Lessons from the trials

The Copenhagen City Heart Study (Østerbroundersøgelsen)

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ABSTRACT

The Copenhagen City Heart Study, also known as "Østerbroundersøgelsen", is a large prospective cardio-vascular population study of 20,000 women and men that was launched in 1975 by Dr Peter Schnohr and Dr Gorm Jensen together with statistician Jørgen Nyboe and Prof. A. Tybjærg Hansen. The original purpose of the study was to focus on prevention of coronary heart disease and stroke. During the years many other aspects have been added to the study: pulmonary diseases, heart failure, arrhythmia, alcohol, arthrosis, eye diseases, allergy, epilepsia, dementia, stress, vital exhaustion, social network, sleep-apnoe, ageing and genetics. In this review we highlight unique aspects of the Copenhagen City Heat Study (CCHS) and its outcome in investigations of clinical and molecular aspects of health and disease in the regional and global population. To increase the impact of population studies with a focus on risk and prevention of cardiovascular and related diseases and to maximize the likelihood of identifying disease causes and effective therapeutics, lessons learned from past research should be applied to the design, implementation and interpretation of future studies.

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INTRODUCTION

In 1975 a large prospective cardiovascular population study of 20,000 men and women was launched by Dr. Peter Schnohr and Dr. Gorm Jensen together with statistician Jørgen Nyboe and Prof. A. Tybjærg Hansen as their mentor. The study was named "Østerbroundersøgelsen", or in English, "The Copenhagen City Heart Study".[1−3]

The original purpose of the study was to focus on prevention of coronary heart disease and stroke. During the years many other aspects have been added to the study: pulmonary diseases, heart failure, arrhythmia, alcohol, arthrosis, eye diseases, allergy, epilepsia, dementia, stress, vital exhaustion, social network, sleep-apnoe, ageing and genetics.

HISTORY

At a young age Dr. Peter Schnohr was one of the ten fastest runners in Denmark. The unpleasant symptoms he experienced during his strenuous training, such as dizziness, made him wonder, whether this kind of training could be unhealthy. Years later, intrigued by the question "Do top athletes have more or less ill-health than non-athletes" and after a six-week Epidemiology Research Training Program, at the University of California at Berkeley, Schnohr returned to Denmark as a 'trained epidemiologist' and spent the majority of his career researching physical activity and athleticism as tools for CVD prevention.[4]

He set up the Copenhagen City Heart Study (CCHS) as a privately sponsored formal cohort study of CVD risk, which still ongoing under his direction and executed by a team of physicians, scientists, statisticians, medical laboratory technicians, nurses and students.

The study was based at Rigshospitalet from 1975 to 1997. From 1997, the Copenhagen City Heart Study has been based at Bispebjerg University Hospital, where the fourth survey was performed in 2001−2003.

PURPOSE OF THE COPENHAGEN CITY HEART STUDY

When the Copenhagen City Heart study was initiated its aims were

– Describing the distribution of known cardiovascular risk factors in a random sample of a population in a well-defined area of Copenhagen.
– Describing the prevalence and incidence of cardio and cerebrovascular disease, hypertension, lung disease and other diseases.
– Relating morbidity and mortality to the variables collected.
– Forming the background for special studies concerning aetiology, prevention and treatment of various disease entities, especially ischaemic heart disease, stroke and lung diseases.

At the third examination several new aspects were included:

– Studying genetics, psychosocial factors, arthritis, epilepsy, dementia, excessive alcohol intake and microalbuminuria.

METHODS

Study population: selection and invitation procedure

The primary population was a random sample of almost 20,000 men and women 20−93 years old, drawn from a population of approximately 90,000 inhabitants aged 20 years or older living within 10 wards (the entire of Østerbro and 1/3 of Nørrebro) surrounding Rigshospitalet, Copenhagen (Figure 1). Using the unique personal identification number (Central-Personal-Register-code), consisting of date of birth and a registration number, the sample was age-stratified within 5-year age groups, with the main emphasis on the age groups from 35 to 70 years.

Individuals selected for the study were invited according to their date of birth, converting the date to a six-digit number (day, month, year of birth). These numbers were used in ascending order, starting with individuals born on January 1st, February 1st etc. and ending with December 31th, ensuring that subsets of the sample examined during any period of time would constitute a random subsample.

Three weeks prior to the examination, the individuals selected were invited by letter (signed by Prof. T. Hansen, Dr. G. Jensen and Dr. P. Schnohr) to participate in a health examination, Østerbroundersøgelsen at Rigshospitalet. The letter described the main purpose of the study: prevention and treatment of cardio-vascular diseases. Attached to the invitation was a postage-paid
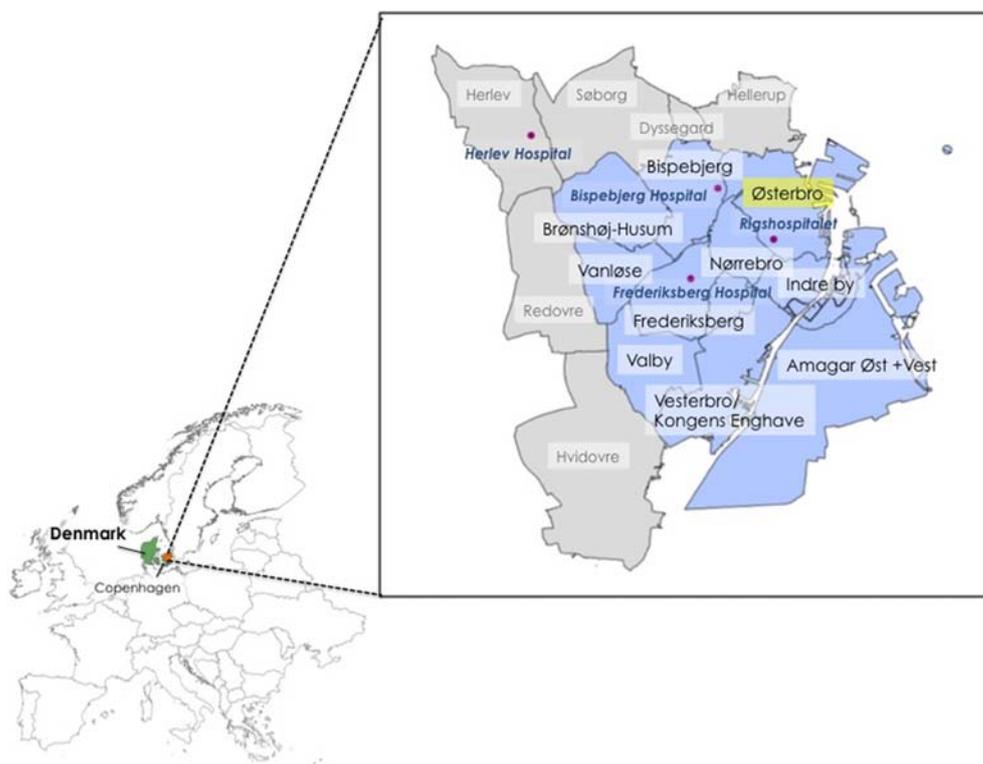
Figure 1. CCHS Study area and participating Hospitals. Since a reform in 2006–08, Copenhagen Municipality has been divided into 10 official districts Indre By, Østerbro, Nørrebro, Vesterbro/Kongens Enghave, Valby, Vanløse, Frederigsberg, Brønshøj-Husum, Bispebjerg, Amager Øst, and Amager Vest. The primary population was a random sample of almost 20,000 men and women 20 – 93 years old, drawn from a population of approximately 90,000 inhabitants aged 20 years or older living within 10 wards (the entire of Østerbro and 1/3 of Nørrebro) surrounding Rigshospitalet, Copenhagen. The study was based at Rigshospitalet from 1975 to 1997. From 1997, the Copenhagen City Heart Study has been based at Bispebjerg University Hospital, where the fourth survey was performed in 2001–2003. The Copenhagen City Population study (a sister study) is based in a suburb of Copenhagen named Herlev in the Herlev Hospital, a Copenhagen University Hospital.

postcard, by means of which the person could confirm the appointment, change the date or decline to participate. In case of no response till a week prior to the examination, a second invitation was posted and a final re-invitation was sent 6 months later. No further attempt to contact the non-responders was made.

