Reducing the Risk of Birth Defects Associated with Maternal Influenza: Insights from a Hungarian Case-Control Study

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**Running title:**

First trimester maternal influenza and non-chromosomal birth defects

# FIGURE LEGENDS

**Table S1.**  representing the STROBE Checklist

**Table S2.** representing the prevalence of specific types of congenital anomalies after first-trimester influenza infection.

**Table S1.**  representing the STROBE Checklist

|  |  |  |  |
| --- | --- | --- | --- |
|  | Item No. | Recommendation |  |
| **Title and abstract** | 1 | (*a*) Indicate the study’s design with a commonly used term in the title or the abstract |  |
| (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |  |
| Introduction | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported |  |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses |  |
| Methods | | | |
| Study design | 4 | Present key elements of study design early in the paper |  |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |  |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants |  |
| (*b*)*Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed  *Case-control study*—For matched studies, give matching criteria and the number of controls per case |  |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |  |
| Data sources/ measurement | 8\* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |  |
| Bias | 9 | Describe any efforts to address potential sources of bias |  |
| Study size | 10 | Explain how the study size was arrived at |  |

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| --- | --- | --- | --- | --- | --- |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | |  | |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | |  | |
| (*b*) Describe any methods used to examine subgroups and interactions | |  | |
| (*c*) Explain how missing data were addressed | |  | |
| (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed  *Case-control study*—If applicable, explain how matching of cases and controls was addressed  *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |  | |
| (*e*) Describe any sensitivity analyses | |  | |
| Results | | |  | |  | |  |
| Participants | 13\* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | |  | |
| (b) Give reasons for non-participation at each stage | |  | |
| (c) Consider use of a flow diagram | |  | |
| Descriptive data | 14\* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | |  | |
| (b) Indicate number of participants with missing data for each variable of interest | |  | |
| (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | |  | |
| Outcome data | 15\* | *Cohort study*—Report numbers of outcome events or summary measures over time | |  | |
| *Case-control study—*Report numbers in each exposure category, or summary measures of exposure | |  | |
| *Cross-sectional study—*Report numbers of outcome events or summary measures | |  | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | |  | |
| (*b*) Report category boundaries when continuous variables were categorized | |  | |
| (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |  | |

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| --- | --- | --- | --- | --- |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | |  |
| Discussion | |  |
| Key results | 18 | Summarise key results with reference to study objectives | |  |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | |  |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | |  |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | |  |
| Other information | |  |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | |  |

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

**Table S2.** representing the prevalence of specific types of congenital anomalies after first- trimester influenza infection

