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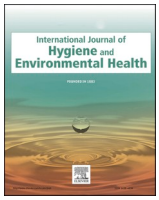

HBM4EU feasibility studies: Lessons learned in combining health and human biomonitoring studies

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ABSTRACT

Background: The European Human Biomonitoring Initiative (HBM4EU) is a joint program evaluating humans' exposure to several environmental substances and their potential health effects. One of the main objectives of HBM4EU is to make use of human biomonitoring (HBM) to assess human exposure to chemicals in Europe to better understand the associated health impacts and to improve chemical risk assessment. In parallel to HBM studies, health examination surveys (HESs), nutrition/dietary surveys, and disease specific health surveys are conducted in many European countries. In HESs, information collected by questionnaire(s) is supplemented with physical examinations and analysis of clinical and biological biomarkers in biological samples. HBM and health examination survey (HES) use similar data collection methods and infrastructures hence the feasibility of combining these two is explored in this paper.

Methods: Within HBM4EU, three feasibility studies (in Finland, Germany, and UK/England) were conducted to evaluate opportunities and obstacles of combining HBM and health studies. In this paper we report lessons learned from these feasibility studies.

Results: The Finnish feasibility study called KouBio-KUOPIO study was a new initiative without links to existing studies. The German feasibility study added a HBM module to the first follow-up examination of the LIFE-Adult-Study, a population-based cohort study. The UK feasibility integrates a sustainable HBM module into the Health Survey for England (HSfE), an annual health examination survey. Benefits of combining HBM and HESs include the use of shared infrastructures. Furthermore, participants can receive additional health information from HES, and participation rates tend to be higher due to the potential to obtain personal health information. Preparatory phases including obtaining ethical approval can be time-consuming and complicated. Recruitment of participants and low participation rates are common concerns in survey research and therefore designing user-friendly

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questionnaires with low participant burden is important. Unexpected events such as the COVID-19 pandemic can cause substantial challenges and delays for such studies. Furthermore, experiences from several countries demonstrated that long-term funding for combined studies can be difficult to obtain.
Conclusions: In the future, incorporating HBM modules into existing HESs can provide a feasible and cost-effective method to conduct HBM studies and obtain a wide range of relevant data to support public health policies and research.

1. Introduction

To respond to a variety of public health questions, and guide policy decisions and possible prevention activities, a holistic picture of health determinants and health outcomes of individuals are needed. Information on potential background variables, chemical exposures as well as health determinants and outcomes are crucial to provide a valuable data source. Combining human biomonitoring (HBM) studies and health examination surveys (HESs) is an option to collate these vast datasets in an effective way.

In many European countries, HBM studies, HESs, nutritional/dietary surveys and disease specific health surveys are conducted (Tolonen et al., 2018). HBM studies are focused on obtaining information on chemical exposures and measuring exposure levels as well as biomarkers of effect plus focused questionnaires, while in HESs, information on socio-economic background and lifestyles collected by questionnaire(s) is supplemented with physical examinations such as blood pressure and anthropometric measurements, and analysis of health-related biomarkers such as blood lipids including total, LDL and HDL cholesterol, and blood glucose from biological samples. The European Health Examination Survey (EHES), established in 2010, coordinates the development of national HESs in Europe (EHES, 2021a). Between 2014 and 2021, ten European countries have conducted a national HES, and in many countries regional HES or disease specific surveys or dietary surveys have been carried out (EHES, 2021b). In both HBM studies and HESs, data is collected through fieldwork, which is one of the most expensive and time-consuming components. As the infrastructures required for both types of studies are similar, and there are overlaps in the information gathered, the potential to combine them has been considered in several countries. It is anticipated that this could represent a cost-effective and mutually beneficial way of conducting health and HBM studies and provide data to study exposure-health outcome relationships.

To date, very few studies have been conducted, which have combined HBM and HES despite the seemingly clear benefits of combining these studies. Many HBM studies already include some health questions, however extensive objective health measurements or analysis of health-related biomarkers are still lacking. Recently, extensive combined surveys have been conducted at the national level in countries such as Germany, France, Israel, USA, and Canada (Kolossa-Gehring et al., 2007; Balicco et al., 2017; Berman et al., 2017; Centers for Disease Control and Prevention, 2021; St-Amand et al., 2014.). Although several smaller, regional or disease specific combined studies of HES and HBM have been performed throughout Europe (Tolonen et al., 2021), there is no systematic evaluation of synergies and benefits obtained or challenges encountered in these studies.

The aim of the feasibility studies conducted in HBM4EU was to assess the opportunities and obstacles encountered when combining two similar survey types with intrinsic differences. Previously conducted combined HBM and HESs have mainly been part of well-established national HBM monitoring programs, but these new feasibility studies were setup for countries/regions without prior experience of such combined studies, except for Germany. Therefore, the aim of these specific feasibility studies was to test the operability and viability of the studies and their protocols rather than obtain comprehensive results of chemical exposures and their health effects.

This paper reviews the protocols and outcomes of these feasibility studies and reports the lessons learned.

2. Methods

Feasibility studies were conducted in the framework of HBM4EU. HBM4EU is a joint project of 30 countries and the European Environment Agency (EEA), co-funded by the European Commission (EC) under Horizon 2020. The HBM4EU initiative was a five-year-project running from January 2017 to June 2022, which coordinated and advanced HBM activities in Europe. The initiative generated evidence of the actual exposure of EU residents to chemicals through HBM. HBM4EU aimed to harmonize HBM across Europe to facilitate the assessment of human exposure to chemicals. The aims were to better understand the health impacts, enhance chemical risk assessment, and support chemical policy. In HBM, the body burden of environmental chemicals and their metabolites can be measured in biological matrices such as blood (whole blood, serum, and plasma), urine, hair, and breast milk. HBM offers an aggregated measure of the level of exposure to chemicals and chemical mixtures via various exposure pathways and sources. HBM is an important tool for assessing exposures of the human population to chemicals, and when harmful chemicals are concerned, estimating potential health risks related to the exposure (HBM4EU, 2021; Ormsby et al., 2017; Ganzleben et al., 2017.).

