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Heart disease in women and men

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CHAPTER 2

Prevalence and treatment of cardiovascular disease in the northern part of the Netherlands

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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 9,700 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 cohort, we identified a remarkable high percentage of untreated CVD risk factors suggesting that not all opportunities to reduce the CVD burden are utilized.

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 competitiveness¹. 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 behaviour, 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 worldwide⁶. In the EU, the main cause of death is CVD and accounts for 1.9 million deaths every year². CVD also causes substantial morbidity with an annual hospital discharge rate of 2,400 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 factors⁷. 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 century⁸. 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. 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.

METHODS

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 or 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 analysed 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.

Cardiovascular Data collection

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 support⁸. 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 LifeLines¹⁰.

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 were measured with SECA 200 measuring tape and rounded to the nearest 0.5 cm. Blood pressure was measured ten times during ten minutes with Dynamap, PRO 100V2. The blood pressure registered was calculated by averaging the final three readings in mmHg. 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).

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 Centre 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.

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.

Ultra-low-dose CT imaging

A substudy (IMA-LIFE) 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/>.

Definitions

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 Figures 1-7*) show the operationalization methods for defining cardiovascular risk factors). Overweight was defined as a body mass index (BMI) above 25.0kg/m². In juvenile participants, overweight was defined according to World Health Organization (WHO) child growth standards with BMI-for-age¹¹.

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 hours a week. Cancer and blood clotting disorders 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 measurements¹².

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 Figures 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.

Statistical analysis

Normally distributed continuous variables were presented with means and standard deviations. 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 across the weights of the general population, based on the population distribution of age and sex of adults 18 years and over (13,060,511) in the Netherlands in 2010. This is implemented with the *dstdize* command in STATA, an algebraically equivalent of the Cochran's formula¹⁴. Logistic regression was performed to assess the correlation between cardiovascular risk factors and CVD, presented with odds ratios. Adjustments for family relations were performed with the *cluster* option. Analyses were performed with STATA/IC version 13.0 (StataCorp LP, College Station, Texas, USA).

Ethics policy

Declaration of Helsinki: The Lifelines cohort study state that the study complies with the Declaration of Helsinki. The local ethics committee approved the research protocol and informed consent was signed by every participant.

RESULTS

The LifeLines cohort study population included 68,850 male and 83,330 female adults and 7,231 male and 7,605 female juveniles. In total 60,401 participants were part of 42,351 families, including first-, second- and third-degree relatives, generating 112,050 family clusters. The age and gender distribution of Lifelines participants differed substantially from the general population distribution in the Netherlands (*Figure 1 and Table 1*).

Table 1. Demographics and cardiovascular risk factors in the LifeLines cohort study

Characteristics	Juvenile 8-18 years	N	Adults 18-65 years	N	Adults 65+ years	N	Crude estimate	Standardized estimate
Age (years, mean \pm SD)	9.11 \pm 4.7	14,836	43 \pm 11	141,327	71 \pm 5	10,853	-	-
Female	51.3%	7,605	59.0%	83,330	52.7%	5,720	-	-
Ethnicity								
White/East and West European	-	-	97.9%	109,574	99.0%	7,484	-	-
Mediterranean or Arabic	-	-	0.4%	406	0.1%	9	-	-
Black	-	-	0.2%	189	<0.1%	3	-	-
Asian	-	-	0.5%	570	0.2%	17	-	-
Other	-	-	1.0%	1,136	0.6%	47	-	-
Cardiovascular risk factors								
Self-reported hypertension	-	-	19.9%	28,059	36.8%	3,993	21.1%	22.2%
Hypertension	0.4%	57	22.5%	31,748	69.0%	7,487	25.8%	32.6%
Self-reported hypercholesterolemia	-	-	11.5%	16,234	29.2%	3,168	12.8%	14.7%
Hypercholesterolemia	0.2%	35	12.8%	18,102	43.8%	4,753	15.0%	19.1%
Self-reported diabetes mellitus	-	-	2.0%	2,819	9.8%	1,063	2.6%	3.5%
Diabetes mellitus	0.2%	31	2.6%	3,646	11.7%	1,270	3.2%	4.4%
Self-reported kidney disease	-	-	0.5%	655	1.0%	103	0.5%	0.6%
Kidney disease	0.3%	41	1.4%	1,910	11.8%	1,281	2.1%	4.6%
Overweight	13.0%	1,933	54.0%	76,282	71.2%	7,730	55.2%	56.2%
Active smoker	1.2%	184	21.5%	30,412	8.2%	893	20.6%	19.0%
Former smoker	0.4%	65	32.5%	45,953	52.4%	5,687	33.9%	35.3%
Active lifestyle (30 min/day)	42.4%	6,292	21.4%	30,257	23.7%	2,567	21.6%	21.1%
Family health - CVD	-	-	8.9%	12,510	10.0%	1,083	8.9%	8.8%
Cancer	-	-	3.8%	5,331	15.8%	1,709	4.6%	6.2%
COPD	-	-	9.9%	14,037	23.4%	2,540	10.9%	12.6%
Rheumatoid arthritis	-	-	1.2%	1,658	1.8%	199	1.2%	1.2%
Thyroid disease	0.2%	30	2.2%	3,074	4.9%	536	2.4%	2.6%
Blood clotting disorder	-	-	0.6%	852	0.7%	77	0.6%	0.6%

