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HEALS

Health and Environment-wide Associations based on Large population Surveys

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D20.1 Interim report on compliance with ethical review requirements

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1 Introduction

Ethical approval is required in each country involved in European EXposure and Health Examination Survey (EXHES), since this study will directly involve human participants. To understand the extent of this issue, we are going to present briefly the EXHES objectives and protocol so to present the data and material that will obtained from the participants and for which an ethical approval will be needed. Some data will be obtained by non-invasive, semi-invasive or invasive methods. In addition, we are also going to re-use and analyse data from pre-existing studies. Although these studies have already got the approval of an ethical committee, sometimes this is not going to cover the data of interest for the HEALS project.

Another issue that is worth mentioning in this report is the compliance with privacy of the individuals. In some countries, privacy and ethics are strictly interconnected. You cannot get the authorization from one without having the authorisation from the other. This has been observed in HEALS.

1.1 Objectives of EXHES study

The overall aim of EXHES is to provide relevant harmonized and standardized data to unravel the relationship between body burden from internal and external exposures (internal and external exposome respectively) and the onset/exacerbation of the health outcomes targeted by HEALS, i.e. asthma and allergies, neurological disorders, overweight, obesity and diabetes in childhood.

Secondly, EXHES aims at validating and helping refine the development of the HEALS methodological framework and platform in view of the implementation of an European protocol for investigating health and environment interaction with the exposomic approach.

EXHES will make use of all the technologies developed in streams 2 and 3 and of information settled in stream 5 in order to assess exhaustively internal and external exposures of the individuals as well as related impacts on health. Successively, the obtained data will be used in WP12 (for storage and management) and WP13 (for constructing environment-wide associations between the health conditions targeted by HEALS and environmental stressors of relevance to the EXHES subjects).

Prospective cohort studies are a resource for current and future research, potentially for many decades and across generations. Our aim is that the EXHES cohort study provides a

robust and broad platform for existing and future research questions. A list of specific research objectives agreed in the HEALS consortium will be specifically developed.
Ethnic minorities will be considered as an added value in HEALS in order to better construct the HEALS paradigm (see section on Ethnic minorities in HEALS in the DOW).
Data allowing the exposome assessment will be made available to other HEALS partners, namely:

- biological samples (e.g. *umbilical cord blood, blood, urine* so far) useful for -omics analyses;
- information about health and lifestyle from questionnaires and follow-up studies,
- individual and environmental geocoded data for the assessment and management of temporally-spatially resolved data and models.

To sum up, the HEALS and EXHES objectives have been implemented in the respect of ethical principles in order to preserve the dignity and the privacy of the individuals independently of his/her situation. The data collected in HEALS are similar to those collected in other studies in Europe and in the rest of the world.

1.2 Study design and population from the point of view of ethics and privacy

1.2.1 Study design

EXHES comprises 2 phases:

EXHES Phase I (EXHES I) is a 3 year follow-up including in each country singletons and twins Their parents will be also recruited. Grandparents and siblings will be addressed through *ad hoc* questions.

Two recruitment schemes are possible in EXHES I according to the situation of the country:

1. Recruitment during the pregnancy (first trimester)
2. Recruitment at birth

Children and parents will be recruited in **Croatia, France, Germany, Greece, Italy, Portugal, Slovenia, Spain, Poland and the United Kingdom**.

EXHES PHASE II (EXHES II) is a nested case-control study (based on the targeted diseases and healthy controls) conducted in a sub-sample of 210 individuals (140 twins and 70 singletons) and 140 mothers in each country in which -omics analysis and lifespan geo-localisation and remote sensors will be performed **for a total of 2,100 children and 1,400 mothers**.

1.2.2 Study population

In each country, maternity hospitals will be selected. The eligible population for this cohort study is all pregnant women who plan to, and then do, give birth at these maternities over the period of recruitment, their subsequent live born offsprings (singleton or twins), and their partners.