Feasibility studies were selected to represent different settings and age groups in countries/regions which mostly have no prior experience in conducting combined HBM and HES. The minimum requirements for the feasibility studies were defined (Tolonen et al., 2017), and studies were selected through a competitive call process. The three selected studies were from Finland, Germany, and UK/England. Criteria for the studies selected were the following: feasibility studies are conducted with already planned/starting surveys/studies only in countries which do not have experience in combining HBM and health studies in the past. Furthermore, fieldwork should take place in 2019 (Tolonen et al., 2017.). These criteria were used as basis for the Internal Call (IC) process of the HBM4EU published in 2018. Topics for the first Internal Calls (ICs) were selected and approved, and the Management Board (MB) made decision on the outcomes of the IC in 2018 based on the external reviews, Scientific Advisory Board recommendations and detailed discussions. Thus, the following three feasibility studies were selected: Finland, Germany, and UK/England (Tolonen et al., 2019.).

In Finland, a new study among children was organized while in Germany and UK/England, a HBM module was added to an existing HES. The German study focused on adults and used a follow-up cohort study as a basis while the UK/English study was based on a cross-sectional survey among adolescents and adults. For these feasibility studies, the sample size was not chosen to provide nationally or even regionally representative results but to test the feasibility of combining HBM and HES in a real-world setting.

3. Planning and implementation of the feasibility studies

3.1. Finnish Feasibility Study - KouBio-KUOPIO

The Finnish feasibility study called KouBio-KUOPIO study is a new initiative without any links to existing studies. The KouBio-KUOPIO study was originally planned as an extension of the regular school health examinations, which are organized annually for all pupils in

primary school (grades 1–9). In grades one, five, and eight, an extensive health examination is performed by a doctor and for other grades more limited examination is conducted by a nurse. The aim was to recruit 300 pupils from 5th and 6th grade aged 9–13 years from the selected primary schools of Kuopio city area. (THL, 2021.) The schools were chosen based on their willingness to participate, and both new and old school buildings were included. Since some of the chemicals, such as some of the phthalates, have been prohibited in building materials already ten years ago, one of the research questions was to see do the used building materials impact identified exposure levels. The study aimed to assess the extent of school aged children's exposure to phthalates and bisphenols measured in urine samples. Eight volunteer schools were enrolled for the study.

Preparation of the study plan started in November 2018 with outlining the study design including development of the questionnaires and sample collection procedures. Fieldwork commenced in February 2020 and finished in November 2020. Thereafter phthalates and bisphenol A from collected biological samples were analysed and questionnaire data was entered (paper questionnaires) and evaluated.

During the preparatory phase, several obstacles were faced and needed to be solved before the fieldwork could commence. The preparation of the study protocol benefited from the long experience of organizing HESs in Finland. The HBM4EU standardized questionnaire was used in the study (Pack and Fiddicke, 2021). Parents or guardians made the decision whether their child/children would participate and filled in the questionnaires with them or for them. The questionnaire included questions/response alternatives which are not relevant for the Finnish society, culture, and study area. For example, for question 'Is there any of the following facilities within 300 m of your home? ', response alternatives 'A waste incineration plant', 'A site where photovoltaic devices and sollar cells are produced' among few others were removed as those facilites did not exist in the study area. Therefore, the questionnaire was modified by removing irrelevant questions or response alternatives, and only including those suitable for the Finnish society and for this specific feasibility study. There were 40 questions altogether in the questionnaire. The participants had a choice of completing the questionnaire either in pen and paper or online, with most opting for the paper version (61%).

The Finnish feasibility study experienced delays in the preparatory phase due to the lengthy process of obtaining ethical approval. It took seven months to complete the ethical approval process. Since the target group included pupils who were approached through the schools, approval from the City of Kuopio (health board and school board) was required before application for ethical approval could be submitted to the Ethical Board of Kuopio University Hospital. Approval from the city was obtained four months after initial contact. The process with the Ethical Board of Kuopio University Hospital required two revision rounds before final approval. During the revision rounds, substantial changes to the planned study protocol were required. The biggest change had to be made when the Ethical board declined the permission to conduct the study as an extension to the regular school health examinations. They didn't want the HBM study to be associated as a part of the school health examination. Also, collection of blood samples from children and use of movie tickets as incentives were denied by the Ethical board. These requirements changed the entire study protocol so that collection of blood samples was omitted, and urine samples had to be collected and frozen at home and sent to the study team. Other requested modifications to the information notice were mainly due to requirements of EU General Data Protection Regulation (GDPR), i.e., how data can be shared with the non-EU countries. The GDPR caused detailed requirements for the information notice and informed consent and fulfilling them was time consuming and required consultation of the Data Protection Officer.

The original plan was to provide pupils with questionnaires and sample collection kits with personalized identification information (study ID and corresponding bar code stickers linked to the specific pupil). Since the lists of pupils' names were not accessible due to the GDPR, the recruitment strategy had to be modified in the middle of the process. New protocol included additional steps for the coordination team to ensure that each pupil could be identified at the end and linked to written informed consent and possibly also to data from administrative registers. In the new protocol, the number of pupils in each school were estimated based on the information on the web pages of the schools, and suitable number of pseudonymized material packages were prepared. The material package included invitation and information letters, instructions for spot urine sample collection, questionnaire, and informed consent form together with sample collection materials. Identification stickers were placed on all these materials to allow linkage between the different materials.

Although contacts preceding the visits to the schools went well, engaging the pupils to the study proved difficult. There were no incentives or compensations for participation as it was prohibited by the ethics committee. In the Finnish study, the participation rate turned out to be low, approximately 6%, since 66 responses and urine samples were received from 1200 potential participants originally recruited.

