Potential of Epidemiological Imaging for Image Analysis and Visualization Applications: A Brief Review

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Abstract—**Recently, large population-based studies gain increasing focus in the research community. Epidemiological studies acquire numerous data by means of questionnaires and examinations. Many of these studies also collect imaging data, for instance, magnetic resonance imaging or ultrasonography from hundreds or even thousands of participants. Here, we consider several on-going epidemiological studies conducted in Europe as well as challenges of subsequent image analysis and visualization of heterogeneous data, which were obtained within these studies. In particular, the main focus is on airway extraction tasks and the visual analytics problems. Available solutions and future directions for computer science specialists are presented and analyzed in terms of user-friendliness, speed, and efficiency.**

I. INTRODUCTION

Epidemiology is a scientific discipline, which provides knowledge on how often diseases occur in different groups of people and why. A key feature of epidemiology is the measurement of disease outcomes in relation to a population at risk, namely, the group of people (healthy or sick), who would be counted as cases if they had the disease being studied. Epidemiological information is used to plan and evaluate strategies to prevent illness and as a guide to the management of patients in whom disease has already developed [1], [2]. Moreover, the results from the cohort studies represent a valuable tool for personalized medicine, namely, to describe a comprehensive picture of a person's demographic, socioeconomic, psychosocial, genetic and clinical characteristics and to predict the individual risk of outcomes [3].

In recent years, longitudinal observational cohort studies have been gaining increasing popularity in the research community. A cohort study consists of the following main steps: design and conceptualization of study, selection of the population of interest and sampling, collection and cleaning the data.

Research tasks in epidemiology aim to find risk factors of a specific disease, analyze correlations between different parameters, health outcomes, and evaluate the efficiency of possible prevention or treatment strategies.

Cohort studies increasingly collect enormous amount of heterogeneous information (for instance, interview, medical examination, and medical imaging data) from large numbers of randomly selected individuals. These data are then processed in numerous research projects by epidemiologists, statisticians, and clinical researchers.

Recent image-centric cohort studies assess also non-invasive imaging data [4], usually, with non-radiation nature, such as magnetic resonance imaging (MRI) [5] and ultrasound data. The Rotterdam Study [6] was the first European study, which employed MR imaging, namely, brain MRI, in a general population setting.

Manual post-processing and analysis of huge amount of them is usually infeasible due to extreme time consumption. Moreover, the results obtained with manual processing often suffer from inter- and intra-observer variability.

Apart from that, MRI data do not exhibit standardized intensity values in contrast, for instance, to computed tomography (CT) data [7]. Moreover, there are numerous artefacts present in MR data, such as intensity inhomogeneity, ghosting, aliasing, patient motion and breathing, and even patient make-up and tattoos [8]. Hence, automatic or even semi-automatic processing of such data represents a significant challenge for researchers.

The ultimate goal of computer science specialists (namely, image processing, data and information visualization, and visual analytics researchers) working for epidemiological studies is to develop highly accurate, reliable, intuitive, and computationally robust tools to allow the medical doctors and epidemiologists to conduct their research in an efficient and reproducible way.

This paper is organized as follows. We present general information on epidemiological studies and shortly describe several studies conducted in Germany and the Netherlands, referring to their study designs and main goals in Section II. The related data analysis tasks (both accomplished and work-in-progress) with emphasis on segmentation and evaluation of airway imaging, multi-variate visual analysis of heterogeneous data and accompanying challenges are presented and analysed in Section III. Section IV concludes the paper.

II. EPIDEMIOLOGICAL STUDIES

Population-based epidemiological studies are based on a sample selected from a general population. Their level of generalizability is higher in contrast to studies conducted, for instance, in specialized hospitals.

The individuals are randomly selected, for instance, through the population registry databases. The more people are recruited and actually take part in a study, the more representative the study results are for the target population.

Large-scale epidemiological studies gain an increasing popularity in the research community, aiming to investigate the causes of the development of different diseases and certain health conditions. Examples of such studies are, for instance, the German National Cohort (GNC), an interdisciplinary project, which will cover a large population sample ($\approx 200,000$ people) across German [9], and The Rotterdam Elderly Study [10], which investigates the risk factors of cardiovascular, neurological, ophthalmological and endocrine diseases in the elderly starting from 1990.