At the beginning 150 pairs of twins (n=300 twins), 300 matched singletons (2 per pairs, matched on day of birth, sex, social class, region…) and 300 additional unselected singletons are recruited over 18 months for a total of 900 children per centre. In more detail:

- All the women with twins up to 75 women accepting to participate in the EXHES I → 150 twins
- For each woman with twins, 2 women with a singleton born in the same day, of the same sex of the twins accepting to participate in the EXHES I, two singletons of different sex in the case of DZ twins of different sex → 300 singletons
- Women with singletons up to 300 women accepting to participate in the EXHES I → 300 singletons

1.2.3 Eligibility and exclusion criteria for mothers and children

For the mothers

All women giving birth at the maternities will be eligible for recruitment, regardless of parity. Liveborn, adopted or fostered children will be excluded. Another exclusion criterion for recruitment of a woman will be if she plans to move away from the town before or after the birth. The woman, and her subsequent offspring, will be eligible for only one pregnancy.

For the children

All babies born to women who have agreed to participate in the cohort study will be eligible for recruitment. Children without the mother will not be eligible. If the woman does not want to participate in the cohort herself, even if she agrees that her child participates, the child is not eligible.

For stillborn babies recruitment to the cohort will be at birth, as it is for liveborn babies. For these babies, of course, there would not be further participation.

For the fathers

Fathers of babies who have been recruited to the cohort will be invited to participate when the mother attends for her compulsory visit (if any), at another convenient time during pregnancy, or soon after the birth. The normal procedure will be to invite the woman's current partner to participate, regardless of whether or not he is the baby's genetic/biologic father. If there is uncertainty about who to approach, the woman will be asked who should be offered participation. If the woman has a new partner in the future, he will also be invited to participate.

1.2.4 Recruitment

In each centre, recruitment begins only after obtaining the authorization from the Ethic Committee. People from majority populations as those from ethnic minorities are as likely to agree to participate in research, provided they receive an appropriate invitation in a language they understand as the language constitute a barrier to participation. They also sign a consent form written in their language.

So far, 3 different types of recruitment of pregnant mothers have been identified:

- During pregnancy (Ex: France)
- 1 month before pregnancy with mother and father (Ex: Slovenia)
- At birth (Ex: Portugal)

There is no discrimination in the recruitment, which depends on the health care system of the countries. Each surveyor will regularly fill the EXHES Recruitment form to collect data on the number of births that have been recruited and at which period so that to update the PCT and the consortium about the recruitment.

To sum up, EXHES in the respect of ethics does not exclude from the recruitment any individual on the basis of his/her situation. In particular, ethnic minorities have been

included. HEALS has also considered the issue of biological or not fathers leaving the choice to the mothers whether and whom to include.

1.3 Health and environmental assessments in EXHES

Three types of methods are used in EXHES to collect the data. For purpose of clarity:

- data that will be obtained by non-invasive methods will be colored in green.
- data that will be obtained by semi-invasive will be colored in orange.
- data that will be obtained by invasive methods will be colored in red.

1.3.1 Health assessments

Health assessments are conducted based on interviews, questionnaires, medical visits (maternity …) and biological samples.

During pregnancy:

- self-administered questionnaires on mother's/father's health ever and the period of pregnancy
- collection of samples of urine, blood, saliva and hair from the mother and the father.

At delivery:

- baby characteristics anthropometric assessments (height, weight, head…)
- delivery's report on mother's and child's health status
- collection of umbilical cord blood (IgE,…), child's hair, child's saliva, mother's saliva.

Post-Partum:

Compulsory

- interviewer- and self–administered questionnaires handed to the mother and the father about their health.
- collection of colostrum or maternal milk and meconium

Optional

- father's urines, father's saliva, father's hair, father's blood.

Follow-up of the child:

- at 6 months, 1 year, 2 years and 3 years: interview and self-administrated questionnaire handed to the mother and the father about their health and the child's health
- biological samples: urine, saliva and hair taken each year.

EXHES II:

- interview and self-administrated questionnaire handed to the mother and the father on their and child's health
- in a subsample (those with remote sensors): more detailed information on health.

Mothers and fathers will be invited to use a tablet to fill the questionnaires.

1.3.2 Environmental assessments

During pregnancy (EXHES I):

- self-administered questionnaires on mother's/father's exposure ever and the period of pregnancy
- Geolocalisation of the family address

Post-Partum (EXHES I):

- interviewer- and self–administered questionnaires handed to the mother and the father on their exposure during the *in utero* life of the child
- Geolocalisation of the family address

Follow-up of the child (EXHES I):

- At 6 months, 1 year, 2 years and 3 years: interview and self-administrated questionnaire handed to the mother and the father (potential environmental risk factors, lifestyle, beahviour). Geolocalisation of the family address
- In a subsample: use of remote sensors, and objective assessments of indoor air quality

EXHES II:

- interview and self-administrated questionnaire handed to the mother and the father (potential environmental risk factors, lifestyle, behaviour). Geolocalisation of the family address
- in a subsample: use of remote sensors, objective assessments of indoor air quality and exhaled breath to assess airways inflammation.