|  |  |  |
| --- | --- | --- |
| ICD-10 | Congenital malformation | No. |
| Q0000 | Anencephaly | 79 |
| Q0010 | Craniorachischisis | 69 |
| Q0020 | Iniencephaly | 62 |
| Q0100 | Frontal encephalocele | 41 |
| Q0110 | Frontal encephalocele | 41 |
| Q0120 | Occipital encephalocele | 33 |
| Q0180 | Encephalocele of other sites | 32 |
| Q0190 | Encephalocele, unspecified | 30 |
| Q02H0 | Microcephaly | 28 |
| Q0300 | Malformations of aqueduct of Sylvius | 19 |
| Q0310 | Atresia of foramina of Magendie and Luschka | 19 |
| Q0380 | Other congenital hydrocephalus | 19 |
| Q0390 | Congenital hydrocephalus, unspecified | 19 |
| Q0400 | Congenital malformations of corpus callosum | 14 |
| Q0410 | Arhinencephaly | 13 |
| Q0420 | Holoprosencephaly | 13 |
| Q0430 | Other reduction deformities of brain | 12 |
| Q0440 | Septo-optic dysplasia | 12 |
| Q0450 | Megalencephaly | 12 |
| Q0460 | Congenital cerebral cysts | 11 |
| Q0480 | Other specified congenital malformations of brain | 10 |
| Q0490 | Congenital malformation of brain, unspecified | 10 |
| Q0500 | Cervical spina bifida with hydrocephalus | 9 |
| Q0510 | Thoracic spina bifida with hydrocephalus | 9 |
| Q0520 | Lumbar spina bifida with hydrocephalus | 9 |
| Q0530 | Sacral spina bifida with hydrocephalus | 9 |
| Q0540 | Unspecified spina bifida with hydrocephalus | 8 |
| Q0550 | Cervical spina bifida without hydrocephalus | 8 |
| Q0560 | Thoracic spina bifida without hydrocephalus | 7 |
| Q0570 | Lumbar spina bifida without hydrocephalus | 6 |
| Q0580 | Sacral spina bifida without hydrocephalus | 6 |
| Q0590 | Spina bifida, unspecified | 6 |
| Q0600 | Amyelia | 6 |
| Q0610 | Hypoplasia and dysplasia of spinal cord | 5 |
| Q0620 | Diastematomyelia | 5 |
| Q0630 | Other congenital cauda equina malformations | 5 |
| Q0640 | Hydromyelia | 5 |
| Q0680 | Other specified congenital malformations of spinal cord | 5 |
| Q0690 | Congenital malformation of spinal cord, unspecified | 5 |
| Q0700 | Arnold-Chiari syndrome | 4 |
| Q0780 | Other specified congenital malformations of nervous system | 4 |
| Q0790 | Congenital malformation of nervous system, unspecified | 4 |
| Q1010 | Congenital ectropion | 4 |
| Q1020 | Congenital entropion | 4 |
| Q1030 | Other congenital malformations of eyelid | 3 |
| Q1040 | Absence and agenesis of lacrimal apparatus | 3 |
| Q1050 | Congenital stenosis and stricture of lacrimal duct | 3 |
| Q1060 | Other congenital malformations of lacrimal apparatus | 3 |
| Q1070 | Congenital malformation of orbit | 3 |
| Q1100 | Cystic eyeball | 3 |
| Q1110 | Other anophthalmos | 2 |
| Q1120 | Microphthalmos | 2 |
| Q1130 | Macrophthalmos | 2 |
| Q1200 | Congenital cataract | 2 |
| Q1210 | Congenital displaced lens | 2 |
| Q1220 | Coloboma of lens | 2 |
| Q1230 | Congenital aphakia | 2 |
| Q1240 | Spherophakia | 2 |
| Q1280 | Other congenital lens malformations | 2 |
| Q1290 | Congenital lens malformation, unspecified | 2 |
| Q1300 | Coloboma of iris | 2 |
| Q1310 | Absence of iris | 2 |
| Q1320 | Other congenital malformations of iris | 2 |
| Q1330 | Congenital corneal opacity | 2 |
| Q1340 | Other congenital corneal malformations | 2 |
| Q1350 | Blue sclera | 2 |
| Q1380 | Other congenital malformations of anterior segment of eye | 2 |
| Q1390 | Congenital malformation of anterior segment of eye, unspecified | 1 |
| Q1400 | Congenital malformation of vitreous humour | 1 |
| Q1410 | Congenital malformation of retina | 1 |
| Q1420 | Congenital malformation of optic disc | 1 |
| Q1430 | Congenital malformation of choroid | 1 |
| Q1480 | Other congenital malformations of posterior segment of eye | 1 |
| Q1490 | Congenital malformation of posterior segment of eye, unspecified | 1 |
| Q1500 | Congenital glaucoma | 1 |
| Q1580 | Other specified congenital malformations of eye | 1 |
| Q1590 | Congenital malformation of eye, unspecified | 1 |
| Q1600 | Congenital absence of (ear) auricle | 1 |
| Q1610 | Congenital absence, atresia and stricture of auditory canal (external) | 1 |
| Q1620 | Absence of eustachian tube | 1 |
| Q1630 | Congenital malformation of ear ossicles | 1 |
| Q1640 | Other congenital malformations of middle ear | 1 |
| Q1650 | Congenital malformation of inner ear | 1 |
| Q1690 | Congenital malformation of ear causing impairment of hearing, unspecified | 1 |
| Q1700 | Accessory auricle | 1 |
| Q1710 | Macrotia | 1 |
| Q1720 | Microtia | 1 |
| Q1730 | Other misshapen ear | 1 |
| Q1740 | Misplaced ear | 1 |
| Q1750 | Prominent ear | 1 |
| Q1780 | Other specified congenital malformations of ear | 1 |
| Q1790 | Congenital malformation of ear, unspecified | 1 |
| Q1800 | Sinus, fistula and cyst of branchial cleft | 1 |
| Q1810 | Preauricular sinus and cyst | 1 |
| Q1820 | Other branchial cleft malformations | 1 |
| Q1830 | Webbing of neck | 1 |
| Q1840 | Macrostomia | 1 |
| Q1850 | Microstomia | 1 |
| Q1860 | Macrocheilia | 1 |
| Q1870 | Microcheilia | 1 |
| Q1880 | Other specified congenital malformations of face and neck | 1 |
| Q1890 | Congenital malformation of face and neck, unspecified | 1 |
| Q2000 | Common arterial trunk | 1 |
| Q2010 | Double outlet right ventricle | 1 |
| Q2020 | Double outlet left ventricle | 1 |
| Q2030 | Discordant ventriculoarterial connection | 1 |
| Q2040 | Double inlet ventricle | 1 |
| Q2050 | Discordant atrioventricular connection | 1 |
| Q2060 | Isomerism of atrial appendages | 1 |
| Q2080 | Other congenital malformations of cardiac chambers and connections | 1 |
| Q2090 | Congenital malformation of cardiac chambers and connections, unspecified | 1 |
| Q2100 | Ventricular septal defect | 1 |
| Q2110 | Atrial septal defect | 1 |
| Q2120 | Atrioventricular septal defect | 1 |
| Q2130 | Tetralogy of Fallot | 1 |
| Q2140 | Aortopulmonary septal defect | 1 |
| Q2180 | Other congenital malformations of cardiac septa | 1 |
| Q2190 | Congenital malformation of cardiac septum, unspecified | 1 |
| Q2200 | Pulmonary valve atresia | 1 |
| Q2210 | Congenital pulmonary valve stenosis | 1 |
| Q2220 | Congenital pulmonary valve insufficiency | 1 |
| Q2230 | Other congenital malformations of pulmonary valve | 1 |
| Q2240 | Congenital tricuspid stenosis | 1 |
| Q2250 | Ebstein's anomaly | 1 |
| Q2260 | Hypoplastic right heart syndrome | 1 |
| Q2280 | Other congenital malformations of tricuspid valve | 1 |