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new birth cohort justified

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Mini Review

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Perinatal health in the Danube region – new birth cohort justified

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Abstract: In 2013–2015, a consortium of European scientists – NEWDANUBE – was established to prepare a birth cohort in the Danube region, including most of the countries with the highest air pollution in Europe, the area being one-fifth of the European Union’s (EU’s) territory, including 14 countries (nine EU member states), over 100 million inhabitants, with numerous challenges: big socio-economic disparities, and a region-specific environmental pollution. The consortium reflects the EU Strategy for the Danube Region Strategy (2010), which identified 11 thematic Priority Areas – one of which is the environmental risks. Birth cohorts have been established in all other areas of Europe and collaborative efforts in promoting maternal and fetal health by minimizing the environmental exposures have been initiated with national, European, and international financial support. A birth cohort in the Danube area could apply the established methodologies for prenatal exposure and birth outcome measurements and establish a platform for targeted health promotion in

couples planning pregnancies. The consortium included a strong socioeconomic part focusing on the participant’s active registration of exposures to environmental toxicants and health indicators of disease and wellbeing, combined with investigation of their risk-reducing behavior and interventions to change their lifestyle to avoid the adverse health risks. Willingness to pay for reducing the health risks in children is also proposed to be estimated. Further collaboration and networking is encouraged as the Danube region has several decades of experience and expertise in biomonitoring adult populations exposed environmentally or occupationally. Additionally, some countries in the Danube region launched small-scale birth cohorts encouraged by participation in several ongoing research projects.

Keywords: birth cohort; child health; Danube region; environmental exposures; health promotion.

Introduction

In 2010, the European strategy for the Danube region was launched (1): ‘The Danube Region is a functional area defined by its river basin. Geographically it concerns primarily but not exclusively: Germany (Baden-Württemberg and Bavaria), Austria, the Slovak Republic, the Czech Republic, Hungary, Slovenia, Romania and Bulgaria within the EU, and Croatia (now in EU), Serbia, Bosnia and Herzegovina, Montenegro, the Republic of Moldova and Ukraine (the regions along the Danube) outside. The Strategy remains open to other partners in the Region. Since the Danube flows into the Black Sea, it should be coherent with Black Sea perspectives. With over 100 million people, and a fifth of the EU’s surface, the area is vital for Europe’.

Health and perinatal health are not mentioned in the Danube strategy, however, they are highly relevant, since reproductive health data from the region demonstrate low fertility rates, high maternal and fetal mortality in some of Danube region countries when compared with the rest of

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Europe. The levels of air pollution are also high, with possible impacts on health.

Table 1 is composed from data publically available in the World Bank database. Total population data are based on the de facto definition of population, which counts all residents regardless of legal status or citizenship except for refugees not permanently settled in the country of asylum, who are generally considered part of the population of their country of origin. The values shown are midyear estimates (2). Surface area shown in the table is defined as a country's total area, including areas under inland bodies of water and some coastal waterways, based on the Food and Agriculture Organization, electronic files and web site. Population density is midyear population divided by land area in square kilometers. Land area is a country's total area, excluding area under inland water bodies, national claims to continental shelf, and exclusive economic zones. In most cases the definition of inland water bodies includes major rivers and lakes. Total fertility rate represents the number of children that would be born to a woman if she were to live to the end of her childbearing years and bear children in accordance with age-specific fertility rates of the specified year. Crude birth rate indicates the number of live births occurring during the year, per 1000 population estimated at midyear (2). Neonatal mortality rate is the number of neonates dying before reaching 28 days of age, per 1000 live births in a given year (3). Maternal mortality ratio is the number of women who die from pregnancy-related causes while pregnant or within 42 days of pregnancy termination per 100,000 live births. The data are estimated with a regression model using information on the proportion of maternal deaths among non-AIDS deaths in women aged 15–49 years, fertility, birth attendants, and gross domestic product (GDP) (4). Population-weighted exposure to ambient air pollution is defined as the average level of concentrations of suspended particulate matter (PM) measuring <2.5 microns in aerodynamic diameter, which are capable of penetrating deep into the respiratory tract and causing severe health damage. Exposure is calculated by weighting mean annual concentrations of PM2.5 by population in both urban and rural areas (5).

From well-established studies on maternal and fetal health in birth cohorts, the adverse effects of environmental exposures on reproductive health like reduced fertility, decreased fertility rate, increased numbers of preterm births and children born with low birthweights as well as increased risk of allergies, adverse effects on respiratory system and neurobehavior have been demonstrated (6–10). These studies mainly originate in the northern and western parts of Europe with only studies published in the Czech and Slovak Republics of the Danube area (11–13). Globally much attention is toward birth cohorts

Table 1: Country and health statistics, 2014 (GDP per capita is expressed in EUR PPS for 2015; PM2.5 in 2010).