19,329 persons, 9,145 men and 10,184 women, were invited for the first examination.[2] The total number of participants invited to the first four examinations was: 19,329 + 500 + 3,000 + 1, 062 = 23,891 men and women. Of the original 14,223 examined at the first examination 3,092 (21.7%) have been examined in all four examinations, and of the 5,106 non-responders from the first survey in 1976–1978, 1,698 responded and were examined in one or more of the following surveys.

Follow-up of all-cause mortality was performed based on Information obtained from the National Central Person Register, using the unique personal identification number. Follow-up completion rate was almost 100 percent (less than 0.1% were lost to follow-up), which is very uncommon for large population studies. Figure 2 shows a scheme of the population invited and examined for the CCHS.

Examination procedures

Procedures for cardiovascular epidemiological surveys established by Rose & Blackburn (1968) were employed for the examination procedures.[5] The participants had to fill in a questionnaire, concerning symptoms and diseases, use of medicine, familial disposition, socioeconomic status, smoking and drinking habits, physical activity at work and during leisure time, and contact with the health care system upon arrival to the examination. Throughout the different examination stations (Figure 3), the questionnaire was checked by the staff. If "chest pain on effort" or "pain in the legs on walking uphill"

Examination stage	I	II	III	IV
Duration	1976–1978 (25 mths)	1981–1983 (29 mths)	1991–1994 (36 mths)	2001–2003 (22 mths)
Invited	19,329 (age 20–93)	18,059	16,563	12,600
	9,145 ♂ + 10,184 ♀	500 new (age 20–25)	3000 new (20–49)	3,062 new (20–29)
Examined	14,223	12,698	10,135	6,238
Response rate	73.6 %	70.2 %	61.2 %	49.5 %

Figure 2. Study population: invited and examined. The total number of participants invited to the first four examinations was: 19,329 + 500 + 3,000 + 1,062 = 23,891 men and women. Of the original 14,223 examined at the first examination 3,092 (21.7%) have been examined in all four examinations, and of the 5,106 non-responders from the first survey in 1976–1978, 1,698 responded and were examined in one or more of the following surveys.

occurred, the staff interviewed the participant according to Rose's questionnaires concerning angina pectoris and intermittent claudication.[1,2]

Sub-studies
Additionally, the participant was asked to give the study investigators permission to keep frozen serum and plasma in the biological-bank and to make inquiries about examination results and treatments in the healthcare system and signed a Certificate of Consent. If the participant was eligible to enroll to any of the sub-studies (Figure 4), the respective procedure was started upon his acceptance.

RESULTS, LESSONS AND SOCIAL IMPACT
The CCHS books of tables
The CCHS with its design, a combination of questionnaires and several clinical examinations and laboratory tests, was from the start expected to generate large amounts of data. Data acquired from the first examination and a five-year follow-up, the second examination, were published in the study's first book of tables.[2] The second book of table contains breakdowns of data from the third examination according to sex and age groups.[3] These tables give information on the distribution of a great number of risk factors important for prevention of ischaemic heart disease, stroke and other diseases, providing researchers with updated reference values (for a defined population) and valuable information for more precise study planning. By comparing values from the second and first book of tables, change in risk factors can be evaluated, covering and age-span of 15 years. The third book of tables has not been published yet, but results from the fourth examination are currently being published.

Physical activity and jogging in leisure time
Medical evidence had made it obvious in the past, that our hearts, lungs, muscles and minds need the effects of regular and vigorous exercise.[6] In longitudinal studies, physically active men and women have an approximately 30% lower risk of death during follow-up compared with inactive people. No upper threshold for physical activity has ever been recommended.[7–9] One of the main focuses of CCHS is to investigate the association between physical activity, such as jogging and cycling, in leisure time on all-cause mortality.

The Copenhagen City Heart Study reported that it was not the duration of walking and cycling that was of most importance in relation to all-cause and CHD mortality, it was the relative intensity of the

Examination I & II
1st station (the reception):

- Check: questionnaire and eligibility for other sub-studies
- Blood sample, non-fasting plasma: cholesterol, HDL-cholesterol, triglycerides and glucose.
- Pulmonary function text
- Xantelasmata and ear-lobe crease

2nd station:

- Height, weight, hip, sagittal body diameter
- 12-lead resting electrocardiogram
- Arcussenilis & other signs of ageing (degree of grey hair, baldness, wrinkles at crows feet area)

3rd station:

- Questionnaire check
- Blood pressure
- Explanation of results to the participant

Examination III
Addition of following laboratory investigations [see ref. 3]:

- Microalbuminuria and renal creatine clearance
- Lipoprotein A
- Apolipoprotein A1, apolipoprotein B
- Fibrinogen
- Plasminogen activator
- Plasminogen activator inhibitor
- Factor VII
- DNA-analyses

Examination IV
Addition of the following invesigations

- Echocardiography, including tissue Doppler, pulse wave velocity, ankle-arm blood pressure

Almost "total biochemical analyses", including:

- Brain natriuretic peptide (BNP)
- Homocystein
- High sensitivity C-reactive protein
- Glycosylated haemoglobin (HbA1c)
- Lipase
- Uric acid
- DNA and messenger RNA

Additional plasma was stored from each patient for future analyses.

Figure 3. Examinations were performed at three different workplaces, each lasting 6–8 minutes per station per person examined. At the end of the examination the participant was asked to contact the general practitioner after two weeks (or earlier in case of any abnormal findings) to receive results of the blood sample analyses.

activity (Figures 5 & 6).[10,11] It was surprising to learn that jogging up to 2.5 h per week at a slow or average pace and a frequency of #3 times per week was associated with the lowest mortality (increase in survival: 6.2 years in men and 5.6 years in women). Those who jogged > 4 h per week, at a fast pace, and > 3 times per week appeared to lose many of the longevity benefits noted with less strenuous doses of jogging.[12] This analysis was performed in a random sample of 1,878 joggers who were followed for up to 35 years and compared with 16,827 non-joggers. A study published this year, suggests a U-shaped association between all-cause mortality and dose of jogging as calibrated by pace, quantity, and frequency of jogging. Light and moderate joggers have lower mortality than sedentary non-joggers, whereas strenuous joggers have a mortality rate not statistically different from that of the sedentary group. Data from the fourth examination (2001–2003) were used for these investigations.[13]

This is particularly interesting in light of previous studies, which showed that long-term strenuous endurance exercise might induce pathological structural remodeling of the heart and large arteries. Emerging data suggest that long-term training and competing in extreme endurance events such as marathons, ultra-marathons, ironman distance triathlons, and very long distance bicycle races can cause transient acute volume overload of the atria and right ventricle, with transient reductions in right ventricular ejection fraction and elevation of cardiac biomarker levels.[14] Months to years of repetitive injury in some people may lead to patchy myocardial fibrosis, particularly in the atria, interventricular septum, and right ventricle, creating a substrate for atrial and ventricular arrhythmias.[15] Additionally,
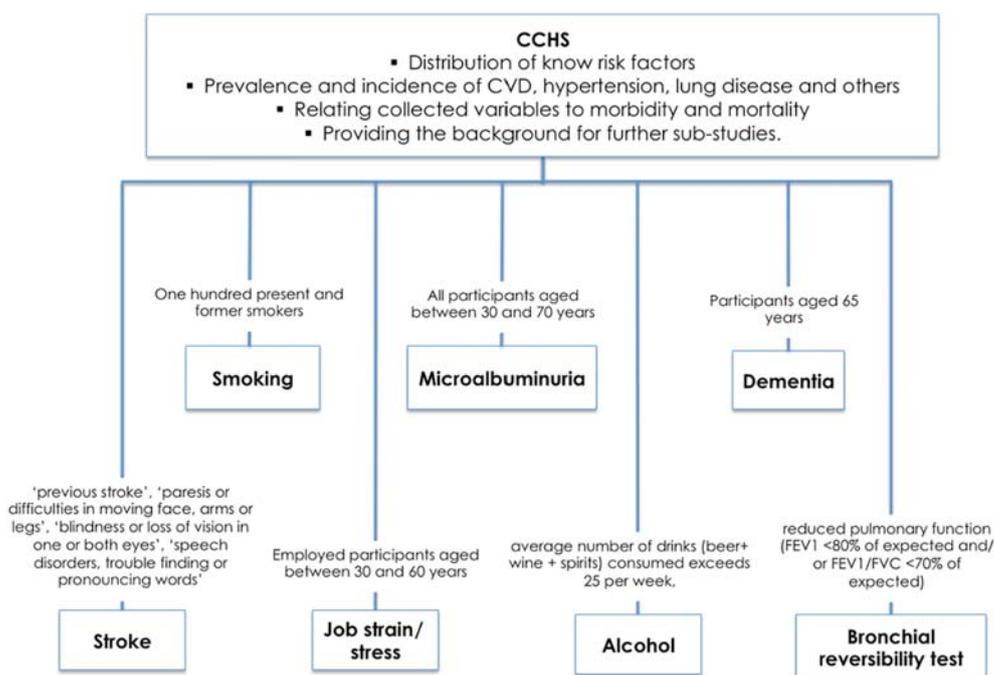
Figure 4. The CCHS provides a strong background for numerous sub-studies. If a participant was eligible for any of the sub-studies, the procedure was started after his acceptance.