CVD = cardiovascular disease, COPD = Chronic Obstructive Pulmonary Disease, N = number, SD = standard deviation

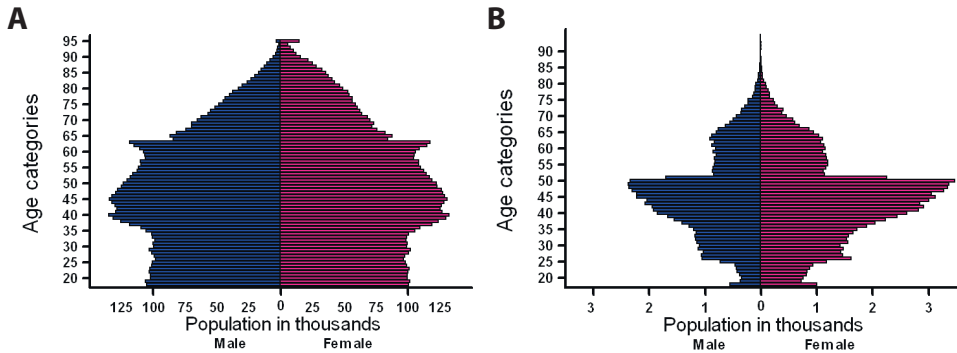


Figure 1. A. Population distribution in the Netherlands in 2010. **B.** Population distribution in the Lifelines cohort study, inclusion 2006-2013.

Baseline characteristics and cardiovascular risk factors

Physical examination was available on all participants. Lower weight was seen in the older aged group compared to the middle age category; in women the mean weight was 74 ± 14 (old age category) and 74 ± 12 kg (middle age category, $p=0.001$) respectively and in men 88 ± 14 and 85 ± 11 kg ($p<0.001$) respectively. The mean height of women in the middle age category was higher compared to the older age category (170 ± 7 cm versus 164 ± 6 cm, $p<0.001$). The height of men was lower in the older aged group: 183 ± 7 cm in the middle age category compared to 177 ± 7 cm in the older aged group ($p<0.001$). In total 61.9% ($n=35,878$) of men were overweight in the middle age category compared to 48.5% ($n=40,450$) of women (Figure 2). In the older age group, these proportions were higher: 73.5% ($n=3,774$, $p<0.001$) of men and 69.4% ($n=3,967$, $p<0.001$) of women.

In contrast to the lower heart rate (72 ± 11 bpm in the young and middle-age adults versus 68 ± 14 bpm in the older aged, $p<0.001$), systolic blood pressure was higher in older age categories (124 ± 15 over 74 ± 9 mmHg in the young and middle-age adults vs. 137 ± 24 over 74 ± 12 mmHg in the older aged, $p<0.001$). Additional biomarkers and cardiovascular drug use were available (Supplementary Table 1 and Table 2).

The prevalence of cardiovascular risk factors is presented in Table 1. In 110,502 (72.6%) participants, at least one classical cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, kidney disease, overweight or current smoking) was present. As expected, the burden of cardiovascular risk factors (SCORE) increased with age (Figure 3A).

Cardiovascular drug use increased with age. Amongst the most prescribed cardiovascular drugs were agents acting on the renin-angiotensin system, lipid drugs and beta-blockers. Overall, 12.3% ($n=17,341$) of the participants in the young and middle-age adults used one or more cardiovascular drug compared to 54.8% ($n=5,945$, $p<0.001$) of the participants in the older aged group. However, of the participants with hypertension 75.2% had no antihypertensive drugs, for hypercholesterolemia 95.9% had no lipid lowering drugs, for diabetes 41.2% had no anti-diabetic drugs.