1.3.3 Study population privacy

In Heals, data privacy or protection is intended as the relationship between collection and dissemination of data, technology, the public expectation of privacy, and the legal and political issues surrounding them. Data protection is warranted by the fact that data were made anonymous by destroying all identifiers connected to the data in the dasets they contain. Some of the data in some types of analysis involving geo-localisation through remote sensors with GPS were also encrypted to avoid the localization of the individuals, which could allow to identify them. Indeed, reidentification of individuals by comparing anonymous data to other sources of data can be surprisingly easy. However, removing and encrypting the identifying information, such as addresses, can solve the problem.

To sum up, health and environmental data are collected in EXHES in the respect of persons ethics through methods and sampling largely used in other surveys. Of the samplings only blood sampling is invasive. However, mother's blood during pregnancy will be obtained during routine exams. In this respect, a minimal amount of blood will be taken not to increase the amount of sampling. Umbilical cord blood is taken on clamped cord once this has been cut. Generally, this cord blood, which amount can be of almost 7 ml is lost. Previous population-based survey have shown that individuals participation rate to blood sapling is satisfactory.

2 Compliance to the ethical review requirements in EXHES on the field

All the countries involved in EXHES require and legally enforce approval by an Ethic Committee before starting the study. The protocol for recruitment and collection of baseline data and biological sample for the cohort has to be approved by Ethics Committee. Samples will be collected and stored in accordance with the Human Tissue Act 2004, including ensuring appropriate licences are in place.

There are a number of ethical standards, which all researchers are expected to comply with:

2.1 Informed consent

All participants must be fully informed of the study and what is being asked of them, including the potential risks/benefits and exclusion criteria, in order to make a fully informed decision about whether or not to participate in the research. This must be an active step on behalf of the participant and not due to any inducement, coercion or perceived pressure to participate. In EXHES, an informed consent has been prepared (see Annex 1) and will be handed to the mothers and fathers. All participants will be asked to sign this consent form, which includes permission to use genetic data obtained from biological samples.

2.2 Use of biological material

In EXHES, all biological samples will be coded samples: these samples will be identified by a code (See Annex 2) rather than with personally identifying information, such as a name or Social Security number. Because medical research can reveal clinically relevant information about individuals, we must ensure that those who participate in research are adequately protected from unwarranted harms resulting from the inadvertent release of such information.

2.3 Benefit not harm

Research involving human participants must have a benefit to society and the risks involved

to participants must be balanced against the potential benefit to the overall community. EXHES study threatens no harm, since it is an observational study.

2.4 Data protection

Files containing personal identifiers (such as name, address, telephone number) will be stored in locked cabinets or rooms within the project coordinating centre, and separate from the data used for analysis. Researchers who are not part of the project coordinating centre will not have access to personal identifiers. Back-up copies will be subject to the same degree of data security. Data will be released for analysis using the unique study identifier only, hence protecting the identity of individual participants. Overall, personal data will be anonymous and encrypted.

2.5 Confidentiality and privacy

The following definitions of confidentiality and privacy were introduced in HEALS.

Confidentiality pertains to the **treatment of information** that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure. During the “informed consent” process, the subjects were informed of the precautions that will be taken to protect the confidentiality of the data and were informed of the parties who will or may have access. This allowed subjects to decide about the adequacy of the protections and the acceptability of the possible release of private information to the interested parties.

Privacy is the control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. For example, persons may not want to be seen entering a place that might stigmatize them, through GPS with remote sensors. The evaluation of privacy also involves consideration of how the researcher accesses information from or about potential participants (e.g., recruitment process). HEALS considered strategies to protect privacy interests relating to contact with potential participants, and access to private information.

All HEALS participants have the right for their participation to remain confidential in that only the researcher will be aware who has participated. Data will be made anonymous and encrypted in the case of addresses. Generally, all data will also be anonymous in the final report so that nothing can be attributed back to an individual participant.