long-term excessive exercise may be associated with coronary artery calcification, diastolic dysfunction, and large artery wall stiffening.[16]

In all four CCHS surveys physical activity in leisure time has been graded into 4 levels ("The Copenhagen City Heart Study Leisure Time Physical Activity Questionnaire").[4] Furthermore, specific questions regarding walking, cycling, and jogging were added. Gradually the survey method was developed. At the first examination in 1976–1978, the participants were asked about whether they were joggers, and in 1981–1983 and 1991–1994 they were further asked for their weekly quantity of jogging. In the fourth survey (2001–2003), information about weekly frequency of jogging and the individual's own perception of pace (slow, average, fast) was obtained. Interestingly, a relative scale of pace (intensity) turned out to be more appropriate than an absolute scale when the age span is very wide (20–98 years) and when the participants have wide differences in levels of physical fitness.

The fact that the dose of running that was most favorable for reducing mortality was jogging 1 to 2.4 h per week, with no more than 3 running days per week, at a slow or average pace can have interesting implications when being translated into practice, however, further studies are needed to explore the mechanisms by which excessively strenuous exercise adversely affects longevity before the pattern of association between exercise intensity and long-term mortality can be applied to patient care strategies or incorporated into physical activity recommendations to the general public. Nevertheless, the current state of knowledge is already being celebrated by the media and the public (Figure 7).

CCHS bridges the gap between clinical and molecular investigations

In the first years publications from the CCHS were mainly focusing on the prevalence of different disease types such as stroke, ischemic cardiovascular disease, chronic obstructive lung disease, diabetes mellitus[17–19] and related epidemiological aspects such as indicators of disease, educational and socioeconomic factors and factors of presumably hereditary nature.[18,20] The first studies included 1 to 5 year follow-ups.

One of the first gender specific studies was published in 1993.[21] The purpose of this study was to determine how lifestyle influences the risk of cerebrovascular disease in women participating in the Copenhagen City Heart Study. Numerous studies addressing gender-specific aspects followed, such as sex-specific increase in the prevalence of atrial fibrillation.[22]

In 1994 a study was published, in which the probability of stroke was compared between the Copenhagen City Heart Study and the Framingham Study.[23] The aim of the study was to test the validity

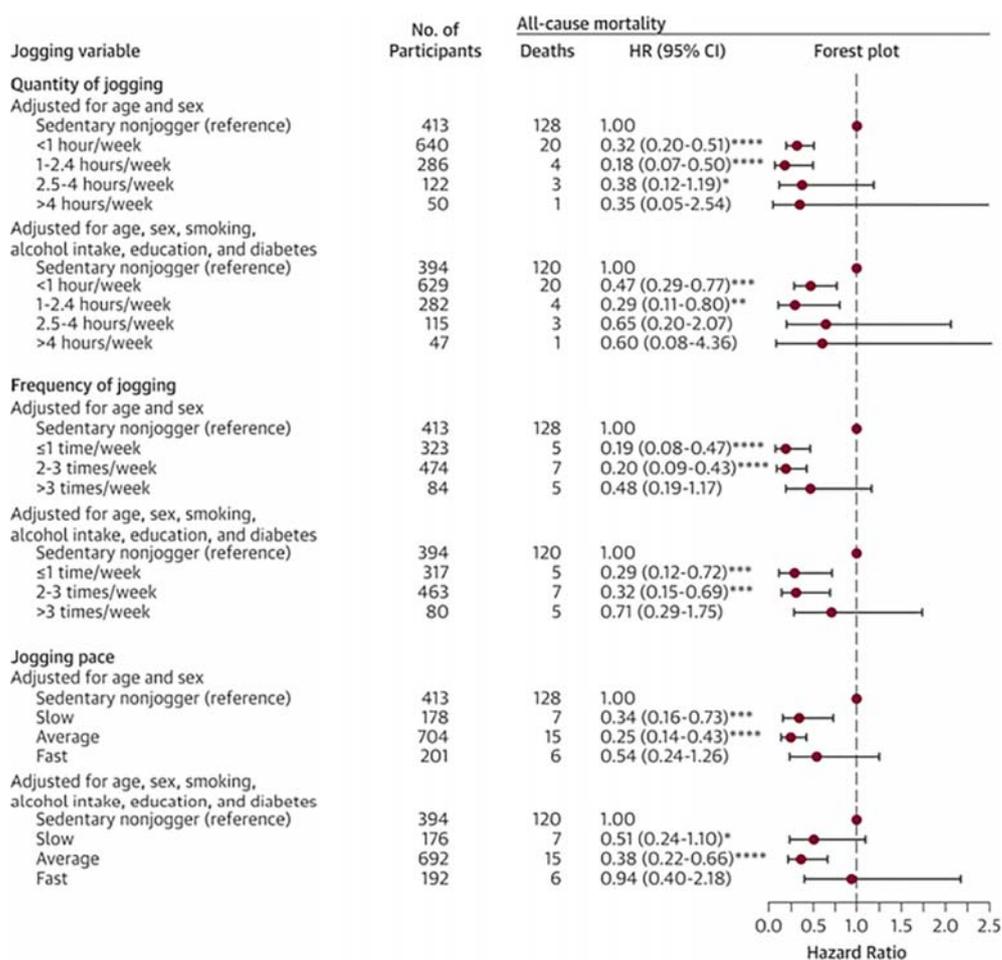| Jogging variable	No. of Participants	All-cause mortality		Forest plot
		Deaths	HR (95% CI)	
Quantity of jogging				
Adjusted for age and sex				
Sedentary nonjogger (reference)	413	128	1.00	
<1 hour/week	640	20	0.32 (0.20-0.51)****	
1-2.4 hours/week	286	4	0.18 (0.07-0.50)****	
2.5-4 hours/week	122	3	0.38 (0.12-1.19)*	
>4 hours/week	50	1	0.35 (0.05-2.54)	
Adjusted for age, sex, smoking, alcohol intake, education, and diabetes				
Sedentary nonjogger (reference)	394	120	1.00	
<1 hour/week	629	20	0.47 (0.29-0.77)***	
1-2.4 hours/week	282	4	0.29 (0.11-0.80)**	
2.5-4 hours/week	115	3	0.65 (0.20-2.07)	
>4 hours/week	47	1	0.60 (0.08-4.36)	
Frequency of jogging				
Adjusted for age and sex				
Sedentary nonjogger (reference)	413	128	1.00	
≤1 time/week	323	5	0.19 (0.08-0.47)****	
2-3 times/week	474	7	0.20 (0.09-0.43)****	
>3 times/week	84	5	0.48 (0.19-1.17)	
Adjusted for age, sex, smoking, alcohol intake, education, and diabetes				
Sedentary nonjogger (reference)	394	120	1.00	
≤1 time/week	317	5	0.29 (0.12-0.72)***	
2-3 times/week	463	7	0.32 (0.15-0.69)***	
>3 times/week	80	5	0.71 (0.29-1.75)	
Jogging pace				
Adjusted for age and sex				
Sedentary nonjogger (reference)	413	128	1.00	
Slow	178	7	0.34 (0.16-0.73)***	
Average	704	15	0.25 (0.14-0.43)****	
Fast	201	6	0.54 (0.24-1.26)	
Adjusted for age, sex, smoking, alcohol intake, education, and diabetes				
Sedentary nonjogger (reference)	394	120	1.00	
Slow	176	7	0.51 (0.24-1.10)*	
Average	692	15	0.38 (0.22-0.66)****	
Fast	192	6	0.94 (0.40-2.18)	

Hazard Ratio: 0.0 0.5 1.0 1.5 2.0 2.5

Figure 5. All-cause mortality HRs, adjusted for age and sex and multivariable adjusted for joggers compared with sedentary nonjoggers. Jogging variables: Quantity, frequency, and pace of jogging in relation to all-cause mortality. HR = hazard ratio. *p < 0.10; **p < 0.05; ***p < 0.01; ****p < 0.001. From: Schnohr et al., 2015, http://dx.doi.org/10.1016/j.jacc.2014.11.023.

of a stroke probability point system from the Framingham Study for a sample of the population of Copenhagen. The majority of risk factors for stroke identified by the Framingham Study also had a significant effect in the Copenhagen City Heart Study population. Although estimated stroke probabilities based on point systems from the Copenhagen City Heart Study and the Framingham Study were similar, the points scored in the two systems did not always correspond to the same combination of risk factors. The authors concluded that such systems can be used for estimating stroke probability in a given population, provided that the statistical confidence limits are known and the definitions of risk factors are compatible. The lesson learnt form this study was that because of the large statistical uncertainty, a prognostic index should not be applied for individual prediction unless it is used as an indicator of high relative risk associated with the simultaneous presence of several risk factors.