In this Section we discuss several on-going epidemiological studies, namely, the Study of Health in Pomerania (SHIP) [11], the Cooperative Health Research in the Augsburg Region (KORA) [12], and the Generation R [13]. These studies cover both adult (population-based and high-risk for SHIP and KORA, respectively) and child cohorts.

A. SHIP

The Study of Health in Pomerania (SHIP) is a population-based epidemiological project consisting of two independent cohorts (SHIP and SHIP-TREND). The SHIP investigates common risk factors, subclinical disorders and manifest diseases with highly innovative non-invasive methods in the high-risk population of northeast Germany. The main aims include the investigation of health in all its aspects and complexity involving the collection and assessment of data relevant to the prevalence and incidence of common, population-relevant diseases and their risk factors [11].

The project started in 1997, and for the base-line $SHIP-0$ (1997-2001), a sample of 7008 women and men aged 20 to 79 years was drawn in the cities of Greifswald, Stralsund and Anklam and 29 communities in the surrounding region which is part of West Pomerania, a region in the northeast of Germany, adjacent to the Baltic Sea in the north and to the Polish border in the east. West Pomerania is the north-eastern part of Mecklenburg-Vorpommern, one of the 16 federal German states. In the first 5-year-follow-up ($SHIP-1$ conducted 2002-2006) and in the 11-year-follow-up (SHIP-2 conducted 2008-2012) the same participants were invited again. A separate stratified random sample of 8016 adults aged 20 - 79 years was drawn for SHIP-TREND-0 (2008-2012) from virtually the same area. Currently, data are collected for the third follow-up examination SHIP-3 as well as the first follow-up examination for the new cohort (SHIP-TREND-1).

In parallel to the examination follow-ups, comprehensive information on vital status, causes of death and incident diseases is collected by active (follow-up questionnaires) and passive (record linkage with external data sources) follow-ups.

SHIP is the first population based cohort study worldwide which includes whole-body MRI [14], [15] with a standardized imaging protocol for all participants of SHIP, starting from SHIP-2 and SHIP-TREND-0. The goals of the SHIP-MRI study are:

- To provide prevalence, incidence, and progression estimates for different MR findings in a general adult population.
- To establish population-based MRI reference parameters for various organs and organ parts such as left and right ventricular size or volume of lungs, trachea, liver, spleen, kidney, prostate, and brain structures. Clinical MR reference parameters currently in use were derived from small, non-representative samples and are thus prone to selection bias.
- To correlate MR findings with clinical examination results, metabolomic and genome-wide analysis in order to help elucidate the complex associations that exist between risk factors and diseases as well as incident clinical outcomes.

The exact MR protocol is given elsewhere [15]. Additionally to the standard whole-body MRI protocol, men have the option to undergo contrast-enhanced cardiac MRI and MR angiography and women cardiac MRI and MR mammography. Participants with a drug allergy or allergy to any kind of contrast agent are excluded from the contrast-enhanced modules and only undergo standard protocol [14].

B. KORA

KORA (Cooperative Health Research in the Region Augsburg) is a research platform for population-based surveys and subsequent follow-up studies in the south of Germany. The main research areas are lifestyle and environmental risk factors for chronic diseases like diabetes, cardiovascular and lung disease and integrating these with functional genomics, as well as health economics [16].

KORA was established in 1996 to continue and expand the MONICA project in Augsburg (1984-1995). The KORA cohort comprises about 18,000 participants drawn from the population registry as a random sample of all 25- to 74-year-old German residents in the city of Augsburg and its two adjacent counties Augsburg and Aichach-Friedberg. Since 1984, there have been four surveys of initial examinations conducted at five-year intervals (S1-S4). Regular follow-up information is collected by questionnaire and re-examinations in addition to vital status information and disease validation from the general practitioner of the participant . Since 2004 an extensive biobank has been set up. In 2013-2014 the KORA-FF4 study was conducted (2279 participants), the 14-year follow up study of the KORA-S4 study (1999-2001; 4261 participants).

A subgroup of participants was selected to undergo a whole-body MRI protocol, the KORA-FF4 MRI substudy (2013-2014, 400 participants with diabetes, prediabetes and controls aged 38-72). It was designed as a case control study to assess metabolic and cardiovascular disorders [17]. For further details on the substudy design we refer to Hetterich et al. [17].

