The dependent variable is the presence of an anomaly of the eyelid, lacrimal apparatus and orbit. OR: odds ratio.

Annex Table 3f: Impact of all characteristics on anomalies of the congenital non-neoplastic naevus

Variable	Modalities	Pr>ChiSq	OR
mother's age		*0.426*	
	12-19 vs 25-29	0.926	0.98
	20-24 vs 25-29	0.803	1.02
	30-34 vs 25-29	0.812	1.02
	35-39 vs 25-29	0.823	0.97
	40-44 vs 25-29	0.017	0.25
	45-49 vs 25-29	.	.
father's age		*0.354*	
	15-19 vs 30-34	0.739	0.85
	20-24 vs 30-34	0.835	1.03
	25-29 vs 30-34	0.201	1.11
	35-39 vs 30-34	0.125	1.17
	40-44 vs 30-34	0.128	1.25
	45-69 vs 30-34	0.051	1.43
mother's education		*0.083*	
	basic vs secondary	0.158	0.83
	vocational vs secondary	0.227	1.10
	university vs secondary	0.147	1.16
mother's marital status		*0.911*	
	single vs married	0.666	1.04
	divorced+widowed vs married	0.971	1.01
multiple birth		*0.226*	
	2+ vs 1	0.226	0.79
previous miscarriage		*0.226*	
	1 vs 0	0.965	1.00
	2+ vs 0	0.087	1.37
previous perinatal death		*0.828*	
	yes vs no	0.828	1.09
previous live birth		*0.877*	
	0 vs 1	0.709	1.03
	2+ vs 1	0.655	1.05
mother's diabetes		*0.467*	
	gestational vs none	0.218	0.72
	pre-existent vs none	.	.
mother's smoking		*0.684*	
	yes vs no	0.684	0.94

Note: The dependent variable is the presence of an anomaly of the congenital non-neoplastic naevus. OR: odds ratio.

Annex Table3g: Impact of all characteristics on cleft lip and cleft palate

Variable	Modalities	Pr>ChiSq	OR
mother's age		*0.020*	
	12-19 vs 25-29	0.007	1.65
	20-24 vs 25-29	0.001	1.38
	30-34 vs 25-29	0.909	0.99
	35-39 vs 25-29	0.850	1.03
	40-44 vs 25-29	0.920	0.97
	45-49 vs 25-29	.	.
father's age		*0.098*	
	15-19 vs 30-34	0.767	0.90
	20-24 vs 30-34	0.571	1.08
	25-29 vs 30-34	0.703	0.97
	35-39 vs 30-34	0.045	1.23
	40-44 vs 30-34	0.162	0.77
	45-69 vs 30-34	0.198	1.29
mother's education		*0.000*	
	basic vs secondary	0.002	1.46
	vocational vs secondary	0.000	1.52
	university vs secondary	0.350	0.89
mother's marital status		*0.377*	
	single vs married	0.848	0.98
	divorced+widowed vs married	0.175	1.21
multiple birth		*0.592*	
	2+ vs 1	0.592	1.10
previous miscarriage		*0.326*	
	1 vs 0	0.393	1.09
	2+ vs 0	0.193	1.29
previous perinatal death		*0.528*	
	yes vs no	0.528	1.25
previous live birth		*0.848*	
	0 vs 1	0.624	0.96
	2+ vs 1	0.889	1.02
mother's diabetes		*0.187*	
	gestational vs none	0.892	1.03
	pre-existent vs none	0.068	2.50
mother's smoking		*0.965*	
	yes vs no	0.965	0.99

Note: The dependent variable is the presence of an anomaly. OR: odds ratio.

Annex Table 3h: Impact of all characteristics on anomalies of the nervous system

Variable	Modalities	Pr>ChiSq	OR
mother's age		*0.800*	
	12-19 vs 25-29	0.356	0.75
	20-24 vs 25-29	0.919	0.99
	30-34 vs 25-29	0.516	1.09
	35-39 vs 25-29	0.240	1.28
	40-44 vs 25-29	0.265	1.59
	45-49 vs 25-29	.	.
father's age		*0.604*	
	15-19 vs 30-34	0.333	1.57
	20-24 vs 30-34	0.630	0.90
	25-29 vs 30-34	0.285	1.14
	35-39 vs 30-34	0.468	0.89
	40-44 vs 30-34	0.688	1.09
	45-69 vs 30-34	0.789	0.93
mother's education		*0.006*	
	basic vs secondary	0.001	1.70
	vocational vs secondary	0.749	1.04
	university vs secondary	0.979	1.00
mother's marital status		*0.220*	
	single vs married	0.084	1.24
	divorced+widowed vs married	0.691	1.09
multiple birth		*0.001*	
	2+ vs 1	0.001	1.89
previous miscarriage		*0.695*	
	1 vs 0	0.459	1.11
	2+ vs 0	0.625	1.15
previous perinatal death		*0.143*	
	yes vs no	0.143	1.83
previous live birth		*0.975*	
	0 vs 1	0.931	1.01
	2+ vs 1	0.821	1.04
mother's diabetes		*0.240*	
	gestational vs none	0.093	0.43
	pre-existent vs none	0.861	1.19
mother's smoking		*0.965*	
	yes vs no	0.617	1.10

Note: The dependent variable is the presence of an anomaly of the nervous system. OR: odds ratio.