Gradually, data from the Copenhagen were not only used to analyze factors of hereditary nature, they contributed to identifying genetic and determinants of cardiovascular and other diseases. A study published by Tybjaerg-Hansen aimed at identifying genetic determinants for the development of hyperlipidemia and/or atherosclerosis.[23] The study demonstrated for the first time the clinical expression (phenotype) of a newly discovered monogenic disorder named Familial Defective Apolipoprotein B-100 (FDB) caused by a G to A mutation in the binding protein (apolipoprotein B-100) for the cholesterol-rich low density lipoprotein (LDL), that the affinity of LDL to the LDL receptor is severely reduced. The study included 135 individuals with FDB from 56 families and 8 different countries. The CCHS provided the general population sample from Denmark.[23] This was one of the first analysis in which the CCHS started to show its potential with regards to epidemiological genetic and

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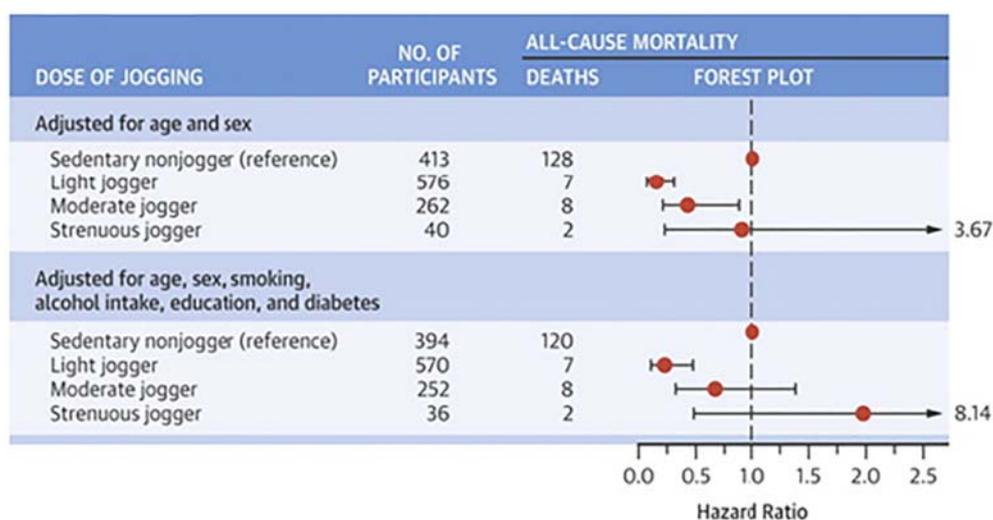Aguib & Al Suwaidi. Global Cardiology Science and Practice 2015:33

Figure 6. Dose of jogging and long-term mortality. Forest plot indicating all-cause mortality in light, moderate, and strenuous joggers compared with sedentary nonjoggers. From: Schnohr et al. JACC. 2015, http://dx.doi.org/10.1016/j.jacc.2014.11.023.

molecular investigations. One year later, Nordestgaard et al. declared that the CCHS DNA bank, back then consisting of more than 10,000 individuals, has a huge potential in understanding the clinical and molecular genetics of the development of cardiovascular as well as other diseases.[24]

In one of the following studies ACE gene polymorphism in ischemic heart disease was analysed in a case-referent and retrospective cohort study based on the Copenhagen City Heart Study.[25] Homozygosity for the deletion allele (D) of the angiotensin-converting enzyme (ACE) gene insertion-deletion polymorphism had been suggested to be a potent risk factor for myocardial infarction, but except for one analysis, the samples had been small and/or ethnically heterogeneous, and most investigators have studied men only. The CCHS-based study investigated the association between ACE genotype and myocardial infarction as well as other manifestations of ischemic heart disease for both women and men in a case-referent study (n = 10,150) as well as in a retrospective cohort study (n = 7263). In these two large studies, a case-referent study and a retrospective cohort study in an ethnically homogeneous white population, there was no evidence for a statistically significant difference in the development of myocardial infarction or any other manifestations of ischemic heart disease between genotype classes of the ACE gene polymorphism in either women or men.

Further studies addressed common cholesteryl ester transfer protein mutations, decreased HDL cholesterol, and possible decreased risk of ischemic heart disease,[26] Angiotensinogen mutations and risk for ischemic heart disease, myocardial infarction, and ischemic cerebrovascular disease,[27] Organochlorines, p53 mutations in relation to breast cancer risk and survival,[28] Factor von Leiden (FVL) as a risk factor for myocardial infarction (MI), ischemic stroke (IS), or non-MI ischemic heart disease (non-MI-IHD),[29] the role of Fibrinogen in the prediction of ischaemic stroke, advanced atherosclerosis and atrial fibrillation,[30,31] Integrin beta3 Leu33Pro homozygosity and risk of cancer,[32] genetically reduced antioxidative protection and increased ischemic heart disease risk,[33] single nucleotide polymorphisms in the low-density lipoprotein receptor is associated with a threefold risk of stroke,[34] Zink Finger Protein 202 as a new candidate gene for ischemic heart disease[35] and other investigations of different factors contributing to diseases.

One of these prominent factors is alcohol intake. Truelson et al. had analysed data on the Intake of Beer, Wine, and Spirits and the risk of Stroke.[36] In another study, information on alcohol intake and on liver disease were obtained from the CCHS to test the hypothesis that alcohol, alone and in combination with alcohol dehydrogenase (ADH) 1B and ADH1C genotypes, affects liver damage and disease in the Danish general population.[37]

An interesting study analysed whether elevated inflammatory biomarkers in individuals with stable COPD are associated with an increased risk of having exacerbations, which have profound and long-lasting adverse effects on patients. The cohort examined for this study originate from CCHS and its

Figure 7. Upper panel: *Berlingske*, **one of the most renowned and best-selling Danish national daily newspaper (based in Copenhagen) published an article in 2013 with a photo showing Dr. Schnohr jogging.** The articles title: The Man who ran ahead. The figure's caption: Peter Schnohr, cardiologist and the man behind Eremitageløbet (a jogging competition held in the deer park north of Copenhagen each year in early October), today 70 years old, still jogs twice a week around the lakes in Copenhagen. With the large population study, The Copenhagen City Heart Study, he and his team show that jogging prolongs life. Lower panel: An article published by *The Telegraph* (UK) in early 2015 entitled "Fast running is as deadly as sitting on couch, scientists find".

sister study the Copenhagen General Population Study. Simultaneously elevated levels of CRP and fibrinogen and leukocyte count in individuals with COPD were indeed associated with increased risk of having exacerbations, even in those with milder COPD and in those without previous exacerbations.[38]

Another recent study analysed the association of elevated lipoprotein(a) levels and corresponding LPA risk genotypes (rs10455872, rs3798220, kringle IV type 2) combining data from both, the Copenhagen City Heart Study (1991 to 2011; n = 10,803) and the Copenhagen General Population

Study (2003 to 2011; n = 66,877), following up 77,680 Danish participants for as long as 20 years, during which time 454 were diagnosed with AVS. Observational and genetic instrumental variable analyses in a Mendelian randomization study design were conducted and confirmed that Elevated Lp(a) levels and corresponding genotypes were associated with increased risk of AVS in the general population, with levels > 90 mg/dl predicting a threefold increased risk.[39] 7 years earlier, the team had the hypothesis that extreme lipoprotein(a) levels predict MI in the general population and had observed a stepwise increase in risk of MI with increasing levels of lipoprotein(a). Extreme lipoprotein(a) levels predict a 3- to 4-fold increased in risk of MI in the general population and absolute 10-year risks of 20% and 35% in high-risk women and men[40] (Figures 8, 9).