C. Generation R

The Generation R Study is a population-based prospective cohort study, which is initiated in Rotterdam, the Netherlands, from fetal life until adulthood. The study is designed to identify the early environmental and genetic causes and causal pathways leading to normal and abnormal growth, development and health during fetal life, childhood and adulthood. The study focuses on six areas of research: maternal health; growth and physical development; behavioral and cognitive development; respiratory health and allergies; diseases in childhood; health and healthcare for children and their parents.

Main exposures of interest include environmental, endocrine, genetic and epigenetic, lifestyle related, nutritional and socio-demographic determinants. In total, $9,778$ mothers with a delivery date between April 2002 and January 2006 were enrolled in the study. Response at baseline was 61 %, and general follow-up rates until the age of 6 years exceed 80 %.

Data collection in mothers, fathers and children include questionnaires, detailed physical and ultrasound examinations, behavioral observations, and biological samples. From the age of 5 years, regular detailed hands-on assessments are performed in a dedicated research center including advanced imaging facilities such as Magnetic Resonance Imaging (MRI). Eventually, results forthcoming from the Generation R Study contribute to the development of strategies for optimizing health. The MRI-study comprises about 4000 children aged 9, and its aim is to assess cardiac, pulmonary, fat, and liver parameters [18], [19].

III. DATA PROCESSING TASKS

In this section three main directions for the processing of heterogeneous epidemiological data. We discuss the problems related to segmentation challenges in airway image analysis, and the multi-variate visual analytics approaches for hypothesis generation and evaluation. For discussions of further computer science analysis of epidemiological data, we refer the readers among others to the works of Preim et al. [7], Toennies et al. [20], Botha et al. [21].

A. Image Processing: MRI-based Airway Segmentation and Analysis Example

Contemporary MRI techniques allow one to obtain the images of airways, which include nose, nasopharynx, oropharynx, hypopharynx, larynx, trachea, and lungs, with high resolution and rather fine level of details [22]–[24]. The nonionizing nature makes this modality especially attractive for paediatric patients and pregnant women or for scientific, for instance, epidemiological use [25].

For example, the airway-related research tasks in SHIP, KORA, and Generation R include (but are not limited to)

- lung segmentation and volumetry
- evaluation of tracheal anatomy
- analysis of pharyngeal structures

In SHIP, a 3D method for lung segmentation for healthy subjects was proposed [26]. The approach was found to be accurate (over 95% accordance with expert readings). Moreover, the ground truth was acquired from two independent experts and interreader agreement was about 93.5%, which shows that the automatic result accuracy lies close to the inter-reader variability. The method was successfully applied to available lung data from SHIP-2 and SHIP-TREND-0.

A pilot study on trachea segmentation was started and some preliminary results were obtained [27].

A study on pharynx segmentation was conducted and a minimally interactive approach for segmentation of pharynx in T1-weighted axial head sequence was proposed [28], [29]. The automatic part of the approach consisted of three steps: smoothing, thresholding, 2D and 3D connected component analysis. The processing time for 1 dataset was less than one minute to extract the pharyngeal structures. The approach was evaluated quantitatively on 30 data sets using region-based and edge-based measures. Thereafter, a context-based automatic algorithm for segmenting pharyngeal structures was proposed [30]. It consisted of a pipeline of steps including pre-processing to extract coarse 3D objects, classification of the objects, visual feature space analysis, and silhouette coefficient computation to segregate pharynx from other structures automatically, and post-processing to refine the shape of the identified pharynx. This approach was further extended with an context-based automatic segmentation algorithm delineating the fat pads to complete the analysis of the pharyngeal region [31].

For KORA data an algorithm for automated lung segmentation was proposed and applied to available 400 datasets [32]. Here, the data was similar, since the participants were adults, to SHIP with a bit lower quality. In both studies subjects were placed in the supine position, and the acquisition was performed in the middle inspiration phase. Therefore, the MRI defined lung volumes were not directly comparable to spyrometry-based volumes.

