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NEW STUDY

The Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES) project—design, population and data harmonization of a large-scale, international study

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Abstract There is a public health demand to prevent health conditions which lead to increased morbidity and mortality among the rapidly-increasing elderly population. Data for the incidence of such conditions exist in cohort studies worldwide, which, however, differ in various aspects. The Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES) project aims at harmonizing data from existing major longitudinal studies for the elderly whilst focussing on cardiovascular diseases, diabetes mellitus, cancer, fractures and cognitive impairment in order to estimate their prevalence, incidence and cause-specific mortality, and identify lifestyle, socioeconomic, and genetic determinants and biomarkers for the incidence of and mortality from these conditions. A survey instrument assessing ageing-related conditions of the elderly will be also developed. Fourteen cohort studies participate in CHANCES with 683,228 elderly (and 150,210 deaths), from 23 European and three non-European countries. So far, 287 variables on health conditions and a variety of exposures, including biomarkers and genetic data have been harmonized. Different research hypotheses are investigated with meta-analyses. The results which will be produced can help international organizations, governments and policy-makers to better

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understand the broader implications and consequences of ageing and thus make informed decisions.

Keywords Cohort · Ageing · Elderly · Meta-analysis

Introduction

The elderly population of the world is rapidly increasing as a result of an overall increase in life expectancy and other demographic characteristics [1, 2], leading to an increasing awareness of the need to promote healthy ageing in older populations. According to the World Health Organization (WHO), successful ageing is defined as a process of optimizing opportunities for health, participation and security in order to enhance quality of life as people age. Being strongly associated with older age, chronic diseases have become leading causes of morbidity, disability and mortality world-wide [3]. In addition there are often shared risk factors or mechanisms between the ageing process and the occurrence of these chronic diseases, for example, oxidative processes that cause DNA damage [4]. Therefore better prevention strategies for chronic diseases can be developed as a result of clinical and epidemiological research on the determinants of healthy ageing in different populations.

A large proportion of the morbidity and mortality burden in the elderly population is attributed to a relatively small group of health conditions, namely cardiovascular diseases (CVDs) and diabetes, cancer, osteoporotic fractures and cognitive impairment which are highlighted in the paragraphs below.

Cardiovascular diseases and diabetes

Cardiovascular diseases are the leading causes of death worldwide, accounting for approximately 17.5 million deaths every year [5, 6]. Despite a notable decrease in CVD mortality in high-income countries, coronary heart disease remains a leading cause of death in older men and women in those countries; in the United States, more than 83 % of persons who die of CVDs are aged 65 or older [7, 8]. Stroke and ischemic heart disease are leading causes of lost disability-adjusted life-years in high-income countries and of death worldwide [9].

According to WHO, an estimated 3.4 million people died from consequences of diabetes mellitus in 2004 [10]. About two-thirds of diabetes deaths occur in subjects aged 65 or more [10]. Population ageing is expected to affect also the prevalence of diabetes; in the 2012 report of WHO it is predicted that the number of deaths due to diabetes, primarily from life-style-associated type-2 diabetes, will double between 2005 and 2030 [10].

Cancer

According to Ferlay et al. [11], in 2008 an estimated 12.7 million new cancer cases and 7.6 million cancer deaths occurred worldwide. Overall cancer incidence increases with age: globally, 47 % of all malignant tumours occur in people aged over 65 years, and by 2020, approximately 60 % of all cancers are expected to be diagnosed in elderly patients [12]. Cancer-related mortality also increases with age: 55 % of all deaths due to cancer occur in people aged 65 years or older [12].

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Osteoporotic fractures

As people age, the risk of fractures increases, mainly due to a decline in bone mass and muscle [13]. In the year 2000, there were an estimated 9 million age-related fractures, approximately a third (35 %) of which occurred in Europe [14]. Age-related osteoporotic fractures represent one of the most important causes of functional impairment, disability, poor quality of life and death among the elderly [15–17].

Cognitive impairment

The disability caused by mental and neurological disorders is high in all regions of the world [18, 19]. However, compared to the implications related to the above-indicated diseases, it is less important in low-income countries, mainly because of the large burden of communicable diseases and accidents in those regions which lead to early death. Nevertheless, neuropsychiatric disorders account for 17.6 % of all years lived with disability (YLDs) even in low-income regions such as Africa [20]. There are about 26 million sufferers from Alzheimer's disease (AD) world-wide. AD and other forms of dementia are a disease of the elderly: 86 % of the disability-adjusted life years (DALYs) and 95 % of deaths attributable to this group of health conditions occur after age 65. AD has a profound impact on the patient, the family and the community but with the current trend in population ageing the global number of patients is expected to increase four times by 2050.