Data generated from The CCHS were also used in order to elucidate the molecular basis of Nonalcoholic fatty liver disease (NAFLD); an exome-wide association study of liver fat content was performed. Three variants were associated with increased liver fat at the exome-wide significance level:
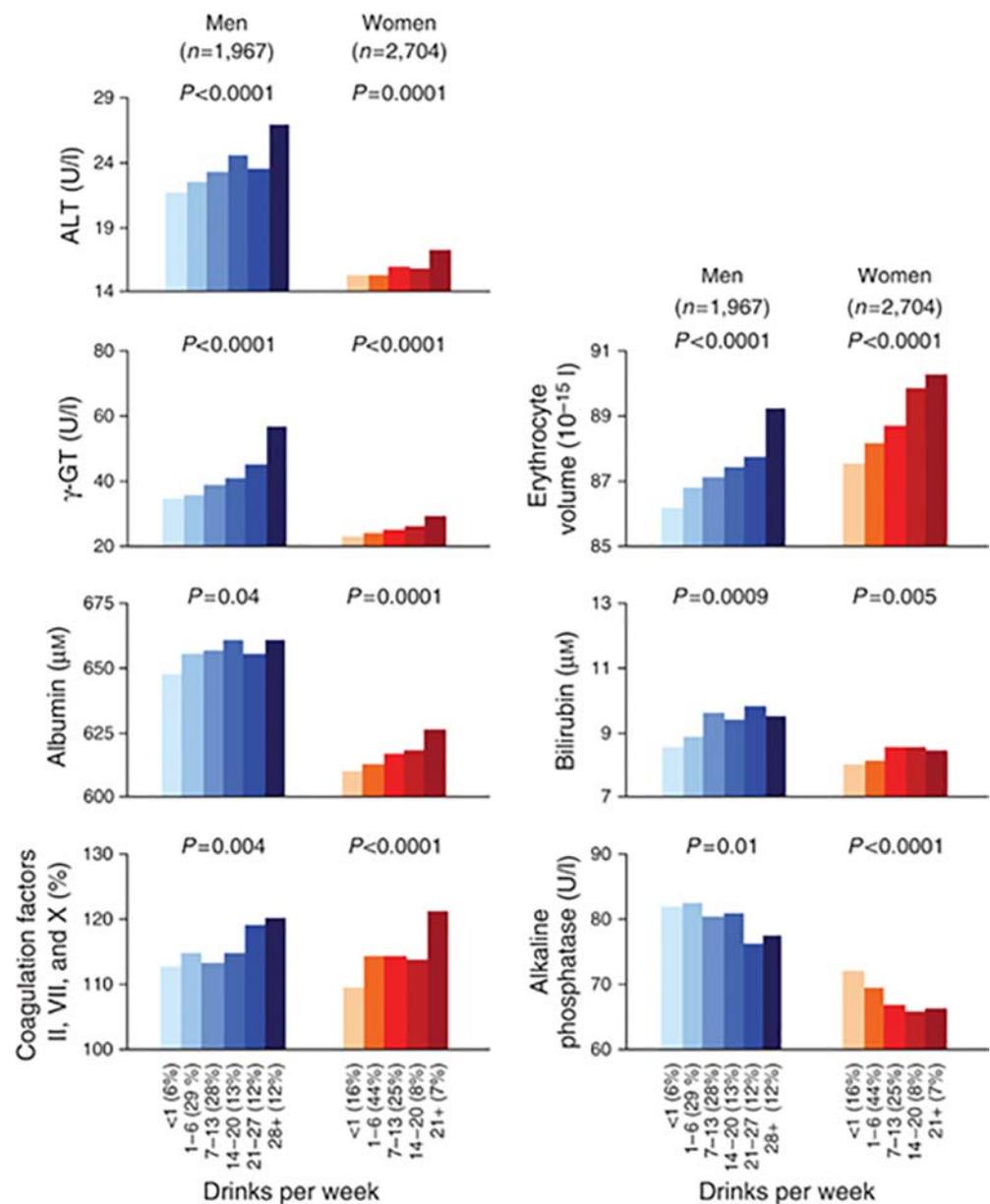

Figure 8. Biochemical signs of liver damage according to alcohol intake in the general population. Values are from the 2001–2003 examination of the Copenhagen City Heart Study. Average values shown are estimated from generalized linear models and apply for a reference person (age 40 years, never smoker, and education less than or equal to7 years). P values are for linear trend. ALT, alanine aminotransferase, γ-GT, γ-glutamyl transpeptidase. From: Tolstrup et al. 2009. doi: 10.1038/ajg.2009.370.
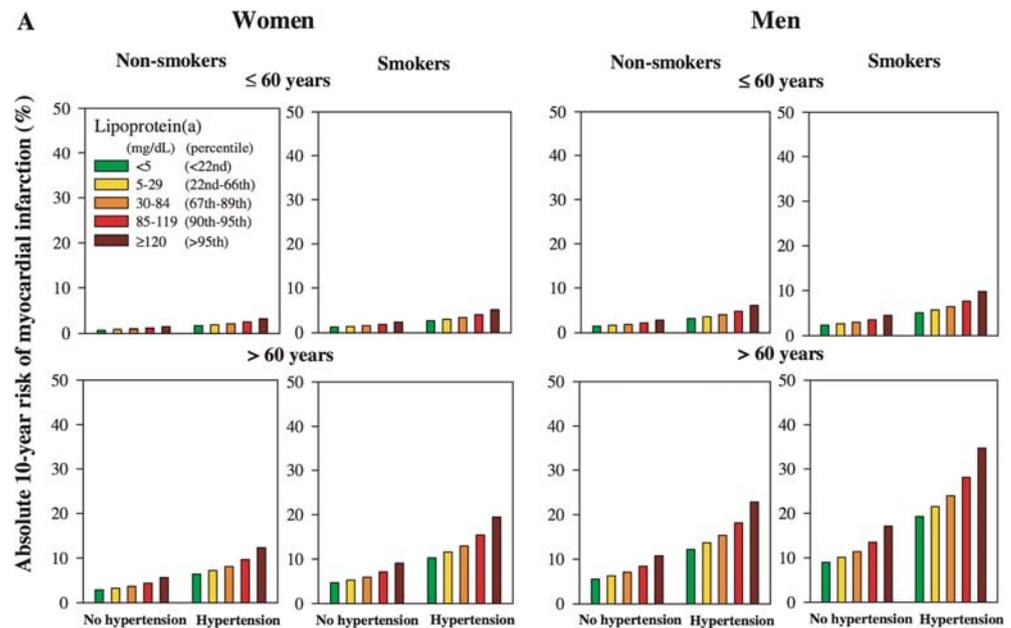
Figure 9. Absolute 10-year risk of MI (A) and by lipoprotein(a) levels, gender, smoking, hypertension, and age.
Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. Circulation. 10.1161/circulationaha.107.715698.

two in *PNPLA3*, an established locus for NAFLD, and one (Glu167Lys) in *TM6SF2*, a gene of unknown function. The results were confirmed by comparing between 3 different cohorts: Dallas Heart Study, Dallas Biobank and the Copenhagen Study (CCHS + Copenhagen Population study) (Figure 10).[41]

In another study aiming at the assessment of the seasonality of cardiovascular risk factors (CVRF) in a large set of population-based studies, cross-sectional data from 24 population based studies from 15 countries, with a total sample size of 237 979 subjects were analysed.[42] CVRFs showed a seasonal pattern characterised by higher levels in winter, and lower levels in summer. This pattern could contribute to the seasonality of CV mortality.