In the Generation R, a child cohort was used. Here, MR technique was not so easily implementable, since the participants might be scared of the closed environment or the necessity to lie still for some amount of time. Therefore, two repeated pyrometer controlled scans were performed per subject. Additionally, a mock scanner was introduces, where children trained to lie within the MR scanner in a friendly way and got used to the scanner protocols. Since children anatomy can vary widely due to the different stages of growth, anatomical assumptions used to develop algorithms for adult data might not hold. Hence, the methods proposed for SHIP and KORA data may not be directly applicable for such data and an specialized solution was proposed [33].

B. Visualization of Heterogeneous Epidemiological Data

The analysis of electronic health record data has recently gained attention in the visualization community. There has been an IEEE VIS 2014 workshop on Visualizing Electronic Health Record Data (EHRVis) and since 2010 there is a workshop on Visual Analytics in Healthcare (VAHC).

Rind et al. [34] provided an overview of methods that were presented until 2011. A very recent review of the literature was presented by West et al. [35]. Shneiderman et al. [36] point out that health record data are getting more complex by combining different data sources including clinical, personal, and public health information. Botha et al. discussed the main challenging directions in medical visualization using the cohort study data [21]. Preim et al. presented an analysis of visual processing of heterogeneous epidemiological data as well as an overview of visual analytics tools for epidemiology [7].

Many of the existing approaches on visual analysis of health record data investigate time series data, where one attribute is being tracked over time involving many time steps and a larger number of subjects. For example, Hinz et al. [37] investigated patients with diabetes, who were classified into four groups and for whom the development over time was analyzed. In cohort studies, where participants are being screened every few years, one typically compares some few points in time (mostly only two) such that this type of analysis involving time series visualizations is not so relevant. Other approaches consider geospatial data visualizations. This is useful, if one is interested in seeing how diseases spread, cf. [38]. Such a geospatial approach is relevant for cohort studies when a cohort was recruited from a larger region, e.g., whole nations or even continents.

An approach by Zhang et al. [39], Cohort Analysis via Visual Analytics (CAVA), uses different types of standard visualization methods that are coupled using coordinated views. Their idea is to allow for a selection of a cohort, then run different analytics methods on them and choose a visual representation of a selected analytics outcome. This is a powerful tool, but for multi-variate analysis is a bit limited and the integration of heterogeneous data is not fully employed. In particular, this approach (as well as all the others mentioned above) is not considering any medical imaging data. An approach that considers shape variation of tissues extracted from medical imaging data was presented by Busking et al. [40]. The shape variation of brain ventricles from a cohort were visualized in a shape space, where similar shapes would be shown closer to each other. Steenwijk et al. [41] presented an approach were they derived potential descriptive features from medical imaging data. As such they created a multi-dimensional feature space. Similarly, Oeltze et al. [42] presented an approach where descriptive perfusion parameters were derived and used in an interactive ischemic stroke analysis using parallel coordinate plots. However, all these approach only consider information extracted from imaging data and no additional information about the subjects.

Klemm et al. [43], [44] used a spine segmentation algorithm and extracted the curvature of the spine, which was then fed to a clustering approach. The clusters were visually investigated using color coding on volume visualizations and related to gender and whether back pain was reported. In a follow-up study, more information about the patients was incorporated for the clustering. Similarly, Angelelli et al. [45] proposed the combination of heterogeneous data by user information on subjects including age as well as derived features from diffusion tensor imaging of the brain. They put together a system with coordinated views on different aspects of the data using scatter plots, bar charts, etc. in conjunction with a volume visualization. These studies are very targeted at a given problem that they try to solve, i.e., they are focused on testing a hypothesis for a given problem.

In our opinion, a promising direction would be to develop a general approach that uses a general concept for the integration of heterogeneous data (medical imaging data, health record data, and personal data) even considering genetic information. One could do that introducing a general framework for multivariate analyses of the multi-dimensional feature space for hypothesis validation, which includes an interactive tool for semi-supervised classification supporting hypothesis generation, and presenting a comparative visual analysis for multiple time points in longitudinal studies.

IV. CONCLUSIONS AND OUTLOOK

In this work, we presented several contemporary epidemiological studies and the related image analysis tasks. The highly relevant and challenging research directions were identified. Namely, airway segmentation and analysis tasks as well as the visual analytics problems were discussed. Moreover, we presented the available solutions and defined future challenges for a computer scientist.

We claim that such projects as SHIP, KORA, and Generation R represent a huge potential for computer science researchers working with big data and open new challenging research directions.

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