Country name	Country code	Population	Surface area (sq. km)	Population density (per sq. km)	GDP per capita (EU 28=100)	Fertility rate (births per woman)	Birth rate (per 1000 people)	Mortality rate neonatal (per 1000 live births)	Maternal mortality (per 100,000 live births)	PM2.5 ($\mu\text{g}/\text{m}^3$)
Austria	AUT	8,541,575	83,879	103	127	1.44	9.6	2.2	4	15.37
Croatia	HRV	4,238,389	56,590	76	58	1.46	9.3	2.7	9	15.06
Bosnia and Herzegovina	BIH	3,817,554	51,210	75	29	1.26	8.9	4.2	12	14.47
Bulgaria	BGR	7,223,938	111,000	67	46	1.48	9.4	5.9	11	17.24
Czech Republic	CZE	10,525,347	78,870	136	85	1.46	10.4	1.9	4	16.63
Denmark	DNK	5,643,475	43,090	133	124	1.67	10.1	2.6	7	10.62
Germany	DEU	80,982,500	357,170	232	125	1.39	8.6	2.2	6	15.99
Hungary	HUN	9,866,468	93,030	109	68	1.35	9.5	3.6	16	17.89
Moldova	MDA	3,556,397	33,850	124	13	1.26	10.7	12.1	24	17.69
Montenegro	MNE	621,810	13,810	46	41	1.69	11.6	3.3	7	14.38
Romania	ROM	19,908,979	238,390	87	57	1.41	9.2	6.5	31	18.06
Serbia	SRB	7,130,576	88,360	82	36	1.43	9.3	4.3	17	17.63
Slovenia	SVN	2,061,980	20,270	102	83	1.55	10.3	1.5	9	15.89
Slovak Republic	SVK	5,418,649	49,036	113	77	1.34	10.2	4.4	6	16.31
Ukraine	UKR	45,362,900	603,550	78	21	1.50	10.8	5.7	24	15.94

Source: <http://databank.worldbank.org/data/reports.aspx?source=2&series=SP.DYN.IMRT.IN&country=#>. See text for explanations of variables.

(14–16) and as stated by the WHO (<http://www.who.int/ceh/cohorts/en/>), stressing the current optimal timing of establishing such cohorts and need of developing common protocols. The WHO offers playing a role in

‘defining a list of core elements for inclusion in birth cohort studies. Such core elements could include disease outcome measurements, biomarkers and exposure measurements. This will help to move the science forward by increasing the likelihood that datasets can be easily combined in the future, yielding studies with more power to identify positive results’.

NEWDANUBE

Following the considerations related to the Danube region and to meet the benefits of a mother-child cohort, a group of scientists working with adverse health effects from prenatal exposures to air pollution and other environmental pollutants organized themselves into a newly established research consortium named as NEWDANUBE – Newborns health in the Danube region: environment, lifestyle, and human biomonitoring in a prospective mother-child cohort study with the following aims (17):

- To establish a new birth cohort – NEWDANUBE of 1200 newborns (mother-child pairs) in order to estimate the burden of environmental exposures on early life health in the Danube region.
- To obtain estimates of exposures in outdoor environment (air pollution, climate, water) and to contaminants in indoor air, drinking water, food, and consumer products during pregnancy, in the Danube region.
- To define multiple exposure patterns specific for the Danube region in the individual and outdoor environment, describe their variability and predictors.
- To measure molecular signatures associated with environmental exposures in the Danube region through analysis of profiles of metabolites, proteins, transcripts, genome damage, micro-ribonucleic acids (miRNA), and deoxyribonucleic acid (DNA) methylation disturbances in biological samples.
- To provide exposure-response estimates for the association of multiple and combined exposures with health in early life, focusing on fetal and childhood growth, respiratory health, and neurodevelopment.
- To strengthen regional scientific collaboration between clinicians and scientists in the project, and promote exchange of knowledge and results among regional countries.
- To estimate the burden of common childhood diseases that may be attributed to multiple environmental exposures in the Danube region.
- To analyze actual risk-reducing behavior of parents in order to understand possible behavioral inertia and elicit their preferences and derive corresponding willingness to pay values for avoiding the health risks in children.
- To make socioeconomic evaluation of intervention strategies based on current knowledge, study results, and new survey in the Danube region resulting in information about potential effects (including benefits) of prospective public and private interventions to reduce environmental pressures and/or behavioral change in order to avoid the adverse health risks in children.
- To strengthen the knowledge base for European policy in the area of child and environmental health by engaging with, and effectively disseminating NEWDANUBE knowledge to stakeholders including those responsible for risk management, mitigation as well as prevention strategies.