In 2014, the team of Prof. Tybjærg-Hansen, used the data from 75,725 participants in the CCHS and the Copenhagen Population study to find out that Loss-of-function mutations in APOC3 were associated with low levels of triglycerides and a reduced risk of ischemic cardiovascular disease (Figure 11).[43] Another study by the same group used data also from both studies (67,385 individuals) to confirmed the hypothesis that genetic variation in Niemann-Pick C1-Like protein 1 (*NPC1L1*), mimicking the effect of ezetimibe, an inhibitor of NPC1L1 was associated with reduced risk of ischaemic vascular disease (IVD) with a corresponding reduction in LDL cholesterol, but with a concomitant increased risk of gallstone disease.[44]

WHAT HAVE WE LEARNED?

Whether one is in the process of planning a new population study or developing an ongoing one, there are several lessons to be learned from the CCPHS. Four of the most prominent lessons from this study are:

(1) Rigorous and complete Data Collection: Loss of follow up is one of the major factors that can distort many epidemiological studies, this can happen due to lack of system or discipline of the study parties. In Denmark, for example, every hospital discharge diagnosis is recorded centrally as well as detailed diagnoses, morbidity and mortality and demographic information. This information is extracted yearly from the registries on all participants at major Danish population studies. This globally unique feature made it possible for the CCHS to manage and follow a large number of participants with a limited budget.

(2) An evolving study design: In the recent years the CCHS has been particularly fruitful with seminal contributions such as the protective relationship of regulated physical activity to a

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Study	Trait	EE[a]	EK[a]	KK[a]	P value
DHS					
	n	4,151	423	13	–
	ALT (U)	23.5 ± 19.9	25.8 ± 18.0	29.6 ± 26.8	0.014
	AST (U)	24.3 ± 20.6	25.1 ± 19.6	25.6 ± 16.5	0.17
	ALP (U)	71.6 ± 26.4	68.0 ± 20.9	63.6 ± 16.4	0.031
	LDL-C (mg/dl)	109 ± 36	105 ± 34	94 ± 39	0.005
	Triglycerides (mg/dl)	123 ± 102	118 ± 91	130 ± 66	0.037
Dallas Biobank (European Americans)					
	n	7,416	1,112	57	–
	ALT (U)	35.9 ± 16.3	36.5 ± 15	44.8 ± 23.8	0.003
	AST (U)	27 ± 13.8	26.9 ± 10.7	30.2 ± 13.5	0.22
	ALP (U)	69 ± 18.9	66.9 ± 17.3	65.9 ± 19.1	1.2×10^{-4}
	LDL-C (mg/dl)	107 ± 34	105 ± 32	97 ± 32	0.029
	Triglyceride (mg/dl)	112 ± 79	105.3 ± 67	97.5 ± 54	6.7×10^{-5}
Copenhagen Study					
	n	61,279	11,700	553	–
	ALT (U)	22.7 ± 17.2	23.8 ± 16.0	26.7 ± 20.9	7.6×10^{-14}
	AST (U) (n = 8,487)	22.8 ± 13.2	23.9 ± 18.6	30.0 ± 36.6	1.8×10^{-4}
	ALP (U)	91.1 ± 37.5	89.7 ± 39.1	85.0 ± 34.2	4.3×10^{-7}
	LDL-C (mg/dl)	128 ± 39	127 ± 38	112 ± 36	4.7×10^{-14}
	Triglyceride (mg/dl)	152 ± 106	148 ± 96	133 ± 90	3.7×10^{-9}

Figure 10. Association between the nonsynonymous TM6SF2 variant (p.Glu167Lys), liver enzymes and plasma lipid levels in DHS, the Dallas Biobank and the Copenhagen Study. Values are means ± s.d. Association was tested using linear regression with adjustment for age, sex, BMI and ancestry (where appropriate). A logarithm transformation was applied to traits with non-normal distributions. AST was only measured in a subset of the Copenhagen Study (n = 8,487). Ancestry breakdown for DHS is provided in Supplementary Table 3.ALT, alanine aminotransferase; AST, aspartate transaminase; ALP, alkaline phosphatase; LDL-C, low-density lipoprotein – cholesterol. [a]EE, homozygotes for the allele encoding Glu167; EK, heterozygotes; KK, homozygotes for the allele encoding Lys167. From: Kozlitina et al., Nat Genet. 2014, 46(4):352-6. doi: 10.1038/ng.2901.

health of physical function, the association of fatigue and depression with CVD risk, the importance of even light tobacco smoking to excess risk, the association of intimate and rich family society with reduced CVD risk, the association of moderate wine drinking with lower risk of CHD and Stroke and understand the relevance of molecular agents in disease development.

(3) The CCHS is one of a number of prominent Population Studies in the field of cardiovascular disease, such as the Framingham Heart Study (launched in 1948 by the National Heart, Lung, and Blood Institute (NHLBI)), the Dallas Heart Study (1999, UT Southwestern, reviewed in
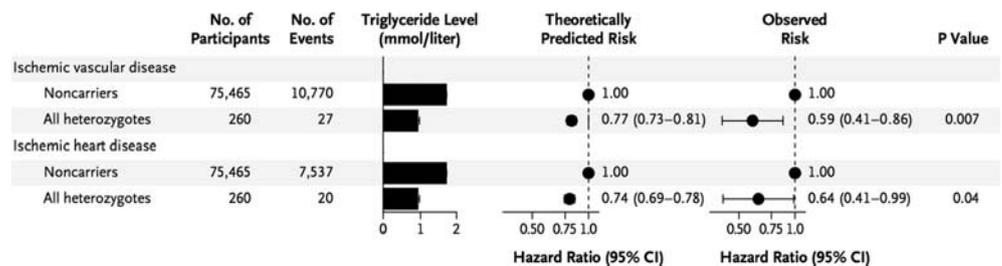
	No. of Participants	No. of Events	Triglyceride Level (mmol/liter)	Theoretically Predicted Risk	Observed Risk	P Value
Ischemic vascular disease						
Noncarriers	75,465	10,770		1.00	1.00	
All heterozygotes	260	27		0.77 (0.73–0.81)	0.59 (0.41–0.86)	0.007
Ischemic heart disease						
Noncarriers	75,465	7,537		1.00	1.00	
All heterozygotes	260	20		0.74 (0.69–0.78)	0.64 (0.41–0.99)	0.04
			0 1 2	0.50 0.75 1.0 Hazard Ratio (95% CI)	0.50 0.75 1.0 Hazard Ratio (95% CI)	

Figure 11. Mean plasma levels of nonfasting triglycerides and hazard rations for ischemic vascular disease and ischemic heart disease as a function of APOC3 genotype. Data are for all heterozygotes for the R19X, IVS2 + 1G → A, or A43T mutation versus noncarriers of these mutations among participants in the CCHS and the CGPS combined. The median follow-up period was 34 years. The theoretically predicted risk ratios were calculated as the risk of ischemic vascular disease or ischemic heart disease associated with a decrease in levels of nonfasting triglycerides among all heterozygotes as compared with noncarriers. P values are for the association between genotype and the observed risk of ischemic vascular disease or ischemic heart disease. The analyses were adjusted for age (as the time scale), sex, current smoking status, presence or absence of hypertension, physical inactivity, and alcohol consumption. From: Jørgensen et al., N Engl J Med. 2014 Jul 3;371(1):32 – 41. doi: 10.1056/NEJMoa1308027.

Al Suwaidi el al.[45] and the London Life Sciences Prospective Population (LoliPop) Study (2002, Imperial College and Ealing Hospital). As obvious in a significant number of investigations, the CCHS is not isolated from other population studies: CCHS data are integrated with its sister studies (The Copenhagen General Population (CGPS) Study and the Copenhagen ischaemic Heart Disease Study (CIHDS)). On a larger scale CCHS data are integrated in global studies, such as the Mendelian randomisation analysis on cardiometabolic effects of genetic upregulation of the interleukin 1 receptor antagonist, which integrated data from the 3 Danish Population Studies with data from the Cardiovascular Health Study (CHS), European Prospective Investigation into Cancer and Nutrition-Cardiovascular Disease study (EPIC-CVD) and more.[46] This enables researchers to look at the bigger, global picture.

(4) In the Middle East and North Africa (MENA) CVD is highly prevalent. Studies of CVD etiology and manifestation in the region results into interesting observations such as that acute cardiac diseases occur at relatively younger age when compared to the developed countries and that the use of evidence-based therapies is suboptimal,[47,48] such findings can directly be translated into practice[49] with a significant improvement in care. Similar observations were reported from the acute heart failure registry. Conducting well-designed population studies in the region, will have a large impact on understanding and curing CVD in the region, integrating the outcome into global studies will contribute to our understanding of CVD world-wide.