The recent SPRINT trial proclaimed lower rates of cardiovascular events in persons with strict blood pressure control (<120 mmHg)¹⁵. In a recent publication investigating eligibility of SPRINT criteria in U.S.A. adults, more than half of the adults with hypertension were not treated¹⁶. In this cohort, of the participants with systolic blood pressure higher than 130 mmHg ($n=54,026$, 35.5%) 79.9% ($n=43,153$) had no antihypertensive drugs. Of participants having a SCORE predicting a $\geq 5\%$ 10-year risk of fatal CVD, 53.2% were not using any cardiovascular preventive drugs.

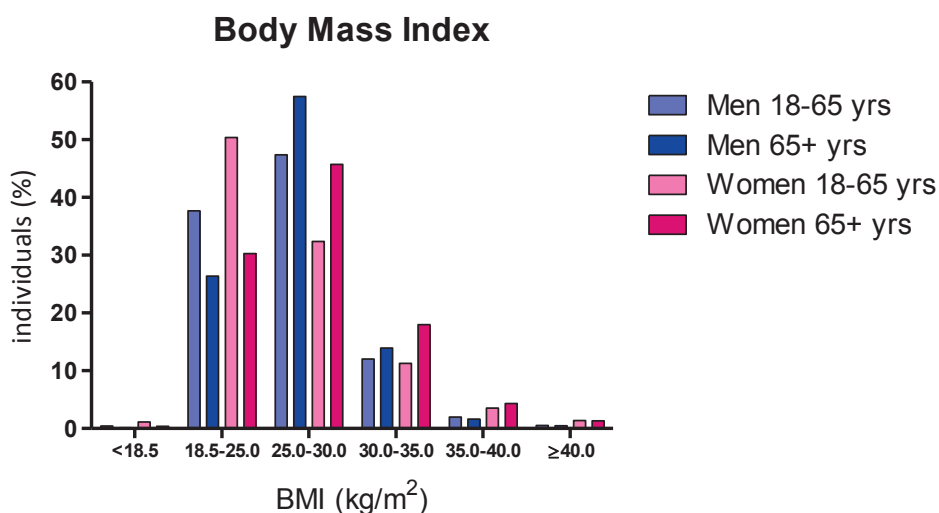


Figure 2. Body Mass Index distribution for males and females in the middle and older age category in the LifeLines cohort study, BMI = Body Mass Index

Cardiovascular disease

Symptoms possibly related to CVD were common. Chest pain and dyspnea on exertion were reported by approximately 25% of all adult participants. CVD and suggestive symptoms along are presented in Table 2. CVD was present in 16,872 (11%) of adult participants and increased with age from 9% in the middle age category to 28% in the older age category. Figure 3B shows total CVD burden in the LifeLines cohort study population. Prevalence of CVD increases substantially from the age of 50 ($p < 0.001$). Interestingly, we observed that not only the number of individuals with CVD increases, but the amount of reported CVD manifestations increases as well. Table 3 shows multivariate logistic regression of CVD risk factors with corresponding odds ratios for CVD. After adjustment for family clusters odds ratios were analogous.

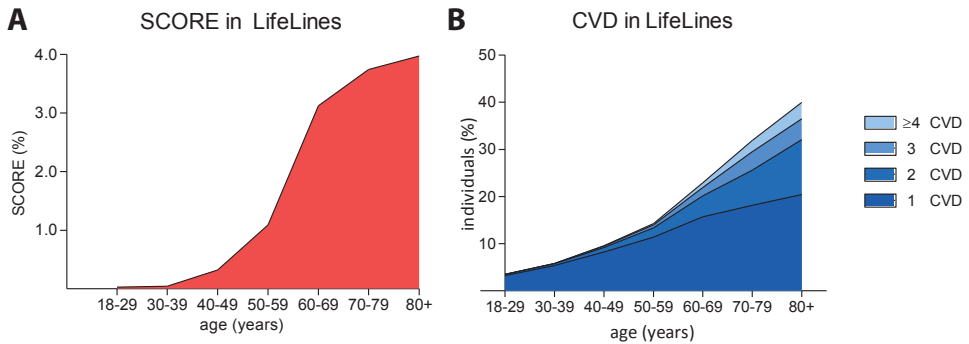


Figure 3. A. Mean SCORE in LifeLines per age category. **B.** Mean number of CVD manifestations in the LifeLines cohort study. CVD = Cardiovascular disease, SCORE = Systematic Coronary Risk Evaluation Project