The study program is detailed in Andersen et al. (17) with the map of proposed participating countries shown in Figure 1 and overviews and ambitions shown in Table 2. Partners in the program gathered from previous collaborations in the EU programs Cytogenetic Biomarkers and Human Cancer Risk, ChildrenGenonetwork, INCHEs, PINCHE, NewGeneris and COPHES/DEMOCOPHES from year 2000 onwards are also involved in national biomonitoring studies. Cohorts were planned to be established in Austria, Croatia, Czech Republic, Hungary, Romania, and Slovakia.

Due to the high relevance of the topic, the NEWDANUBE consortium gathered on this project continue to exchange knowledge and experiences supporting national activities.

The coordination in Denmark was selected from the experiences with mother-child cohorts and adverse effects of air pollution (18, 19). The Czech partners were leading in human biomonitoring and air pollution (20–22) as well as socioeconomic research on health risks benefits (23–26) and consumer behavior (27).

In Croatia, within the Research Center of Excellence for Reproductive and Regenerative Medicine of the University of Zagreb School of Medicine, the first cohort of newborns was analyzed using biomarkers of genome damage and glycan levels in general healthy population of newborns and cohort of newborns whose mothers suffer from diabetes. In the next few years, in addition to other topics like biobanking and infertility (28), studies will be focused on environmental etiology of preterm births (29). The newly started European biomonitoring initiative (HMB4EU) in Austria will include perinatal



Figure 1: Proposed study sights for the NEWDANUBE project.

Table 2: Selected ambitions of NEWDANUBE project.

Objectives	How NEWDANUBE addresses the objectives
Integration of environment, climate and health sectors	Focus is exposure and adverse health effects from outdoor air pollution, indoor air and water including occupational exposures with active involvement at all levels from participant to government/EU
Multidisciplinary approach	Exposure monitoring by outdoor measurements and questionnaires including socioeconomic parameters will be accompanied by human biomonitoring and health monitoring with web-based diaries; environmental epidemiologist and biostatistical expertise for optimal analyses of complex data on multiple exposures, and multiple (intermediate and diseases) health outcomes; health economist expertise in economic evaluation of interventions
Develop interventions	All participants and stakeholders will be actively engaged in collecting and exploiting information about obstacles and incentives for health promotion in young families
Develop success criteria	Participation of young families, local public health authorities and stakeholders; successful sampling of biological material and commitment of the families to diary participation at all sampling sites; public and family engagement in the socioeconomic survey, e.g. by presentation in media; dissemination of project concept and results in local media and inclusion in public health promotion
Identify barriers to inter-sector co-operation	Conceptual misinterpretations of the scope of empowerment and intervention of the project; barriers in communication of common recommendations arising from different scientific traditions
Assess benefits and impact on reducing inequalities	Important drivers in public health promotion will be identified and can be included in targeted health promotion and intervention in common language via web to the entire Danube region

health. The establishment of a biobank is discussed that will include obstetric samples that could later be used either for longitudinal comparisons or even for (birth)

cohort studies. Hungary also takes part in the HBM4EU as well as the rest of the EU countries. In Slovakia an industrial site was selected.

Romanian partners were leading in human biomonitoring – As, Hg (30). Additionally, in Romania, the development of a biobank at the IMOGEN Research Institute (reproductive and perinatal medicine), which include obstetric samples (i.e. placenta, amniotic fluid) was initiated (31).

The outcome of all these activities should be distributed to the general population, similar to the model in application in Denmark, which disseminates knowledge on exposures and adverse health effects from environmental chemicals focused on the following seven pieces of advice to be adapted to the Middle Eastern part of Europe:

- Do not smoke tobacco and avoid passive smoking during pregnancy
- Do not drink alcohol when you are pregnant or planning to get pregnant
- Clean and dust clean once a week and ventilate twice a day.
- Buy products labeled as environmentally friendly, preferably unperfumed
- Limit your contact with cleaning products, paints, spray products and hair dyes
- Vary your nutrition with different food items every day and follow the recommendations for pregnant women
- Medication, including pain killers and herbal medicines, should only be taken in agreement with your general practitioner

The NEWDANUBE consortium receives major international attention, updating of the consortium being considered with openness toward new partners, including the non-EU countries in the Danube region.

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