CONCLUSIONS

The strengths of the majority of CCHS-based investigations include the random population sample, prospective design, detailed information about potential confounding variables, and almost 100% complete follow-up.

The CCHS has still a lot of potential and unreached aims: such as understanding why women survive men by several years. It continues working towards these goals within its national and international multidisciplinary network partners, which is the only way to translate the gained knowledge to disease prevention, healthcare and therapeutic strategies.

The MENA region lacks studies that evaluate individuals in the community with various traditional and novel risk factors, on the clinical and molecular level, such as reported in the current review of the Copenhagen City Heart Study, as well as in other studies such as the Framingham Heart Study and Dallas Heart Study that evaluated indiviuals without cardiovascular disease and followed them up over long-term period. This highlights the urgent need to conduct similar but "tailored" studies in the region.

REFERENCES

[1] Epidemiology of chest pain and angina pectoris, with special reference to treatment needs. In: Jensen G, ed. *Acta Med Scand; suppl 682*. Thesis; 1984.

[2] Appleyard M, Hansen AT, Schnohr P, Jensen G, Nyboe J, The Copenhagen City Heart Study. Øster- broundersøgelsen. A book of tables with data from the first examination (1976–78) and a five year follow-up (1981–83). *Scand J Soc Med*. 1989;170(suppl 41):1–160.

[3] Schnohr P, Jensen G, Lange P, Scharling H, Appleyard M. Tables with data from the third examination 1991–94. *Eur Heart J*. 2001;3(suppl H).

[4] Schnohr P. Physical activity in leisure time: impact on mortality. Risks and benefits. *Dan Med Bull*. 2009;56(1):40–71, Review.

[5] Rose GA, Blackburn H. *Cardiovascular survey methods*. Geneva: Wld Health Org Monogr Ser 56 1968.

[6] Johnson JF. *Adult Physical Fitness: A Program for Men and Women Prepared by the President's Council on Physical Fitness*. Washington, DC: President's Council on Physical Fitness; 1965:64.

[7] Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, Buchner D, Ettinger W, Heath GW, King AC, Kriska A, Leon AS, Marcus BH, Morris J, Paffenbarger RS, Patrick K, Pollock ML, Rippe JM, Sallis JF, Wilmore JH. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA*. 1995;273(402–7):5.

[8] Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116:1081–1093.

[9] Physical Activity Guidelines for Americans. Washington, DC: U.S. Department of Health and Human Services; 2008:1–76.

[10] Schnohr P, Scharling H, Jensen JS. Intensity versus duration of walking, impact on mortality: the Copenhagen City Heart Study. *Eur J Cardiovasc Prev Rehabil*. 2007;14(72–8):15.

[11] Schnohr P, Marott JL, Jensen JS, Jensen GB. Intensity versus duration of cycling, impact on all-cause and coronary heart disease mortality: the Copenhagen City Heart Study. *Eur J Prev Cardiol*. 2012;19:73–80.

[12] Schnohr P, Marott JL, Lange P, Jensen GB. Longevity in male and female joggers: the Copenhagen City Heart Study. *Am J Epidemiol*. 2013;177:683–689.

[13] Schnohr P, O'Keefe JH, Marott JL, Lange P, Jensen GB. Dose of jogging and long-term mortality: the Copenhagen City Heart Study. *J Am Coll Cardiol.* 2015;65(5):411−419, doi: 10.1016/j.jacc.2014.11.023.

[14] Ector J, Ganame J, van der Merwe N, Adriaenssens B, Pison L, Willems R, Gewillig M, Heidbüchel H. Reduced right ventricular ejection fraction in endurance athletes presenting with ventricular arrhythmias: a quantitative angiographic assessment. *Eur Heart J Suppl.* 2007;28:345−353.

[15] O'Keefe JH, Patil HR, Lavie CJ, Magalski A, Vogel RA, McCullough PA. Potential adverse cardiovascular effects from excessive endurance exercise. *Mayo Clin Proc.* 2012;87:587−595.

[16] Bhella PS, Hastings JL, Fujimoto N, Shibata S, Carrick-Ranson G, Palmer MD, Boyd KN, Adams-Huet B, Levine BD. Impact of lifelong exercise dose on left ventricular compliance and distensibility. *J Am Coll Cardiol.* 2014;64:1257−1266.

[17] Sørensen SP, Boysen G, Jensen G, Schnohr P. Prevalence of stroke in a district of Copenhagen the copenhagen city heart study. *Acta Neurol Scand. Jul;* 1982;66(1):68−81.

[18] Lange P, Groth S, Nyboe J, Appleyard M, Mortensen J, Jensen G, Schnohr P. Chronic obstructive lung disease in Copenhagen: cross-sectional epidemiological aspects. *J Intern Med. Jul;* 1989;226(1):25−32.

[19] Lange P, Groth S, Kastrup J, Mortensen J, Appleyard M, Nyboe J, Jensen G, Schnohr P. Diabetes mellitus, plasma glucose and lung function in a cross-sectional population study. *Eur Respir J. Jan;* 1989;2(1):14−19.

[20] Nyboe J, Jensen G, Appleyard M, Schnohr P. Risk factors for acute myocardial infarction in Copenhagen I: Hereditary, educational and socioeconomic factors. *Copenhagen City Heart Study. Eur Heart J.* 1989;10(10):910−916, Stroke, 1994 Apr; 25(4):802-7.

[21] Lindenstrøm E, Boysen G. Nyboe Lifestyle factors and risk of cerebrovascular disease in women. The Copenhagen City Heart Study. *Scand J Clin Lab Invest Suppl.* 1995;220:57−76.

[22] Friberg J, Scharling H, Gadsbøll N, Jensen GB. Sex-specific increase in the prevalence of atrial fibrillation (The Copenhagen City Heart Study). *Am J Cardiol.* 2003;92(12):1419−1423.

[23] Truelsen T, Lindenstrøm E, Boysen G. Comparison of probability of stroke between the Copenhagen City Heart Study and the Framingham Study. *Stroke.* 1993;24(10):1468−1472.

[24] Nordestgaard BG, Agerholm-Larsen B, Wittrup HH, Tybjaerg-Hansen A. A prospective cardiovascular population study used in genetic epidemiology. The Copenhagen City Heart Study. *Circulation.* 1997;95(10):2358−2367.

[25] Agerholm-Larsen B, Nordestgaard BG, Steffensen R, Sørensen TI, Jensen G, Tybjaerg-Hansen A. ACE gene polymorphism: ischemic heart disease and longevity in 10,150 individuals. A case-referent and retrospective cohort study based on the Copenhagen City Heart Study. *Circulation.* 2000;102(18):2197−2203.

[26] Agerholm-Larsen B, Tybjaerg-Hansen A, Schnohr P, Steffensen R, Nordestgaard BG. Common cholesteryl ester transfer protein mutations, decreased HDL cholesterol, and possible decreased risk of ischemic heart disease: The Copenhagen City Heart Study. *Ann Intern Med.* 2001;134(10):941−954.

[27] Sethi AA, Tybjaerg-Hansen A, Grønholdt ML, Steffensen R, Schnohr P, Nordestgaard BG. Angiotensinogen mutations and risk for ischemic heart disease, myocardial infarction, and ischemic cerebrovascular disease. Six case-control studies from the Copenhagen City Heart Study. *Lakartidningen.* 2002;99(21):2392−2393.

[28] Høyer AP, Gerdes AM, Jørgensen T, Rank F, Hartvig HB. Organochlorines, p53 mutations in relation to breast cancer risk and survival. A Danish cohort-nested case-controls study. *Breast Cancer Res Treat.* 2002;71(1):59−65.

[29] Juul K, Tybjaerg-Hansen A, Steffensen R, Kofoed S, Jensen G, Nordestgaard BG, Factor V. Leiden: The Copenhagen City Heart Study and 2 meta-analyses. *Blood.* 2002;100(1):3−10.

[30] Kofoed SC, Wittrup HH, Sillesen H, Nordestgaard BG. Fibrinogen predicts ischaemic stroke and advanced atherosclerosis but not echolucent, rupture-prone carotid plaques: the Copenhagen City Heart Study. *Eur Heart J. Mar;* 2003;24(6):567−576.

