International Journal of Cardiology 228 (2017) 495–500

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

The LifeLines Cohort Study: Prevalence and treatment of cardiovascular disease and risk factors☆

M. Yldau van der Ende [a,1], Minke H.T. Hartman [a,1], Yanick Hagemeijer [a], Laura M.G. Meems [a], Hendrik Sierd de Vries [b], Ronald P. Stolk [b], Rudolf A. de Boer [a], Anna Sijtsma [b], Peter van der Meer [a], Michiel Rienstra [a], Pim van der Harst [a,*]

[a] University of Groningen, University Medical Center Groningen, The Department of Cardiology, Groningen, The Netherlands
[b] University of Groningen, University Medical Center Groningen, LifeLines Cohort Study, Groningen, The Netherlands

ARTICLE INFO

Article history:
Received 4 July 2016
Accepted 5 November 2016
Available online 11 November 2016

Keywords:
Cardiovascular disease
Risk factors
LifeLines
Prospective study
Epidemiology

ABSTRACT

Background: The LifeLines Cohort Study is a large three-generation prospective study and Biobank. Recruitment and data collection started in 2006 and follow-up is planned for 30 years. The central aim of LifeLines is to understand healthy ageing in the 21st century. Here, the study design, methods, baseline and major cardiovascular phenotypes of the LifeLines Cohort Study are presented.

Methods and results: Baseline cardiovascular phenotypes were defined in 9700 juvenile (8–18 years) and 152,180 adult (≥18 years) participants. Cardiovascular disease (CVD) was defined using ICD-10 criteria. At least one cardiovascular risk factor was present in 73% of the adult participants. The prevalence, adjusted for the Dutch population, was determined for risk factors (hypertension (33%), hypercholesterolemia (19%), diabetes (4%), overweight (56%), and current smoking (19%)) and CVD (myocardial infarction (1.8%), heart failure (1.0%), and atrial fibrillation (1.3%)). Overall CVD prevalence increased with age from 9% in participants < 65 years to 28% in participants ≥ 65 years. Of the participants with hypertension, hypercholesterolemia and diabetes, respectively 75%, 96% and 41% did not receive preventive pharmacotherapy.

Conclusions: The contemporary LifeLines Cohort Study provides researchers with unique and novel opportunities to study environmental, phenotypic, and genetic risk factors for CVD and is expected to improve our knowledge on healthy ageing. In this contemporary Western cohort we identified a remarkable high percentage of untreated CVD risk factors suggesting that not all opportunities to reduce the CVD burden are utilised.

1. Introduction

Healthy ageing is one of the topics in 'Horizon 2020 — Personalising Health and Care'; "the biggest European Union Research and Innovation programme" aimed to ensure Europe's global competitiveness [1]. The goal of Horizon 2020 is to gain insight in factors and interactions comprising the development and maintenance of good health and the presence and progression of common diseases and disabilities. Throughout life, underlying genetic make-up and modifiable lifestyle factors such as behavior, environment and nutrition interact in this process in varying degrees.

Despite recent progress with novel therapies, a major threat to healthy ageing is cardiovascular disease (CVD) [2–5]. CVD affects the majority of adults over 60 years of age. In 2012, it was estimated to be the cause of 17.3 million deaths worldwide [6]. In the EU, the main cause of death is CVD and accounts for 1.9 million deaths every year [2]. CVD also causes substantial morbidity with an annual hospital discharge rate of 2400 per 100,000 population.

Epidemiologic studies in the past, including the Framingham Heart study initiated in 1948, have contributed enormously to our understanding of CVD and its risk factors [7]. However, after identification of risk factors with large effect size the power of many previous studies to test for smaller effect sizes or gene-environment interactions is limited. In addition, these cohorts date back to the 90s, and advances in treatment as well as changes in behavior and lifestyle have occurred. To further our knowledge of genes, environment and their interaction determining CVD and healthy ageing contemporary population-based biobanks are essential. The LifeLines Cohort Study, established in 2006, is a contemporary observational population-based study designed to enhance our understanding of healthy ageing in the 21st century [8]. Baseline characteristics of 167,729 inhabitants of the Northern part of the Netherlands have been collected. The first follow-up visit at five years is ongoing and the second 10-year follow-up visit is scheduled.