The recruitment strategy of the Finnish study was not ideal, which could have affected the participation rate. The schools informed the parents of the pupils about the study, after which information was given and relevant materials were distributed to the pupils during events organized at the schools. These events were attended by several classes at the same time, and they were too large to be interactive. After the presentations, more than half of the pupils tried to leave without the sampling packages. Not all the involved teachers were well informed about the study and hence were unable to properly encourage the pupils to participate. Also, it was difficult to communicate the goals and importance of the study to the parents as there was no direct contact between them and the study team. Furthermore, the use of incentives in the form of, e.g., movie tickets, was not allowed by the ethics committee. As the participation in the study was voluntary, this could have affected the willingness to participate considering the age of the pupils.

Finally, the COVID-19 pandemic affected the realisation of the study. For example, in the first phase of the Finnish feasibility study, two schools were left unvisited when the pandemic hit, and even later these remaining schools could not be visited in person according to the original plan due to visiting restrictions. The study material was distributed to the schools, but a substantial amount of information and motivation remained unavailable because the study team could not personally visit the schools and give information about the study.

If the sampling could have been conducted during health check-ups as originally planned, the participation rate would have been most likely higher. In the check-ups both a health professional (nurse and/or physician) and the parent(s)/guardian(s) of the children would have been present, and information provided to them directly with the possibility to ask further questions. To enhance the recruitment of the pupils, co-operation with the parents and teachers is crucial, and motivating all of them is a key element.

3.2. German Feasibility Study

The German feasibility study was conducted by adding a HBM module to the first follow-up examination of the LIFE-Adult-Study (Loeffler et al., 2015; Engel et al., 2022). The LIFE-Adult-Study is a population-based cohort study, where the baseline examination has been completed for 10.000 randomly selected inhabitants from the city of Leipzig in 2014. The sample was drawn from the population register based on age (40–79 years) and gender (50% men and 50% women). In 2017, the first follow-up of the LIFE-Adult-Study started with despatching questionnaires to all the 10.000 participants. Additionally, between 2018 and 2021 approximately 2.700 (mostly 60 years and older) participants in the LIFE basic examination with a brain magnetic resonance imaging (MRI) at baseline and a consent for re-contacting were invited to the study centre for a comprehensive second

examination programme.

Prior to the feasibility study, a study protocol was compiled and approved by the Ethics Committee at the Medical Faculty of the University Leipzig (201/17-ek).

The LIFE-Adult-Study investigates environmental factors influencing development of civilization diseases (e.g., obesity, diabetes, heart disease, and cancer) in a population-based cohort. Therefore, both the original study protocol and informed consent were broad, and it was possible to accomplish all necessary processes of the feasibility study.

The participants received an invitation letter to participate in the follow-up study, after which appointments were arranged by phone. Persons who did not respond to the first letter of invitation received a second followed by phone contact attempts. If the letters were undeliverable, the residential addresses were corrected by using the registration register, after which the invitation process was repeated for these persons.

The follow-up provided an opportunity to integrate a HBM module into the LIFE-Adult-Study programme. A regular component of the LIFE-Adult-Study is a comprehensive physical examination and questionnaire program for all participants. Many of the questionnaire entities of the HBM module (sociodemographic characteristics, health status, nutrition, and medication) have already been fully covered by the LIFE-Adult-Study. A concept for a HBM module and a strategy for its integration in the LIFE-Adult-Study was developed together with Fraunhofer IBMT. The concept was formulated in accordance with the HBM4EU standard operating procedures (SOPs) (see https://www.hbm4eu.eu/online-library/for all SOPs) and the HBM4EU guidelines for linking HBM and health studies (Tolonen et al., 2022). Therefore, the HBM module was compared with the LIFE questionnaires, and only information, which was not already examined with the LIFE questionnaire, was recorded. The surveys were conducted by means of interviews and self-completed questionnaires, and the questionnaire had to be filled in at the day of the examination at the study centre. About 85% of the participants used the electronic data entry forms, however some older participants preferred a paper version. Additional urine collection (spot urine) at the examination side had to be established for HBM and integrated into the study process as this was not part of the LIFE follow-up. In addition to receiving some personal health data, the study participants were allocated a compensation of expenses of €15.

The HBM-module was successfully tested in a subset of 400 LIFE participants in the follow-up, which visited the study centre in 2019/2020. In the feasibility study, phthalates, arsenic (As), and mercury (Hg) together with their compounds were identified as priority chemicals of interest. The spot urine samples of 400 participants were processed and stored. The team of the LIFE-Adult Outpatient Clinic provided instructions to the study participants for collection of urine samples and was also responsible for appropriate labelling and transportation of the samples to the pre-analytical laboratory. Due to lack of funding, analysis of the urine samples was not conducted immediately but samples are stored and can be used for future analysis.

In Germany, recruitment of the participants was not an issue, as the HBM component was integrated into an already running follow-up of a cohort study with adult participants. On the regular examination day of the LIFE-Adult-Study, participants were asked if they wished to participate in the additional HBM module. Combining the HBM module into the LIFE-Adult cohort study ensured exceptionally high participation rate of 91%. The long-established cohort study enabled the HBM module to be considered as an additional "health check-up", which might have augmented the participation rate. Furthermore, the study population consisted of adults, many of whom had already retired, and therefore had possibly more time available and increased interest in health issues compared to working aged adults and children or adolescents.

The COVID-19 pandemic did not cause substantial delays or obstacles to the German study. The participants were included in the HBM study between November 2019 and August 2020. During the first wave of the pandemic, the study centre was closed from mid-March to early June 2020. Nevertheless, the recruitment of 400 subjects for HMB was successfully accomplished.