High quality, longitudinal data, for the incidence of these conditions, are thus essential in order to identify determinants of health in ageing populations, and their implications in terms of disease burden and economic costs. These data are typically collected in large scale cohort studies which do exist in different populations across Europe, USA, Canada and, Australia [21–25] but also in low to middle income countries [26]. All of these studies have produced important results with respect to the determinants of the above-mentioned health conditions with elimination of possible sources of selection and information bias due to the methodological advantage of their prospective nature. Owing to the variety of (a) population characteristics, (b) methods and instruments employed, for measuring outcomes and exposures, (c) statistical analyses undertaken, and (d) power to detect associations of low magnitude, the determinants identified, as well as, the magnitude of the estimated associations may differ across these studies. It would be, therefore interesting from a public health point of view, to be able to combine the information contained in many cohort, or, multi-cohort studies through harmonization of relevant large-scale data and provide overall estimates, even for well known associations.

The CHANCES (Consortium on Health and Ageing: Network of Cohorts in Europe and the United States) (http://www.chancesfp7.eu/) project aims at combining data from existing major longitudinal studies among the elderly in order to address the below indicated objectives.

Objectives

CHANCES is a coordinated multi-country study which aims to harmonize data from on-going prospective cohort studies in Europe and the USA in order to produce evidence on ageing-related health characteristics and on determinants of healthy ageing among the elderly in these countries. More specifically, for the above mentioned health conditions (CVDs and diabetes mellitus, cancer, osteoporotic fractures and cognitive impairment) the project aims at: (a) Estimating their incidence and associated cause-specific mortality, (b) estimating their prevalence and related disability, and (c) identifying ageing- and socioeconomic-related determinants (risk factors, e.g., comorbidities, dietary habits) of these conditions and of the resulting disability, and mortality in the elderly. Another research area of the project relates to genetic and biomarker determinants of mortality among the elderly. Additionally, a novel, brief and reliable survey instrument for the assessment of health and ageing related conditions and outcomes of the elderly population will be developed based on systematic assessment of previously used measures.

Methods

Source population

Cohorts from fourteen studies are included in the project: the Cohort of Swedish Men (COSM) [27], selected centres of the European Prospective Investigation into Cancer and nutrition (EPIC)—Elderly study [28], the Epidemiological Study on Chances for Prevention, Early Detection, and Optimized THERapy of Chronic Diseases at Old Age (ESTHER) study [29], the Health, Alcohol and Psychosocial factors in Eastern Europe (HAPIEE) study [30], the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) study [31], the Northern Sweden Health and Disease Study (NSHDS) study [32], the Rotterdam Elderly study [33], the Survey Europe on Nutrition in the Elderly: a Concerted Action (SENECA) study [34], the Survey of Health, Ageing and Retirement in Europe (SHARE) study [35], the Swedish Mammography Cohort (SMC) [36], The