In addition, participants will have the right to know who has access to their data and what is being done with it. The aim of ethical review is to protect participants: they are a valuable part of the research process and not merely a means of accessing data.

2.6 Reporting Research Results to Subjects

Any clinically significant findings and scientifically relevant information will be disseminated to the participant willing to know about the results of the study.

3 Summary of privacy and ethic committee authorizations within EXES

The table below shows the advancement of the EXHES in the 10 countries conducting it according to the obtained authorisations and approvals.

Partners	Privacy authorization	Ethic Committee authorization	Field survey
Croatia	Submitted	Approved	Starting
France	Obtained	Submitted	Waiting the ethic committee authorisation
Greece	Obtained	Obtained	Started
Poland	Not applicable	Approved	Started
Germany	Obtained	Approved	Started/ongoing
Portugal	Not applicable	Approved	Starting
Spain	Obtained	Obtained	Started/ongoing
Slovenia	Not applicable	Submitted	Starting
Italy	Obtained	Submitted	Starting
UK	Submitted	Submitted	Waiting the ethic committee authorisation

The state of play is very positive. So far, no reject of the EXHES project was observed.

4 Compliance to the ethical review requirements in pre-existing studies in HEALS

In Europe, health and medical administrative data is increasingly accumulating on a national level. In HEALS looking further than re-use of this data on a national level, sharing health and medical administrative data would enable large-scale analyses and European-level public health projects. HEALS is currently a research infrastructure for this type of sharing. Although laudable, these advances also bring with them a slew of ethical and social issues that challenge the normative frameworks used in research until now. With this in mind, we made the difference between studies in which the participants had given since the recruitment the authorisation to conduct additional investigations and studies in which a new consent has to be signed by the participants. In the latter case, we contacted them by inviting them to fill a new consent form after having been informed on the new investigations.

We started also a discussion on incidental findings as they can stem up from the exposomic approach. We are working on the development of recommendations in line with the ethical, legal and cultural particularities of individual European member states.

In these steps we were backed-up by the HEALS Ethics board.

ANNEX 1

MOTHER'S CONSENT FORM

A copy of this consent form will be retained in your hospital case notes

I confirm I have read and understood the information sheet dated and have had the opportunity to ask questions. I also understand that my participation and that of my child is voluntary and that we are free to withdraw at any time, without giving any reason, without our medical care or legal rights being affected

I understand that researchers working for the EXHES project may be look at sections of my medical records and the medical records of my child. I understand the information cannot be linked to me.

I agree that one of the project researchers can approach me in the future.

I agree to have air pollution assessed in my home. Assessed air pollutants include….

I agree to carry a portable sensor for having air pollution assessed in my every day lie. Assessed air pollutants include….

I agree to give biological samples, which may include blood, saliva and urine for use in the above study which may be stored for future use. If I wish to withdraw from the study in the future I agree these samples may be retained and used unless I specifically request they are destroyed, in which case EXHES will make every effort to do so and ensure that no further analysis is conducted on your samples".

I agree to blood being taken from my baby's umbilical cord and placenta after delivery. I understand that my baby's biological samples and mine will be stored. I understand the EXHES team and their research partners will use these samples and that I will not be given the results.

……	……	……..
Print name of participant	date	signature
……	……	……..
Print name of person taking consent (if different from Study Administrator)	date	signature
……	……	……..
Print name of Study Administrator	date	signature

ANNEX 2

EXHES

ID Attribution

- Country number I__I__I__I__I

Croatia = 1

France = 2

Germany = 3

Greece = 4

Italy = 5

Portugal = 6

Slovenia = 7

Spain = 8

Poland = 9

United Kingdom = 10

- Center *(in the case there are 2 centres in the same country)= 1, 2….* I__I__I

- Identification (ID) number in the study I__I__I__I__I__I

– C1xxx for the singleton
– T1xxx for the first twin (that was born before)
– T2xxx for the second twin
– MOxxx for the mother
– FAxxx for the father
– MGMxxx for maternal grandmother
– PGMxxx for paternal grandmother
– PAxxx for a new partner
– MGFxxx for maternal grandfather
– PGFxxx for paternal grandfather
– B1xxx for first brother
– B2xxx for second brother
– …
– S1xxx for first sister
– S2xxx for second sister
– ….

In a same family, xxx is the same