3.3. UK/England Feasibility Study

The UK feasibility study is seeking to integrate a sustainable HBM module into the Health Survey for England (HSfE) (Mindell et al., 2012), an annual health examination survey, which commenced in England in 1991. It is regarded as a Gold Standard health survey collecting information about the health of the population in England, and it is an ideal platform for the integration of a HBM module. HSfE is commissioned by National Health Service (NHS) Digital and carried out by the Joint Health Surveys Unit of National Centre for Social Research (NatCen) in co-operation with the Research Department of Epidemiology and Public Health at University College London (UCL).

Approximately 10.000 people (8.000 adults and 2.000 children) are targeted annually for participation in HSfE. It gathers a population representative sample of children 2–15 years and adults (16+ years as defined by HSfE). The survey utilises a multi-stage stratified probability sampling design, and the populations targeted live in private housing; persons living in institutions are not included. In the HSfE, the 1st contact is by interviewer who conducts an interview, administers the questionnaires and schedules time for the nurse visit during which health measurements and collection of biological samples are conducted.

The first step in the development of a HBM programme involves undertaking a pilot study for the integration of a HBM module into HSfE. The HBM module utilises a subset of 300 participants (minimum 200) from the selected HSfE sample population (N = 10.000), and comprises adolescents aged 16–19 years (N = 60) and adults aged 20–49 years (N = 240). Rather than sampling 150 adults and 150 adolescents, the strategy had to be revised due to the small sample size of the 16-19-year age group. Additionally, it is unclear whether participation of this younger age group may prove more challenging than the adults due to lifestyle etc. Before the start of the pilot study, a dress rehearsal was conducted on a very small number of participants in August/September 2021, and only 12 of the 50 participants recruited for HSfE were with the required age band (18–49 years) and therefore eligible to take part in the HBM module. It was noted that during the dress rehearsal no participants completed the additional online survey for the HBM module. Hence a SMS text reminder will be sent during the fieldwork in 2022 to encourage completion of the online questionnaire. The feasibility study will be conducted in June–December 2022 and many lessons are expected to be learned throughout the process.

Due to the COVID-19 pandemic, there were amendments to the timetable for the 2022 programme (originally scheduled for January–December 2022) as fieldwork for 2021 had to be completed in the first half of 2022. Additionally, there had been some difficulties with the supplies of plastic urine containers, so the HBM module would not have been able to commence in January 2022 had there been no amendment to the field schedule. The revised timetable for the fieldwork is June 2022–March 2023.

Blood and urine samples are being collected from participants to determine their personal exposure to four groups of the HBM4EU priority substances: perfluorinated substances (PFAS), flame retardants, bisphenols, and phthalates, as well as metals.

The most effective and appropriate means to select the households for the HBM module was decided by NatCen at the start of the programme however is subject to change if the participants numbers are low. To align with HBM4EU, the aim will be to reach a minimum 200 but ideally 300 participants (adolescents and adults) including two age groups. Adolescents and adults have been selected due to costs constraints and the inherent difficulties that are experienced when trying to gather samples from children. The households selected for the survey are sent a letter to obtain a permission to be interviewed and participate. At the initial visit, the interviewer administers a questionnaire and asks for

an agreement for a second stage visit of a nurse to collect samples and take measurements. Before 2018, all households included in the initial visit were offered a nurse's visit. Now 16 of the 18 addresses are randomly selected for the stage two. Earlier, a token of £10 voucher was given to the participants in HES.

Regarding the questionnaire module, a maximum of 10 additional minutes of interview for the HBM module could be included in the HSfE. Therefore, there can only be a few questions in the main questionnaire, and a more detailed HBM online questionnaire including questions related to the chemicals of interest is provided for the participants to be completed after the nurse's visit.

During the first phase, the integration of a HBM study into a HES will be limited to England, however the aim is that later the programme is expanded to all four UK nations. The integration of a HBM module to HSfE is currently in progress, with the preparatory work regarding study design, required questionnaires and other materials conducted in 2019–2021.

HSfE have validated methods which have been approved by the Research Ethics Committee (REC). In the UK, the new HBM module needs to follow the timelines and protocols of the HSfE when ethical approval is applied. This means that any additional ethical approval documentation for HBM must be submitted in time for the HSfE ethical approval. Basically, every year since the start of the survey (HSfE) it is reviewed by an independent group of experts to ensure the safety, rights, wellbeing, and dignity of the survey participants. Each year the survey asks for an amendment to their ethical approval, which covers the selected topics for that specific year. For the 2022 programme including the HBM module, ethical approval was sought and gained for the collection of the additional information and biological samples. Substances of interest were listed. However, there was some degree of flexibility in the approval granted for metals since there was no need to list the specific metals to be investigated.

The biological samples collected for the HBM module are transferred to UK Health Security Agency (UKHSA) laboratory in Oxfordshire where they are stored and will be analysed in batches. All analyses will be done in-house but inter-laboratory comparisons for some substances will be conducted in other government department laboratories, e.g., Health and Safety Executive (HSE), Environment Agency (EA) and Department for Environment, Food and Rural Affairs (Defra).

4. Lessons learned

4.1. From previous combined HBM and HES studies

Previously conducted studies provide valuable information about operability of combining HBM and HES in different settings. There were several opportunities but also challenges in previously conducted national HBM programmes from Germany (German environmental survey for children (GerES IV)) (Kolossa-Gehring et al., 2007), France (Esteban survey) (Balicco et al., 2017), and Israel (2011 Israel Biomonitoring study and 2015–2016 Israel MABAT Biomonitoring Study) (Berman et al., 2017) combining HBM and HES surveys. In all these three countries, studies were initiated and implemented at the governmental level with ministerial funding. It has been shown in these studies that utilization of existing logistic infrastructure where a HBM module is added to the existing HES will result in significant cost savings, larger sample size, and access to a wide range of detailed nutrition and health-related data. Since HESs usually benefit from a good public awareness, positive image, and high interest among people, this will also be beneficial to a HBM module and help to increase participation rate. Data from combined surveys allow the investigation of links between exposures and health related outcomes (Tolonen et al., 2018; David et al., 2020.).