Table 1 Selected characteristics of the cohorts included in the CHANCES project

No	Study[a]	Country[b]	Biological samples[c]	Period of enrolment	Follow-up	Participants (N)/elderly[d] (N)	Men (%)	Age (years) Median (range)	References
1	COSM	SE	Yes (in a subsample)	1997	1997–today	22,661[e]/22,661	100	69 (60–79)	Harris et al. in press
2	EPIC-Elderly (selected centres)	DK, GR, NL, ES, SE[f]	Yes	1992–2000	1992–2011	40,663/40,663	37	63 (60–86)	Trichopoulou et al. [28]
3	ESTHER	DE	Yes	2000–2002	2000–today	9,949/6,545	45	63 (50–75)	Schöttker et al. [29]
4	HAPIEE	CZ, PL, RU	Yes	2002–2005	2002–2010	36,030/30,148	47	58 (45–74)	Peasey et al. [30]
		LT[g]		2006–2008	2006–2010				
5	MORGAM[h]	AU, DK, FI, FR, DE, IT, PL, ES, SE, UK	Yes	1982–1997	1982–2010	204,192/44,402	59	52 (18–99)	Evans et al. [31]
6	NHS	USA	Yes	1976	1976-present	121,700/26,763	0	40 (32–57)	Colditz and Hankinson, [35]
7	NIH-AARP	USA	No	1995–1996	1995–2006	566,398/366,919	60	62 (50–71)	Schatzkin et al. [40]
8	NSHDS (Subcohort VIP)	SE[f]	Yes	1985–2013	1995–today	96,807/24,025	50	50 (18–74)	Hallmans et al. [32]
9	Rotterdam Elderly Study	NL	Yes	1990	1990–today	14,926/9,857	41	63 (45-106)	Hofman et al. [33]
10	SENECA[i]	BE, DK, FR, IT, NL, ES, CH, GR[i], HU[i], NO[i], PT[i], PL[i]	Yes	1988–1989	1993 and 1999	2,039/2,039	50	72 (69–77)	De Groot and van Staveren, [34]
11	SHARE[j]	AT, BE, CH, CZ, DE, DK, EE, ES, FR, GR, HU, IE, IL, IT, NL, PL, PT, SE, SI	Yes (but only in DE)	2004–2013	2004–today	86,290/82,626	44	62/(14–104)	Börsch-Supan et al. [35]
12	SMC	SE	Yes (in a subsample)	1987–1990	1987–today	19,581/19,581[e]	0	69 (60–83)	Wolk et al. [36]
13	The Tromsøstudy	NO	Yes	1994–1995	1994–2010	5,851/5,851	45	69 (60–97)	Jacobsen et al. [37]
14	Zutphen Elderly Study	NL	No	1985	1985–2000	878/878	100	71 (64–85)	Buijsse et al. [38]

[a] COSM: the Cohort of Swedish Men; EPIC: European Prospective Investigation into Cancer and nutrition; ESTHER: Epidemiological Study on Chances for Prevention, Early Detection, and Optimized THERapy of Chronic Diseases at Old Age; HAPIEE: the Health, Alcohol and Psychosocial factors in Eastern Europe; MORGAM: MOnica Risk, Genetics, Archiving and Monograph; NHS: Nurses Health Study; NIH-AARP: National Institutes of Health-American Association of Retired Persons Diet and Health; NSHDS: Northern Sweden Health and Disease Study; SENECA: Survey Europe on Nutrition in the Elderly: a Concerted Action; SHARE: Survey of Health, Ageing and Retirement in Europe; SMC: Swedish Mammography Cohort

[b] Austria (AT); Australia (AU); Belgium (BE); Czech Republic (CZ); Germany (DE); Estonia (EE); Sweden (SE); Switzerland (CH); Denmark (DK); Greece (GR); The Netherlands (NL); Portugal (PT); Spain (ES); Finland (FI); France (FR); Italy (IT); Poland (PL); United Kingdom (UK); United States of America (USA); Lithuania (LT); Russia (RU); Hungary (HU); Norway (NO); Ireland (IE); Israel (IL); Slovenia (SI)

[c] For details on the type and number of samples, aliquots and markers available in each study the reader should contact the cohort PIs (contact information available from CHANCES website: www.chancesfp7.eu)

[d] In all cohorts elderly were defined as people who, at recruitment, were 60 years of older except for HAPIEE, SHARE and NHS for which elderly was defined as people who at recruitment were 50 years or older

[e] Total number of participants in COSM and SMC were 48,553 and 39,988 respectively, but only those who were 60 years or older at recruitment (elderly) were included in the CHANCES project

[f] EPIC Elderly and NSHDS overlap with respect to the Umea cohort of elderly (≥60 years old) participants

[g] Lithuanian cohort joined the HAPIEE study approximately 4 years after the start of the project in Russia, Poland and the Czech Republic

[h] For the enrolment period, age range and the number of participants of each MORGAM cohort, please visit: http://www.thl.fi/publications/morgam/cohorts/tables/base_summary.htm

[i] The numbers given in the Table have been calculated after excluding data from Greece, Hungary, Norway, Portugal and Poland for which only baseline information was available

[j] SHARE conducts end-of-life interviews for deceased respondents. These end-of-life interviews are administered to relatives or other persons close to the deceased

Tromsø study [37] and the Zutphen Elderly study [38], as well as two studies conducted in USA: the Nurses Health Study (NHS) [39] and the National Institutes of Health-AARP (formerly known as American Association of Retired Persons Diet and Health Study, NIH-AARP) study [40]. Table 1 provides key characteristics of those cohorts which have been used, so far, in analyses of CHANCES projects. Overall, 683,228 elderly, from twenty countries of the European Union, three other European countries, and three non-European countries are included in the cohorts participating in CHANCES projects. To date, 150,210 deaths have occurred in these cohorts. In most CHANCES participating cohorts, elderly are defined as those who were 60 years or older at recruitment. In HAPIEE, SHARE and NHS people who were 50 years or older at recruitment are included in the CHANCES project.