[31] Mukamal KJ, Tolstrup JS, Friberg J, Grønbaek M, Jensen G. Fibrinogen and albumin levels and risk of atrial fibrillation in men and women (the CopenhagenCity Heart Study). *Am J Cardiol.* 2006;98(1):75−81.

[32] Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG. Integrin beta3 Leu33Pro homozygosity and risk of cancer. *J Natl Cancer Inst.* 2003;95(15):1150−1157.

[33] Juul K, Tybjaerg-Hansen A, Marklund S, Heegaard NH, Steffensen R, Sillesen H, Jensen G, Nordestgaard BG. Genetically reduced antioxidative protection and increased ischemic heart disease risk: The Copenhagen City Heart Study. *Circulation.* 2004;109(1):59−65, Epub 2003 Dec 8.

[34] Frikke-Schmidt R, Nordestgaard BG, Schnohr P, Tybjaerg-Hansen A. Single nucleotide polymorphism in the low-density lipoprotein receptor is associated with a threefold risk of stroke. A case-control and prospective study. *Eur Heart J.* 2004;25(11):943−951.

[35] Stene MC, Frikke-Schmidt R, Nordestgaard BG, Steffensen R, Schnohr P, Tybjaerg-Hansen A. Zink Finger Protein 202: a new candidate gene for ischemic heart disease: The Copenhagen CityHeart Study. *Atherosclerosis.* 2006;188(1):43−50, Epub 2005 Nov 14.

[36] Truelsen T, Gronbaek M, Schnohr P, Boysen G. Intake of beer, wine, and spirits and risk of stroke: the copenhagen city heart study. *Stroke.* 1998;29(12):2467−2472.

[37] Tolstrup JS, Grønbaek M, Tybjaerg-Hansen A, Nordestgaard BG. Alcohol intake, alcohol dehydrogenase genotypes, and liver damage and disease in the Danish general population. *Am J Gastroenterol.* 2009;104(9):182−188, doi: 101038/ajg2009370.

[38] Thomsen M, Ingebrigtsen TS, Marott JL, Dahl M, Lange P, Vestbo J, Nordestgaard BG. Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. *JAMA.* 2013;309(22):2353−2361, doi: 10.1001/jama.2013.5732.

[39] Kamstrup PR, Tybjærg-Hansen A, Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. *J Am Coll Cardiol.* 2014;63(5):470−477, doi: 10.1016/j.jacc.2013.09.038. Epub 2013 Oct 23.

[40] Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. *Circulation.* 2008;117(2):176−184.

[41] Kozlitina J, Smagris E, Stender S, Nordestgaard BG, Zhou HH, Tybjærg-Hansen A, Vogt TF, Hobbs HH, Cohen JC. Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet. Apr;* 2014;46(4):352–356, doi: 10.1038/ng.2901. Epub 2014 Feb 16.

[42] Marti-Soler H, Gubelmann C, Aeschbacher S, Alves L, Bobak M, Bongard V, Clays E, deGaetano G, DiCastelnuovo A, Elosua R, Ferrieres J, Guessous I, Igland J, Jørgensen T, Nikitin Y, O'Doherty MG, Palmieri L, Ramos R, Simons J, Sulo G, Vanuzzo D, Vila J, Barros H, Borglykke A, Conen D, De Bacquer D, Donfrancesco C, Gaspoz JM, Giampaoli S, Giles GG, Iacoviello L, Kee F, Kubinova R, Malyutina S, Marrugat J, Prescott E, Ruidavets JB, Scragg R, Simons LA, Tamosiunas A, Tell GS, Vollenweider P, Marques-Vidal P. Seasonality of cardiovascular risk factors: an analysis including over 230 000 participants in 15 countries. *Heart.* 2014;100(19):1517–1523, Epub 2014 May 30.

[43] Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG, Tybjærg-Hansen A. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. *N Engl J Med.* 2014;371(1):32–41, doi: 10.1056/NEJMoa1308027. Epub 2014 Jun 18.

[44] Lauridsen BK, Stender S, Frikke-Schmidt R, Nordestgaard BG, Tybjærg-Hansen A. Genetic variation in the cholesterol transporter NPC1L1, ischaemic vascular disease, and gallstone disease. *Eur Heart J.* 2015;pii:ehv108. [Epub ahead of print].

[45] Al Suwaidi J. The Dallas Heart Study using the probability sample technique for ethnicity and cardiovascular health differences. *Glob Cardiol Sci Pract.* 2015;2015:1, doi: 10.5339/gcsp.2015.1.

[46] Freitag DF, Butterworth AS, Willeit P, Howson JM, Burgess S, Kaptoge S, Young R, Ho WK, Wood AM, Sweeting M, Spackman S, Staley JR, Ramond A, Harshfield E, Nielsen SF, Grande P, Lange LA, Bown MJ, Jones GT, Scott RA, Bevan S, Porcu E, Thorleifsson G, Zeng L, Kessler T, Do R, Nikpay M, Zhang W, Hopewell JC, Kleber M, Delgado GE, Nelson CP, Goel A, Bis JC, Dehghan A, Ligthart S, Smith AV, Qu L, van't Hof FN, deBakker PI, Baas AF, van Rij A, Tromp G, Kuivaniemi H, Ritchie MD, Verma SS, Crawford DC, Malinowski J, deAndrade M, Kullo IJ, Peissig PL, McCarty CA, Böttinger EP, Gottesman O, Crosslin DR, Carrell DS, Rasmussen-Torvik LJ, Pacheco JA, Huang J, Timpson NJ, Kettunen J, Ala-Korpela M, Mitchell GF, Parsa A, Wilkinson IB, Gorski M, Li Y, Franceschini N, Keller MF, Ganesh SK, Langefeld CD, Bruijn L, Brown MA, Evans DM, Baltic S, Ferreira MA, Baurecht H, Weidinger S, Franke A, Lubitz SA, Müller-Nurasyid M, Felix JF, Smith NL, Sudman M, Thompson SD, Zeggini E, Panoutsopoulou K, Nalls MA, Singleton A, Polychronakos C, Bradfield JP, Hakonarson H, Easton DF, Thompson D, Tomlinson IP, Dunlop M, Hemminki K, Morgan G, Eisen T, Goldschmidt H, Allan JM, Henrion M, Whiffin N, Wang Y, Chubb D, Houlston RS, Iles MM, Bishop DT, Law MH, Hayward NK, Luo Y, Nejentsev S, Barbalic M, Crossman D, Sanna S, Soranzo N, Markus HS, Wareham NJ, Rader DJ, Reilly M, Assimes T, Harris TB, Hofman A, Franco OH, Gudnason V, Tracy R, Psaty BM, Farrall M, Watkins H, Hall AS, Samani NJ, März W, Clarke R, Collins R, Kooner JS, Chambers JC, Kathiresan S, McPherson R, Erdmann J, Kastrati A, Schunkert H, Stefánsson K, Walston JD, Tybjærg-Hansen A, Alam DS, Majumder AA, DiAngelantonio E, Chowdhury R, Nordestgaard BG, Saleheen D, Thompson SG, Danesh J. Interleukin 1 Genetics Consortium. Cardiometabolic effects of genetic upregulation of the interleukin 1 receptor antagonist: a Mendelian randomisation analysis. *Lancet Diabetes Endocrinol. Apr;* 2015;3(4):243–253.

[47] Al Suwaidi J. Acute coronary syndrome in the Middle East: The importance of registries for quality assessment and plans for improvement. *Glob Cardiol Sci Pract.* 2013;2013(1):2–4.

[48] Sulaiman K, Panduranga P, Al-Zakwani I, Alsheikh-Ali AA, AlHabib KF, Al-Suwaidi J, Al-Mahmeed W, AlFaleh H, Elasfar A, Al-Motarreb A, Ridha M, Bulbanat B, Al-Jarallah M, Bazargani N, Asaad N, Amin H. Clinical characteristics, management, and outcomes of acute heart failure patients: observations from the Gulf acute heart failure registry (Gulf CARE). *Eur J Heart Fail. Apr;* 2015;17(4):374–384.

[49] Gehani A, Al Suwaidi J, Arafa S, Tamimi O, Alqahtani A, Al-Nabti A, Arabi A, Aboughazala T, Bonow RO, Yacoub M. Primary coronary angioplasty for ST-Elevation Myocardial Infarction in Qatar: First nationwide program. *Glob Cardiol Sci Pract.* 2013;2012(2):43–55.