Annex Table 3i: Impact of all characteristics on Down syndrome

Variable	Modalities	Pr>ChiSq	OR
mother's age		*0.000*	
	12-19 vs 25-29	0.584	0.79
	20-24 vs 25-29	0.594	0.90
	30-34 vs 25-29	0.014	1.52
	35-39 vs 25-29	0.000	2.73
	40-44 vs 25-29	0.000	9.13
	45-49 vs 25-29	0.000	25.33
father's age		*0.523*	
	15-19 vs 30-34	0.936	1.06
	20-24 vs 30-34	0.968	1.01
	25-29 vs 30-34	0.750	1.06
	35-39 vs 30-34	0.542	0.89
	40-44 vs 30-34	0.126	1.40
	45-69 vs 30-34	0.550	0.83
mother's education		*0.007*	
	basic vs secondary	0.001	1.89
	vocational vs secondary	0.073	1.29
	university vs secondary	0.608	0.90
mother's marital status		*0.130*	
	single vs married	0.678	0.93
	divorced+widowed vs married	0.045	0.58
multiple birth		*0.071*	
	2+ vs 1	0.071	1.60
previous miscarriage		*0.715*	
	1 vs 0	0.469	1.13
	2+ vs 0	0.645	1.16
previous perinatal death		*0.307*	
	yes vs no	0.307	0.36
previous live birth		*0.628*	
	0 vs 1	0.427	1.12
	2+ vs 1	0.425	1.15
mother's diabetes		*0.529*	
	gestational vs none	0.260	0.57
	pre-existent vs none	.	.
mother's smoking		*0.616*	
	yes vs no	0.616	1.13

Note: The dependent variable is the presence of Down syndrome. OR: odds ratio.

Annex Table 3j: Impact of all characteristics on the other chromosomal anomalies

Variable	Modalities	Pr>ChiSq	OR
mother's age		*0.000*	
	12-19 vs 25-29	0.354	1.55
	20-24 vs 25-29	0.832	0.95
	30-34 vs 25-29	0.073	1.41
	35-39 vs 25-29	0.000	3.41
	40-44 vs 25-29	0.000	6.80
	45-49 vs 25-29	0.000	43.78
father's age		*0.774*	
	15-19 vs 30-34	.	.
	20-24 vs 30-34	0.477	0.78
	25-29 vs 30-34	0.215	1.26
	35-39 vs 30-34	0.467	1.16
	40-44 vs 30-34	0.823	1.06
	45-69 vs 30-34	0.715	1.13
mother's education		*0.466*	
	basic vs secondary	0.605	0.87
	vocational vs secondary	0.438	1.13
	university vs secondary	0.363	0.82
mother's marital status		*0.793*	
	single vs married	0.922	0.98
	divorced+widowed vs married	0.509	1.17
multiple birth		*0.406*	
	2+ vs 1	0.406	0.71
previous miscarriage		*0.201*	
	1 vs 0	0.182	1.29
	2+ vs 0	0.174	1.54
previous perinatal death		*0.475*	
	yes vs no	0.475	1.52
previous live birth		*0.642*	
	0 vs 1	0.444	1.13
	2+ vs 1	0.789	0.95
mother's diabetes		*0.156*	
	gestational vs none	0.888	0.94
	pre-existent vs none	0.055	3.94
mother's smoking		*0.849*	
	yes vs no	0.849	1.06

Note: The dependent variable is the presence of an anomaly. OR: odds ratio.

Annex Table 3k: Impact of all characteristics on all other congenital anomalies (residual group)

Variable	Modalities	Pr>ChiSq	OR
mother's age		*0.494*	
	12-19 vs 25-29	0.888	1.02
	20-24 vs 25-29	0.304	1.07
	30-34 vs 25-29	0.628	0.97
	35-39 vs 25-29	0.218	0.88
	40-44 vs 25-29	0.082	0.63
	45-49 vs 25-29	.	.
father's age		*0.100*	
	15-19 vs 30-34	0.856	1.05
	20-24 vs 30-34	0.026	1.22
	25-29 vs 30-34	0.575	1.03
	35-39 vs 30-34	0.268	1.08
	40-44 vs 30-34	0.171	1.15
	45-69 vs 30-34	0.019	1.35
mother's education		*0.001*	
	basic vs secondary	0.210	1.11
	vocational vs secondary	0.000	1.23
	university vs secondary	0.145	1.11
mother's marital status		*0.039*	
	single vs married	0.179	0.92
	divorced+widowed vs married	0.044	1.21
multiple birth		*0.007*	
	2+ vs 1	0.007	1.33
previous miscarriage		*0.006*	
	1 vs 0	0.002	1.23
	2+ vs 0	0.438	1.12
previous perinatal death		*0.588*	
	yes vs no	0.588	1.15
previous live birth		*0.556*	
	0 vs 1	0.747	1.02
	2+ vs 1	0.370	0.94
mother's diabetes		*0.520*	
	gestational vs none	0.278	1.17
	pre-existent vs none	0.723	0.82
mother's smoking		*0.500*	
	yes vs no	0.500	1.07

Note: The dependent variable is the presence of an anomaly. OR: odds ratio.