The CHANCES project has been approved by the Ethics Committees of the participating institutions.

Data assessment and harmonization

Since the data in the CHANCES project have been collected within the framework of independent cohorts, with different protocols for data collection and distinct original research foci, data standardization and harmonization throughout is a major priority task. Harmonization procedures involve deriving sensible and feasible definitions of new common variables for the data analyses to be carried out in CHANCES.

The data standardization and harmonization procedures are largely based on the experience from the MORGAM project [31], cohorts of which also participate in CHANCES. Harmonization of variables in specific fields is based on previous experience of partners in the project—e.g. harmonization of dietary data benefit from the experience of the HECTOR (Healthy Eating Out) study [41] undertaken within the EPIC study, as well as from other studies on nutrition and health, such as SENECA [34]. Data assessment procedures include examination of: availability and comparability of data from each cohort; questionnaires and measurement procedures used in the individual cohorts; methods for the collections of data on health outcomes (medical examination, interview, registry information, self reports etc.) and of blood samples, and; indicators of the quality of the existing data (e.g., proportion of missing values).

Currently, availability and characteristics of the data on each research area of CHANCES were assessed for each cohort. Joint variables were defined based on the results of the assessment and research interests. A CHANCES project-specific wiki site has been developed and used for collecting relevant information from the centres and documenting the cohort descriptions, availability and assessment of the data, the CHANCES variable definitions and the rules for deriving the common (harmonized) variables from the local data sets. The wiki site, where CHANCES investigators from the different centres have access, has been a powerful tool for drafting, commenting, and finalizing the various documents.

Table 2 Research proposals developed within the CHANCES project by outcome of interest (up to 31/1/2013)

Number of projects	Outcome of interest	Research topics investigated within proposed projects
8	Cancer incidence	Smoking; vitamin D; food groups/dietary patterns; alcohol consumption; socio-economic position; disability-adjusted life years (DALY); population attributable fractions for major determinants
17	Cardiovascular diseases and diabetes	Prediction models and adapted prediction scores; HbA1c levels; smoking; alcohol consumption; education; obesity; dietary patterns; Vitamin D; DALY; population attributable fraction for major determinants
5	Fractures and osteoporosis	Socioeconomic status; weight and weight changes; DALY; population attributable fraction for major determinants; excess mortality following hip fractures
6	Cognitive impairment and Alzheimer's disease	Cardiovascular diseases; lipid intakes; dietary patterns; sedentary behavior; lifetime smoking; DALY
16	Disabilities and mortality	Adapted prediction scores; HbA1c levels; smoking; alcohol consumption; education; self-perceived health; physical activity; obesity; dietary patterns; Vitamin D; telomere length; DALY; population attributable fraction for major determinants; predictive value of potential frailty criteria
2	Genetic: telomere length	Lifestyle factors; height

The harmonization procedure can be briefly described through the following steps:

1. A list of exposures and health outcomes of potential interest for the CHANCES project was initially constructed by the Consortium;

2. For each of these a priori defined exposures/outcomes, relevant variables of similar conceptual construct were selected from each participating cohort and compared between cohorts based on detailed information regarding their assessment methods and coding;
3. Based on the data available from the cohorts, new common variables were proposed by the CHANCES partners with research interests on the specific variables. The proposals were reviewed by all partners prior to acceptance as CHANCES variables.
4. The CHANCES variables were generated from the available data in each cohort. The algorithms to generate the CHANCES variables varied in complexity, depending on the level of agreement between the locally available data and the CHANCES variable. For example, there was variation in the smoking questionnaires used in the different cohorts, but it was possible to derive common variables on current daily smoking for all cohorts and the number of years of daily smoking for nearly all cohorts. The algorithms used for generating the variables in each cohort were documented.
5. The availability, comparability and quality of the data for the variables from each cohort were assessed and documented.

Available data on exposures and outcomes

Within the first 3 years of the project, the quality and availability of data were assessed and variables were defined for the following outcomes/exposures:

Outcomes: health conditions and mortality

The following outcomes were included: lung function; prevalence of hypertension, incidence and family history of coronary heart disease, stroke and diabetes; prevalence and incidence of cancer (by organ of origin); prevalence and incidence of fractures and osteoporosis; prevalence and incidence of depression, cognitive impairment and dementia; multi-morbidity; mortality (by cause); disability and frailty; quality of life; and self-perceived health.