On the other hand, combined surveys have some challenges such as limitation in the size of questionnaire and other health parameters and analysis of biomarkers. The respondent burden needs to be kept acceptable not to jeopardize participation rates and therefore, only a limited additional number of questions and measurements of interest can be included to the final study protocol. In addition, the number of biological samples, such as blood and urine, which can be collected from each individual is limited, and a balance between available samples and interested biomarkers may need to be established. There may also be restrictions on when data can be published, and the HBM module will be subject to the timetable of the HES if it is the secondary study. If ethical approval and informed consent are obtained separately for HBM and HES modules, there may be lack of flexibility in the data access and use. Communication between teams responsible for the different modules and to the participants may be challenging and requires extra efforts and training in extensive combined HBM and HES surveys (Tolonen et al., 2018.).

4.2. From HBM4EU feasibility studies

The detailed description of the feasibility studies and their outcomes have been published as outcome of the HBM4EU project (Elonheimo et al., 2021). Here we will describe lessons learned during the preparatory and implementation phase.

There were several benefits identified related to adding a HBM module to existing HESs. To establish a completely new survey requires huge effort and is very costly, and therefore adding a HBM module to an existing survey enables using already existing infrastructure and trained staff. However, HESs are conducted among adults in most countries (see https://ehes.info/national/national_hes_status.htm), and only a few countries such as Germany, France and UK/England have HES designed for children/adolescents.

When organizing a study combining HBM and HES, it is important to identify in the beginning whether data is being collected for research or monitoring purposes, or both. This is due to the difference in the reporting periods; research usually requires longer time scales to accommodate thorough statistical analysis of results before reporting whilst monitoring often report basic results quicker with simple descriptive statistics. The purpose for this data collection may also affect ethical approval and funding possibilities, and country specific differences apply.

Preparation of the combined HBM and HESs is time consuming and requires appropriate resource allocation. In contrast, the effort required to establish a permanent population representative HBM study would require a considerably greater effort, time, and skills. The studies may experience significant delays due to long processes and demands of ethical boards and additional external factors, such as the unexpected global pandemic of COVID-19. Enough time, at least one year, should be allocated for study preparation to ensure everything is in order before starting the fieldwork. GDPR can have a challenging impact on conducting HBM studies in minors. This is particularly true in school settings with children as a target group, as experienced in the Finnish KouBio-KUOPIO study. Thus, information regarding study subjects can be difficult to obtain due to strict legislative rules and regulations. However, obtaining permissions for both modules at the same time can save time, costs, and effort, since there is no need to do these procedures separately for two different modules.

Schools are an appealing setting for conducting a biomonitoring study among children due to an easy access to specific age cohorts. They provide an interesting place for research, because in some countries it can be practical to link sample collection to existing school health check-ups. However, there are also challenges. In addition to children and their parents/guardians, there are many other groups of people involved e.g., principals, teachers, and school nurses, possibly also school boards – all of whom need to be persuaded to commit to the study for recruitment to be successful. Furthermore, ethical rules and requirements, national regulations as well as the GDPR issues are rightfully more protective and stricter regarding children. Children are seen as vulnerable groups and additional protective actions are required for them.

Low participation rates are common, and there is no one-fit-for-all

solution for the recruitment. However, it should be recognized, that participation rates have been higher in those HBM studies which have been combined to HESs. Furthermore, participants of the established cohort study easily consider the HBM module as an additional "health check-up", and they are used to participating in examinations. These facts help in recruiting and increasing participation rates. One additional benefit is that combining HBM data with other health data from HESs provides added value and diversity to data content and gathering. Furthermore, one important aspect to consider is, whether a HBM module can be added to an existing HES without compromising the original participation rate of the HES.

Recruitment efforts should be adjusted for each study. Sufficient information for invitees should be given, and teachers and guardians should be motivated when children in the school setting are concerned. Giving a small incentive and sending frequent reminders via SMS, if applicable, could be used to increase participation rates (Smith et al., 2019; Tolonen et al., 2014). Participation rate can also be increased with a targeted communication concept with trained recruiters and non-material incentives like information materials including (Börsch-Supan et al., 2013), e.g., information on personal health-related results (Morrison et al., 2003). Furthermore, a non-response questionnaire can offer important information about the profiles of non-respondents and reasons for non-response.

Lengthy and complicated questionnaires might decrease response rates, and therefore length and content of the questionnaires should be carefully evaluated. HBM4EU has specific standard questionnaires (Pack and Fiddicke, 2021), however their use in national studies can present challenges since they also include concepts such as specific industries or food items, which are not always relevant to a specific study region, and they do not adequately target e.g., country specific exposure routes. Therefore, national, and local adaptations to the questionnaires may be needed. One alternative to be considered could be, that a short obligatory questionnaire with key questions is included as a part of the main study protocol and more extensive, longer questionnaire is offered for survey participants later to be filled out online. For questionnaire administration online surveys are getting more common, however providing a paper and pen alternative especially for older participants is important.

It should be anticipated that invasive blood sampling can be highly expensive. Also, having trained and qualified staff to conduct HBM data collection is important.

One approach that might be beneficial is accessing samples stored in existing biobanks. In Europe, many biobanks already collect and store human samples for biomedical research and various medical applications. Most of them are organized in infrastructures and/or scientific societies like the European, Middle Eastern, and African Society for Biopreservation and Biobanking (ESBB) and the European Research Infrastructure BBMRI-ERIC. In addition to the primary research and application reasons and depending on the informed consent of the sample donor, many of these biobanks might be open for use of samples for further research including HBM. This might save costs and create reciprocal benefits. However, it needs to be clarified whether the available samples meet the requirement criteria for use in HBM regarding representativeness, target groups, and quality of the samples (Lermen et al., 2020.). Furthermore, sample volume available for biobank samples may be an issue especially if multiple exposure biomarkers are planned to be measured.