☆ These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author: University of Groningen, University Medical Center Groningen, Department of Cardiology, Hanzeplein 1, 9700 RB Groningen, The Netherlands.
E-mail address: p.van.der.harst@umcg.nl (P. van der Harst).

[1] Authors M. Yldau van der Ende, BSc. and Minke H.T. Hartman, M.D., contributed equally to the current study.

http://dx.doi.org/10.1016/j.ijcard.2016.11.061

LifeLines participants will be followed up to 30 years. LifeLines is a facility that is open for all researchers, information on application and data access procedures is summarized on www.lifelines.net. Here we summarize the baseline characteristics, and provide detailed information on the prevalence of CVD, cardiovascular risk factors and treatment thereof. In addition, we aim to inform and encourage researchers to consider LifeLines Cohort Study for their future research projects.

2. Methods

2.1. Overall design of the LifeLines Cohort Study

The overall design and rationale of the LifeLines Cohort Study have been described in detail elsewhere [8,9]. In brief, individuals living in the recruitment area aged between 25 and 50, were invited through their general practitioners (GP). Individuals were not invited when the participating GP considered the patient not eligible by reason of severe psychiatric of physical illness; limited life expectancy or insufficient knowledge of the Dutch language. In addition, inhabitants of the Northern provinces, who were not invited by their GP and not meeting above-mentioned reasons, could register themselves via the LifeLines website. After signing informed consent, participants received a baseline questionnaire and an invitation to a health assessment at one of the LifeLines research sites. During these visits, participants were asked whether their family members would also be willing to participate. Overall, 49% of the participants ($n = 81.652$) were invited through their GP, 38% ($n = 64.489$) via participating family members and 13% ($n = 21.588$) self-registered via the LifeLines website. In total, 167,729 participants were included from the end of 2006 until December 2013 and data of 167,016 participants were suitable for further analysis. The 5-year follow-up visit physical examination at the LifeLines research site is currently ongoing and the 10-year follow-up visit is planned. In addition, participants receive a follow-up questionnaire every 18 months. By using a third-party pseudo-anonymization system, records of GPs, pharmacies and other health and national registries are being linked with the LifeLines database. Data was analyzed for different pre-specified age categories, namely juvenile (aged 8–18 years), young and middle-age adults (≥18 and <65) and older aged (65+) participants. Data collection within LifeLines is dynamic, add-on studies are continuously implemented in LifeLines.

2.2. Cardiovascular data collection

2.2.1. Questionnaires

Self-reported questionnaires were used to obtain information on demographics, family composition, work and education, general health, lifestyle, environmental and psychosocial factors. Lifestyle and environment questions included information on physical activity (SQUASH questionnaire), nutrition (FFQ questionnaire), smoking, physical environment and daytime activities. Psychosocial factors included questions on perceived quality of life, health perception, personality, stress and social support [8]. Drug use was collected in the questionnaire and categorized using the general Anatomical Therapeutic Chemical Classification System (ATC) codes. We recently reported a global overview of the definitions of CVD and non-CVD in a subpopulation of LifeLines [10].

2.2.2. Physical examination

At baseline, participants were invited to visit one of twelve LifeLines Research sites to undergo a physical examination and a series of tests. During the baseline visits height without shoes was measured with the SECA 222 stadiometer and rounded to the nearest 0.5 cm. Weight without shoes and heavy clothing was measured with SECA 761 scale and rounded to the nearest 0.1 kg. Waist and hip circumference was measured with SECA 200 measuring tape and rounded to the nearest 0.5 cm. Blood pressure was measured ten times during 10 min with Dynamap, PRO 100V2. The blood pressure registered was calculated by averaging the final three readings in mm Hg. Heart rate was collected and reported in beats per minute. Pulmonary function was measured once with Welch Allyn version 1.6.0.489 and a 12-lead electrocardiogram (ECG) was recorded with a Welch Allyn DT100 machine. Skin autofluorescence was measured at the lower arm with advanced glycation end products (AGE)-reader (AGEreader, DiagnOptics Technologies B.V., The Netherlands).