Table 2. Cardiovascular disease in the LifeLines cohort study

Characteristics	Adults 18-65Y		Adults 65+Y		N	Crude estimate	Standardized estimate
	N	%	N	%			
MI, heart failure and atrial fibrillation							
Self-reported MI	985	0.7%	665	6.2%	665	1.1%	2.0%
With drug use or ECG abnormalities	852	0.6%	608	5.6%	608	1.0%	1.8%
Silent MI	162	0.1%	58	0.5%	58	0.1%	0.2%
Possible diagnosis silent MI	549	0.4%	152	1.4%	152	0.5%	0.7%
Self-reported heart failure	776	0.6%	342	3.2%	342	0.7%	1.2%
With drug use or therapy otherwise	495	0.4%	307	2.8%	307	0.5%	1.0%
Cardiac implantable electronic device	139	0.1%	87	0.8%	87	0.2%	0.3%
Transplant	10	<0.1%	14	<0.1%	14	<0.1%	<0.1%
Atrial fibrillation	408	0.3%	426	3.9%	426	0.6%	1.3%
Other self-reported CVD							
Balloon angioplasty or bypass surgery	1,323	0.9%	898	8.4%	898	1.5%	2.8%
Heart valve disorder	1,237	0.9%	332	3.1%	332	1.0%	1.4%
Palpitations	9,462	6.7%	1,579	14.6%	1,579	7.3%	8.0%
Aortic aneurysm	266	0.2%	202	1.9%	202	0.3%	0.6%
Stroke	842	0.6%	336	3.1%	336	0.8%	1.2%
Thrombosis	1,550	1.1%	316	2.9%	316	1.2%	1.4%
Atherosclerosis	491	0.4%	214	2.0%	214	0.5%	0.8%
Narrowing carotid arteries	271	0.2%	124	1.5%	124	0.3%	0.4%
Symptoms							
Peripheral edema	20,038	14.4%	2,082	23.9%	2,082	14.5%	13.9%
Chest pain	36,972	26.5%	2,446	28.1%	2,446	25.9%	25.8%
Shortness of breath	31,567	22.9%	1,703	19.6%	1,703	21.9%	20.8%
Dyspnea	14,436	10.3%	572	6.6%	572	9.9%	9.1%
Dyspnea on exertion	36,087	25.9%	2,403	27.7%	2,403	25.3%	24.7%
Orthopnea	4,899	3.5%	360	4.2%	360	3.5%	3.2%

CVD = cardiovascular disease, ECG = electrocardiogram, MI = myocardial infarction

Table 3. Multivariate logistic regression: risk factors and CVD

Characteristics	p-value	Odds ratio	95% CI
Female	<0.001	1.08	1.04-1.12
Age per year	<0.001	1.04	1.03-1.04
Overweight	0.003	1.06	1.02-1.10
Smoking	<0.001	1.21	1.17-1.26
Active lifestyle			
Active 0 out of 7 days	Reference	-	-
Active 1 out of 7 days	<0.001	0.82	0.74-0.90
Active 2 out of 7 days	<0.001	0.80	0.73-0.88
Active 3 out of 7 days	<0.001	0.80	0.73-0.88
Active 4 out of 7 days	<0.001	0.78	0.72-0.86
Active 5 out of 7 days	<0.001	0.84	0.77-0.92
Active 6 out of 7 days	<0.001	0.84	0.77-0.92
Active 7 out of 7 days	<0.001	0.86	0.79-0.93
Family CVD	<0.001	1.30	1.24-1.38
Cancer	<0.001	1.15	1.08-1.24
Thyroid disease	<0.001	1.53	1.39-1.68
Kidney disease	<0.001	1.23	1.11-1.36
Hypercholesterolemia	<0.001	1.84	1.77-1.92
Hypertension	<0.001	2.14	2.06-2.23
Diabetes	0.025	1.10	1.01-1.19