Long-term funding, analytical capabilities, facilities for sample handling and storage, and data management procedures are needed for sustainable monitoring programmes. However, receiving funding is a common problem. Finally, the policy value of combined HBM and HES studies might be increased by relatively short transition time between the data collection, analysis, and reporting results.

5. Discussion

The common features and known differences in the organization of HBM and HES studies has been reported separately (Tolonen et al., 2018, 2022). We will discuss some of the key elements which were found most challenging in the feasibility studies namely obtaining ethical approval, non-response, and preparation of the survey questionnaire.

Ethical approval is always required for health-research which includes human participants; this must be obtained before approaching research participant and commencing data collection (Gelling, 2016). Procedures for obtaining ethical permissions varies from one country to another however there are shared regulations which are binding for all the EU countries. The most noteworthy is the EU GDPR. GDPR is Europe's data privacy and security law, which assigns obligations not only on European countries but also any other countries/organisations wishing to target or collect data related to people in the EU. (Gdpr.eu, 2021)

National and regional ethics committees can have varying practises concerning ethical approvals and regulatory requirements. In these three feasibility studies, receiving the ethical approvals were more complicated in Finland and UK/England in comparison to Germany. More harmonized interpretation of the GDPR between European countries would be needed. It should be anticipated that ethical processes can take months, and sometimes several update rounds of ethical approvals may be required. Therefore, enough time should be allocated for the preparation of the materials for the ethics committees and possible revisions.

In all the feasibility studies, the preparatory phases including obtaining of ethical approvals were very time consuming and country-specific differences existed. In Finland a completely new HBM module was created to be performed in the school settings, whereas in Germany and the UK/England the HBM modules were linked with existing cohorts or HESs. The study designs of HES and HBM surveys have major operational and infrastructural aspects in common, such as recruitment of participants, questionnaires, and collection of samples and data (David et al., 2020). However, the studies can differ in specific requirements regarding fieldwork, pre-analytical and analytical phases, as well as sample storage, and taking these into account during the study preparation is essential. Furthermore, recruiting a HBM module as a part of HES will reduce recruitment efforts.

Non-response questionnaires, a short questionnaire offered to non-respondents to obtain their background information and reasons for non-response including ideally a couple of key survey content questions, can provide important information for future activities and studies, and these questionnaires should be scrutinized and analysed to gain experience and learn lessons. Even though incentives are not allowed in Finland, sending out SMS-reminders is not prohibited, and reminders can be a cost-effective way to encourage participation in health studies (Karvanen et al., 2019). However, this requires that mobile phone numbers are included in the sampling frame. In both Germany and the UK, small incentives to the participants are allowed, and therefore small vouchers can be provided, which can help in recruiting more participants to take part in the HBM module of the study. Furthermore, recruiting young participants may prove difficult and the success of recruiting the youth may require additional efforts to motivate guardians and teachers as well.

Participation rates of the two feasibility studies already conducted varied substantially. In the Finnish study, the participation rate was very low (6%), whereas in Germany the rate was exceptionally high (91%). Reasons for the low participation rate may be diverse including, e.g., deficiencies in the study protocols, inadequate motivating of participants and teachers, and restrictions in using incentives. High participation rate, on the other hand, can be attributed to successfully linking a HBM module with a well-established cohort study. Also, the age of the participants can play a substantial role regarding the participation rate; it is estimated that older people are probably more willing to participate

in health studies compared to younger populations.

Targeted communication in all phases and with all involved parties is essential to convey information about the study and its importance to enhance participation. The positive impact of incentives on participation rates is also well documented (Jia et al., 2021). One of the benefits of combining HBM modules with existing HESs can be higher participation rates in comparison to HBM modules being conducted separately. Health surveys are usually more attractive for the invitees due to the possibility to obtain information about one's own health. Also, a HBM module can offer interesting information on internal exposure of a participant to environmental chemicals. The communication of HBM results need to be accompanied by information on sources and routes of exposure, relevant toxicological effects, and recommendations for action on how the exposure can be minimized. For this purpose, HBM4EU has produced factsheets (HBM4EU, 2022) for several substance groups to guide citizens on how to change behaviors to minimize exposure.

Questionnaires are a key tool to collect information about background variables such as socio-economic status and possible exposure sources for HBM studies. They are also used extensively in health surveys to collect information on health behaviours, lifestyle factors, diagnosed diseases, use of medications and health care services, and other aspects and determinants of health and wellbeing (Pack and Fiddicke, 2021; González-Alzaga et al., 2022.). Therefore, questionnaires for combined HBM and HESs can be extensive and time consuming. Within all the feasibility studies, the experience was that modifications of the HBM4EU standard questionnaires were necessary to ensure practicability in the light of participant burden and country-specific circumstances. The HBM4EU questionnaire was designed to cover all relevant questions regarding exposure to the prioritised substances and substance groups in HBM4EU and provide standardized questions for these substances that can be used for further studies.

Although standardized questionnaires exist, applying context-specific questionnaires, and adapting the questionnaires to specific countries and populations is essential. Alternatively, a short obligatory questionnaire with key questions and longer voluntary questionnaire(s) to obtain additional information could be used, like the protocol being used for HSfE. It is important to ensure that participants understand the reasons behind the questions. Additionally, the length of the questionnaires should be carefully considered, as questionnaires that are too long might hinder response rates and produce inaccurate data as participants become fatigued and restless. Therefore, piloting of the complete questionnaire in a large enough sample is essential. Also, it is important to provide both pen and paper and online questionnaires for different participating groups.