2.2.3. Biomaterial collection and biobanking

At the research sites, blood and 24-hour urine was collected from participants and transported to the central LifeLines laboratory in Groningen. For performing clinical chemistry analyses on fresh blood and 24-hour urine samples, part of the samples was directly transferred to the central laboratory of the University Medical Center Groningen (UMCG). From the remaining blood samples, part has been used for DNA isolation (from whole blood of all LifeLines participants aged 8 years and older) and was stored at −80 °C. Normalized DNA was stored at 4 °C. The remaining blood and 24-hour urine samples were stored at −80 °C and are available for future research questions. In addition to blood and urine, faeces of more than 50.000 participants have been collected and a hair scalp will be collected from all participants during the first follow-up visit.

2.2.4. Genotyping data

Currently, genome-wide genotyping data is available of 13,436 participants. These data have been generated using the Illumina CytoSNP-12v2 array, after which they were called in GenomeStudio (Illumina, Inc., San Diego, California, USA). Quality control was performed with PLINK, after which 268,407 SNPs and 13,436 samples remained.

2.2.5. Ultra-low-dose CT imaging

A substudy (IMALIFE) is currently being established on ultra-low-dose CT scanning of the thorax. To determine normal values of lung density, bronchial wall thickness and coronary calcium by age and gender, 12,000 randomly assigned participants will undergo CT scanning after signing additional informed consent.

For a complete overview of the available LifeLines data visit the LifeLines website at www.lifelines.net and the online data catalogue at https://catalogue.lifelines.nl/.

3. Definitions

3.1. Cardiovascular risk factors

Self-reported CVD risk factors were defined as present when they were affirmatively answered in the questionnaire and as being absent when answered negatively or missing. In addition, physical examination data at baseline visit was used to define and validate CVD risk factors specified by the following criteria (Supplementary Figs. 1–7 show the operationalization methods for defining cardiovascular risk factors). Overweight was defined as a body mass index (BMI) above 25.0 kg/m^2. In juvenile participants, overweight was defined according to World Health Organization (WHO) child growth standards with BMI-for-age [11].

Smoking included past and current smokers. Active smoking in adults was defined as having smoked the past month or now. Former adult smokers were defined as answering the question ‘have you stopped smoking’ confirmatively. Data on smoking was available in juveniles aged 13 years and over. Active smoking in juveniles was defined as answering the question “does your child still smoke” confirmatively. Former smoking was defined as answering the question “did your child smoke daily” confirmatively and followed by the question “does your child still smoke” answered negatively. The question “Being active for at least half an hour a day”, was the definition for active lifestyle in adults, which was obtained from the questionnaire as well. In juveniles aged 8 years and over active lifestyle was defined as doing sports or playing outside for more than 7 h a week. Cancer and blood clotting disorder were considered to be present when they were affirmatively answered in the questionnaire. The Systematic Coronary Risk Evaluation Project (SCORE) risk was determined in adult participants with available cholesterol and blood pressure measurements [12].

3.2. Cardiovascular disease

By questionnaire, participants were asked to report presence of CVD and related symptoms. Operationalization methods were generated for defining (silent) myocardial infarction (MI), heart failure and atrial fibrillation (Supplementary Figs. 8–11). With the help of these operationalization methods self-reported CVD or related symptoms were validated with biomarkers or cardiovascular medication. The total number of CVD per participant was determined. The definition for CVD was based on the ICD-10 and included all CVD that could be verified in the LifeLines database; MI, heart failure, atrial fibrillation, heart valve disorders, arrhythmia, aneurysm, stroke, thrombosis, atherosclerosis, narrowing carotid arteries and a history of coronary artery bypass grafting (CABG) [13].

3.3. Statistical analysis

Normally distributed continuous variables were presented with mean and standard deviation. Continuous variables not normally distributed were presented as medians with interquartile ranges (IQR) and categorical variables as percentages. The Chi-square test was used to compare frequencies of events in the middle (aged ≥18 and <65) and older (aged 65+) aged group. Differences in continuous variables, not normally distributed, were ascertained by two-sample Wilcoxon rank-sum (Mann–Whitney) test. Age and sex standardized estimates were calculated with standardized rates for the variables, defined as the weighted average of stratum-specific rates. These rates are averaged