CI = confidence interval, CVD = cardiovascular disease

DISCUSSION

Here we describe the baseline cardiovascular characteristics of the contemporary three-generations LifeLines cohort study with 167,016 participants. The risk factor burden of the LifeLines cohort study is high and can be extrapolated to the Dutch general population by adjusting for population distribution. Over 70% of the participants had at least one cardiovascular risk factor (hypertension, hypercholesterolemia, diabetes mellitus, kidney disease, overweight or current smoking) and in a substantial proportion (11%) a manifestation of CVD was present. Primary prevention of cardiovascular risk factors, even when SCORE predicted a 5% or more risk, was remarkably low. The burden of risk factors and CVD present in the LifeLines cohort study provides considerable

power to study events and risk factors related to CVD. It is therefore a valuable tool for researchers to further study the role of CVD and its risk factors in relation to healthy ageing.

The LifeLines study population differs from the general population by its design to that effect that the proportion of adults aged 25-50 years are overrepresented¹⁷. Reported prevalences of CVD risk factors from the Dutch National Registry (Statistics Netherlands) based on national health survey in around 15,000 persons, are frequently lower compared to the LifeLines cohort study¹⁷. This may be due to different methods used for identifying and defining disease. For example, according to the Statistics Netherlands for 2013 and 2014 prevalence of hypertension and overweight were around 11% lower¹⁷. Smoking was estimated 4% higher than in the LifeLines cohort study, with a prevalence of 24.9% compared to 20.6%. In contrast, the WHO reported generally higher prevalences with hypercholesterolemia, diabetes and overweight estimated 5% higher than in the LifeLines study¹⁸.

Discrepancies exist regarding physical activity. According to the WHO in 2010 17.9% of adults from the Netherlands were insufficiently active¹⁸ and the Statistics Netherlands reported 63% of the population attained sufficient physical activity. These differences might be due to the use of different definitions and measurements of physical activity. The reported family history of CVD was four times higher in the Rotterdam study compared to the LifeLines, suggesting regional differences, the use of different definitions, or underreporting in the LifeLines cohort study¹⁹. MI and stroke percentages in the LifeLines cohort study were somewhat lower compared to the Statistics Netherlands inquiry in 2014, in which 3.1% of the total population ever had a stroke and 3.3% had a MI compared to respectively 0.8% and 1.1% in the LifeLines study population.

In the Netherlands in 2012, drug use of lipid lowering drugs was 10.7%, beta-blockers 9.8% and diabetes 4.6%, similar as reported by the participants of the LifeLines cohort study¹⁷. Interestingly, taking into account the risk factor burden in participants with a predicted risk of $\geq 5\%$ of which the majority does not use cardiovascular preventative drugs, there is likely to be a considerable underutilisation of primary prevention. The general practitioner has been informed about the risk profile of the LifeLines participant as part of the protocol and in line with the recommendation of the Medical Ethical Committee. Follow-up studies will be performed to study whether this knowledge has increased the percentage of subjects in whom primary prevention was initiated.

Strengths of the Lifelines cohort study include the open protocol and hence a continuous possibility for researches to implement add-on studies. The three-generation structure

in combination with the available genome-wide genetic data enables unique opportunities for the analysis of genetic traits. In LifeLines, over one-thirds of the participants had first-, second-, or third-degree relatives also taking part in the study. The family design of the LifeLines cohort study has advantages with respect to multiple-level information, separation of non-genetic and genetic familial transmission and the investigation of (epi)genetic influences. Another advantage when performing genetic research, is the relatively homogeneous study population due to a low migration rate in the northern part of the Netherlands (net migration rate of 0.80 per 1,000 inhabitants in 2012)¹⁷. Less than 2% of the total included population had an ethnicity other than white-, east- or west-European. Diversity regarding CVD exists within ethnicity groups, and reported prevalences were not corrected for ethnicity. Current data might not be applicable to other ethnicities.

CONCLUSION

The LifeLines cohort study is a large population based cohort accessible to national and international researchers⁸. The three-generation structure in combination with the available genome-wide genetic data enables unique opportunities for the analysis of environmental and genetic traits. The family design of LifeLines enables inclusions of three generation families and has advantages with respect to multiple-level information, separation of non-genetic and genetic familial transmission. The prevalence of CVD risk factors and conditions is abundant in LifeLines and enables researchers to improve our knowledge on CVD and healthy cardiovascular ageing. A remarkable high percentage of untreated CVD risk factors in LifeLines suggest that not all opportunities to reduce the CVD burden are utilised.

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Disclosures

None.

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