Combining HBM modules with representative national HESs is an important aspect to consider and develop. The combined studies have not been very common to present but benefits have already been highlighted. There are recently published guidelines for preparation of combined HBM and HES (Tolonen et al., 2022) which should facilitate establishment of new combined surveys in the future. Also, possibilities to link HBM and HES data with other data sources should be considered (Meltzer et al., 2022).

6. Conclusions

Obtaining comprehensive information on individual's chemical exposures and related determinants, and health outcomes requires surveys which combine features from both HBM studies and HESs. This type of combined HBM studies and HESs can be conducted in many ways as demonstrated with the HBM4EU feasibility studies. Even though these feasibility studies were small on sample size, their study protocols were identical which could be used for a national study and therefore, one would expect that experiences obtained from them hold also for large studies. Establishing a new combined study will be technically and logistically more challenging and expensive than adding a HBM module to an existing HES. HES has already in place logistic infrastructure and recruitment procedures etc. which in many cases is a cost-effective method for collecting and evaluating wide range of health-related data. In theory, it would also be possible to add a HES module to existing HBM study if HBM study has large enough sample size for the needs of the HES (Tolonen et al., 2022).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Balicco, A., Oleko, A., Szego, E., Boschat, L., Deschamps, V., Saoudi, A., Zeghnoun, A., Fillol, C., 2017. Protocole Esteban: une Étude transversale de santé sur l'environnement, la biosurveillance, l'activité physique et la nutrition (2014–2016). Toxicol. Anal. et Clin. 29 (4), 517–537. https://doi.org/10.1016/j.toxac.2017.06.003.

Berman, T., Goldsmith, R., Levine, H., Grotto, I., 2017. Human biomonitoring in Israel: recent results and lessons learned. Int. J. Hyg. Environ. 220 (2), 6–12. https://doi.org/10.1016/j.ijheh.2016.09.008.

Börsch-Supan, A., Krieger, U., Schröder, M., 2013. Respondent incentives, interviewer training and survey participation. SHARE working paper series 12-2013. http://www.share-project.org/uploads/tx_sharepublications/WP_Series_12_2013_B%C3%B6rsch-Supan_Krieger_Schr%C3%B6der.pdf (accessed 07.11.22).

Centers for Disease Control and Prevention, CDC, 2021. Fourth national report on human exposure to environmental chemicals. https://www.cdc.gov/exposurereport/ (accessed 21.12.21).

David, M., Schwedler, G., Reiber, L., Tolonen, H., Andersson, A.M., Esteban López, M., Joas, A., Schöpel, M., Polcher, A., Kolossa-Gehring, M., 2020. Learning from previous work and finding synergies in the domains of public and environmental health: EU-funded projects BRIDGE Health and HBM4EU. Arch. Public Health = Archives belges de sante publique 78, 78. https://doi.org/10.1186/s13690-020-00460-9.

Elonheimo, H., Andresson, A.-M., Baber, R., David, M., Fiddicke, U., Gerofke, A., Haverinen, E., Agegaard Holmboe, S., Koponen, J., Korkalainen, M., et al., 2021. Final evaluation report from the feasibility studies. Deliverable Report D11.5. https://doi.org/10.5281/zenodo.6346357 (accessed 09.11.22).

Engel, C., Wirkner, K., Zeynalova, S., Baber, R., Binder, H., Ceglarek, U., Enzenbach, C., Fuchs, M., Hagendorff, A., Henger, S., et al., 2022. Cohort profile: the LIFE-adult-study. Int. J. Epidemiol., dyac114. https://doi.org/10.1093/ije/dyac114. Advance online publication.

European Health Examination Survey, EHES, 2021a. What is EHES. http://www.ehes.info/index.htm (accessed 07.12.21).

European Health Examination Survey, EHES, 2021b. National HESs conducted between 2000-2021 and known plans for 2022-2030. http://www.ehes.info/national/national_hes_status.htm (accessed 07.12.21).

Ganzleben, C., Antignac, J.P., Barouki, R., Castaño, A., Fiddicke, U., Klánová, J., Lebret, E., Olea, N., Sarigiannis, D., Schoeters, G.R., et al., 2017. Human biomonitoring as a tool to support chemicals regulation in the European Union. Int. J. Hyg Environ. Health 220 (2 Pt A), 94–97. https://doi.org/10.1016/j.ijheh.2017.01.007.

Gdpr.eu, 2021. What is GDPR, the EU's new data protection law? https://gdpr.eu/what-is-gdpr/?cn-reloaded=1.

Gelling, L., 2016. Applying for ethical approval for research: the main issues. Nurs. Stand. 30 (20), 40–44. https://doi.org/10.7748/ns.30.20.40.s46.

González-Alzaga, B., Hernández, A.F., Kim Pack, L., Iavicoli, I., Tolonen, H., Santonen, T., Vinceti, M., Filippini, T., Moshammer, H., Probst-Hensch, N., et al., 2022. The questionnaire design process in the European Human Biomonitoring Initiative (HBM4EU). Environ. Int. 160, 107071 https://doi.org/10.1016/j.envint.2021.107071.

HBM4EU, 2021. What we do. https://www.hbm4eu.eu/what-we-do/ (accessed 07.12.21).

HBM4EU, 2022. Factsheets. https://www.hbm4eu.eu/citizens-corner/factsheets/ (accessed 11.11.22).

Jia, P., Furuya-Kanamori, L., Qin, Z.S., Jia, P.Y., Xu, C., 2021. Association between response rates and monetary incentives in sample study: a systematic review and meta-analysis. Postgrad. Med. 97 (1150), 501–510. https://doi.org/10.1136/postgradmedj-2020-137868.

Karvanen, J., Härkänen, T., Reinikainen, J., Tolonen, H., 2019. Recommendations for design and analysis of health examination surveys under selective non-participation. Eur. J. Publ. Health 29 (1), 8–12. https://doi.org/10.1093/eurpub/cky161.