Exposures

The following exposures were included:

Lifestyle: (including tobacco smoking, drinking status, physical activity); anthropometry (including weight, height, waist/hip circumference); socioeconomic status (including education, marital status); medical history (including use of drugs; reproductive history);dietary factors (including total energy intake, intake of specific macro-and micronutrients, foods and food groups, ethanol intake); and blood biomarkers [including ApoA1, ApoB, CRP, GGT, glucose, glycated haemoglobin, total and HDL cholesterol, triglycerides, vitamin D; oral glucose tolerance test; biomarkers of oxidative stress (hydroperoxides), antioxidant status (biological antioxidant potency) and redox status (total thiols)].

So far, 409 variables have been proposed; 287 of them have been finalized for use in CHANCES research while for an additional 122 variables harmonization is under development.

Statistical analyses

Taking into account the inherent differences across cohorts in measurement of exposures/outcomes, statistical analyses for the different research hypotheses are carried out by means of meta-analysis. Cohorts with missing information on exposures or outcomes under study were excluded from these meta-analyses. Given the large number of different cohorts participating in CHANCES and considering the different policies for data sharing in each of them, two approaches are used for the pooled data analyses, which are coordinated by ad-hoc writing groups. The first is to share individual-level data after signing a data transfer agreement. The second approach is to analyze the data locally in the participating centres using programme scripts provided by the writing groups and to share the results of the local analyses for a meta-analysis.

Up to January 2013, 54 research proposals focusing on different aspects of healthy ageing relevant to the CHANCES project have been developed. These are shown in Table 2 by area of research.

The study periods differ among cohorts. Analyses are adjusted for age and calendar period to take into account these differences. In addition, it is possible to explore whether associations differ by time.

Discussion

As the proportion of older people and the length of life increases throughout the world, issues like maintaining good health and productivity for longer periods and sustaining the sense of well-being become crucial for the lives of the growing number of older people around the world, as well as, for the patterns of health care spending in both developed and developing countries. Therefore the need to identify determinants of healthy ageing is very important for research and policy. International and multi-country large-scale data can be used effectively towards this direction.

Pooled analyses of data collected in independent studies is a cost-efficient approach to address health research questions for which, single studies, are often underpowered to investigate. CHANCES is effectively building an infrastructure of comprehensive and comparable data on health conditions and factors that may influence these conditions among older people in order to understand the implications of ageing at the individual and societal level. Harmonization of such data is a key requirement, and a major challenge for CHANCES has indeed been the ability to assure the quality and harmonize data collected in the different cohorts. The experience of CHANCES so far is that harmonization of data on diverse health outcomes and exposures, albeit complex, is possible and can provide a unique data set to address a variety of research questions, some of which could not otherwise be investigated (i.e., within any of the participating cohorts). Large datasets resulting from pooling independent studies represent a formidable tool for research, and provisions should be developed and implemented to allow the research community at large to access them. In CHANCES, a use and access strategy has been successfully developed and implemented for researchers who were proposed by the various participating cohorts, with the plan to develop rules for expanding it to researchers outside the consortium.

Already the dividends for such an enterprise have been apparent for genetic researchers in the many large consortia established to interrogate pooled GWAS data. However the challenges for phenotype and risk factor data pooling are somewhat different from those of laboratory quality assurance. Much data on risk factors have a social context and are patterned in different ways in different countries, as is most obvious in attempts to codify diet or occupational physical activity, or in the routine testing that may take place in primary care to assign outcome diagnoses (e.g. HbA1c thresholds for diabetes). The benefit from investing care in these harmonization stages is that subsequent analyses may be more sensitive and less subject to misclassification and bias.

Limitations of the CHANCES projects are (1) the need to rely on data collected according to different protocols; (2) the variable level of information available across studies on exposure and—to a lesser extent—outcome variables; (3) the lack of harmonized information of potential confounders (e.g., occupational exposures); (4) the heterogeneity in cohort definition (e.g., age range at baseline, period of follow-up); (5) the limited amount of repeated measurements of exposure. These limitations imposed some constraints to the type of analyses that can be performed within CHANCES.

In conclusion CHANCES has created a large-scale, multi-national, ageing-related database with comparable demographic and health indicators. This resource not only can reveal historical trends but also identify factors (modifiable or not) which can help international organizations, governments and policy-makers to better understand the broader implications and consequences of ageing and thus make informed decisions.

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