Kolossa-Gehring, M., Becker, K., Conrad, A., Lüdecke, A., Riedel, S., Seiwert, M., Shultz, C., Szewzyk, R., 2007. German environmental survey for children (GerES IV)–first results. Int. J. Hyg Environ. Health 210 (5), 535–540. https://doi.org/10.1016/j.ijheh.2007.07.018.

Lermen, D., Gwinner, F., Bartel-Steinbach, M., Mueller, S.C., Habermann, J.K., Balwir, M. B., Smits, E., Virgolino, A., Fiddicke, U., Berglund, M., et al., 2020. Towards harmonized biobanking for biomonitoring: a comparison of human biomonitoring-related and clinical biorepositories. Biopreserv. Biobanking 18 (2), 122–135. https://doi.org/10.1089/bio.2019.0092.

Loeffler, M., Engel, C., Ahnert, P., Alfermann, D., Arelin, K., Baber, R., Beutner, F., Binder, H., Brähler, E., Burkhardt, R., et al., 2015. The LIFE-Adult-Study: objectives and design of a population-based cohort study with 10,000 deeply phenotyped adults in Germany. BMC Publ. Health 15, 691. https://doi.org/10.1186/s12889-015-1983-z.

Meltzer, H.M., Jensen, T.K., Májek, O., Moshammer, H., Wennberg, M., Åkesson, A., Tolonen, H., 2022. Enhancing human biomonitoring studies through linkage to administrative registers-status in Europe. Int. J. Environ. Res. Publ. Health 19 (9), 5678. https://doi.org/10.3390/ijerph19095678.

Mindell, J., Biddulph, J.P., Hirani, V., Stamatakis, E., Craig, R., Nunn, S., Shelton, N., 2012. Cohort profile: the health survey for England. Int. J. Epidemiol. 41 (6), 1585–1593. https://doi.org/10.1093/ije/dyr199.

Morrison, D.S., Thomson, H., Petticrew, M., 2003. Effects of disseminating research findings on response rates in a community survey: a randomised controlled trial. J. Epidemiol. Community Health Jul 57 (7), 536–537. https://doi.org/10.1136/jech.57.7.536.

Ormsby, J.-N., Lecoq, P., Ougier, E., Rousselle, C., Ganzleben, C., 2017. Prioritisation strategy and criteria. HBM4EU Deliverable Report D 4.3. https://www.hbm4eu.eu/wp-content/uploads/2017/03/HBM4EU_D4.3_Prioritisation_strategy_criteria-1.pdf (accessed 30.11.21).

Pack, K., Fiddicke, U., 2021. Overview of HBM4EU harmonised questionnaires and interview manuals available in the Online Library. https://www.hbm4eu.eu/online-library/ (accessed 07.12.21).

Smith, M.G., Witte, M., Rocha, S., Basner, M., 2019. Effectiveness of incentives and follow-up on increasing survey response rates and participation in field studies. BMC Med. Res. Methodol. 19 (1), 230. https://doi.org/10.1186/s12874-019-0868-8.

St-Amand, A., Werry, K., Aylward, L.L., Hays, S.M., Nong, A., 2014. Screening of population level biomonitoring data from the Canadian Health Measures Survey in a risk-based context. Toxicol. Lett. 231 (2), 126–134. https://doi.org/10.1016/j.toxlet.2014.10.019.

Terveyden ja hyvinvoinnin laitos, THL, 2021. Koululaisten biomonitorointi – Kuopio (KouBio – Kuopio). https://www.thl.fi/koubio (accessed 25.01.22).

Tolonen, H., Aistrich, A., Borodulin, K., 2014. Increasing health examination survey participation by SMS reminders and flexible examination times. Scand. J. Publ. Health 42 (7), 712–717. https://doi.org/10.1177/1403494814544403.

Tolonen, H., Andersson, A.-M., David, M., Hansen, S., Agergaard Holmboe, S., Rambaud, L., Tagne-Fotso, R., 2017. Criteria for feasibility studies. Additional HBM4EU Deliverable Report AD 11.2. https://doi.org/10.5281/zenodo.5956638 (accessed 19.07.22).

Tolonen, H., Agegaard Holmboe, S., Ancona, C., Andersson, A.-M., Alimonti, A., Bergdahl, I., Berglund, M., Demarest, S., Dias, C., Dusek, L., et al., 2018. Report on opportunities and obstacle of combining HBM and health studies, availability of health studies with biological samples, availability of administrative registers, and guidelines for combining HBM and health studies. HBM4EU Deliverable report D 11.1. https://doi.org/10.5281/zenodo.5956401 (accessed 19.07.22).

Tolonen, H., Andersson, A.-M., Fiddicke, U., Kold Jensen, T., Májek, O., Meltzer, H.M., Moshammer, H., Paalanen, L., Wennberg, M., Åkesson, A., 2019. Selection of feasibility studies for linking HBM and health studies, and linking to administrative data sources. Additional HBM4EU Deliverable Report AD 11.3. https://zenodo.org/record/5956462 (accessed 28.10.22).

Tolonen, H., Andersson, A.-M., Bicho, M., Capitao, C., Elonheimo, H., Haverinen, E., Martins, R., Mattila, T., Paalanen, L., Rambaud, L., et al., 2021. 2nd update on the report on opportunities and obstacles of combining HBM and health studies, availability of health studies and administrative registers and guidelines. HBM4EU Deliverable Report D 11.4. https://doi.org/10.5281/zenodo.6033258 (accessed 19.07.22).

Tolonen, H., Moore, S., Lermen, D., Virgolino, A., Knudsen, L.E., Andersson, A.-M., Ramboud, L., Ancona, C., Kolossa-Gehrign, M., 2022. What is required to combine human biomonitoring and health surveys? Int. J. Hyg Environ. Health 242, 113964. https://doi.org/10.1016/j.ijheh.2022.113964.