A CASE-CONTROL STUDY OF CORNEAL ARCUS AND CORONARY HEART DISEASE IN YEREVAN

Master of Public Health Thesis Project Utilizing Professional Publication Framework

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Executive Summary

Arcus senilis or corneal arcus is a yellowish-white ring around the cornea. It is caused by the extra cellular lipid deposition in the peripheral cornea. Lipids are normally deposited in the cornea, but it is believed that with aging the amount of lipids deposited increases, possibly resulting in arcus senilis.

Objective: This study investigated whether corneal arcus can predict coronary heart disease and cardiovascular diseases.

Methods: A case-control study was used. The study included 96 participants. Risk factors of coronary heart disease were assessed using a questionnaire. A simple eye examination was completed using an ophthalmoscope. Simple and multiple logistic regressions were used to assess the association between coronary heart disease and corneal arcus. The accuracy of corneal arcus as screening tool to detect coronary heart disease was assessed by calculating sensitivity and specificity.

Results: Coronary heart disease was statistically significantly associated with hypertension and corneal arcus. Multiple logistic regression revealed potential confounder such as hypertension. The sensitivity and specificity of using corneal arcus as screening tool for people 35-50 years of age were 19% and 100% respectively. The positive predictive value (PPV) was 100% and negative predictive value (NPV) was 55%. For those over 50 years of age, PPV dropped to 58% while NPV remained 57%.

Conclusion: This study presents preliminary results concerning the relationship of corneal arcus and coronary heart disease among people in Yerevan. The accuracy of corneal arcus as screening tool for detecting coronary heart disease limits its worth to clinical settings. Considering the limitations of this study (recall bias and misclassification of visitors as controls) more research is needed to sufficiently assess the influence of selected factors on the relationship between coronary heart disease and corneal arcus.

Introduction

Background

Hyperlipidemia affects many patients [1]. A diagnosis of hyperlipidemia is primarily made based on laboratory analysis of blood samples. However the presence of hyperlipidemia may also be inferred by observing lipid deposition, which can occur in various organ systems, such as the vascular system, musculoskeletal system and eyes [1]. Arcus senilis or corneal arcus is a yellowish-white ring around the cornea that is separated from the limbus by a clear zone 0.3 to 1.0 mm in width [2], and is caused by extra cellular lipid deposition in the peripheral cornea. The deposits consist of cholesterol, cholesterol esters, phospholipids, and triglycerides. The fatty acids that make up many of the deposited lipid molecules include palmitic, stearic, oleic, and linoleic acids [2]. Lipids are normally deposited in the cornea, but it is believed that with aging the amount of lipids deposits increases, possibly resulting in arcus senilis [3].

Arcus senilis is more prevalent among the elderly, but it has been observed in younger adults and even in children [2]. The estimated prevalence of arcus senilis is 8% for those 40 to 49 years of age, 45% for those 50 to 59 years of age, and 75% for those 70 to 79 years of age [4]. In a cohort of insulin dependent diabetic patients who were less than 30 years of age, the prevalence was 6% to 12%, and 49% to 54% for diabetics who were more than 30 years of age [5]. Arcus senilis is more common in men than in women [6]. Arcus senilis may also be more common in patients who regularly consume alcoholic beverages, with the prevalence increasing as the amount of alcohol consumption increases [6].

Several epidemiological studies assessed the association of corneal arcus with dyslipidemia [2, 7, 8] in people less than 50 years. A cross sectional study (n=243 subjects) with an age range of 20-63 years conducted to assess the prevalence of corneal arcus and the association between corneal arcus and dyslipidemia [7]. In the 20-29 year group the prevalence of corneal arcus was 0%, in 30-49 year group - 41.5% for males and 26.13% for females, and in 50-69 year group - 86.2% for males and

59.1% for females. There was no difference for corneal arcus and serum lipid in the 50-69 years group between sexes. While corneal arcus is primarily an age-related change, if present in people less than 50 years it should be considered a marker for dyslipidemia [7].

Another study, Lipid Research Clinics Mortality Follow-up Study showed the relationship between corneal arcus and mortality from coronary heart disease (CHD) and cardiovascular disease (CVD). This study included white men (n = 3,930) and women non-hormone users (n = 2,139), ages 30-69, followed for an average of 8.4 years [2]. Corneal arcus was strongly associated with CHD and CVD mortality, but only in hyperlipidemic men aged 30-49 years [2]. The main conclusion was that among 30-49 year old males, corneal arcus appears to be a prognostic factor for CHD, independent of its association with hyperlipidemia in this age group, underlying the usefulness of corneal arcus as a prognostic factor to the practicing clinician [2].

The Western Collaborative Group Study was a prospective study (n=3,154) of employed men aged 39 to 59 years during 8.5 year average follow-up period [8]. The incidence of CHD had a highly significant association with serum cholesterol level, behavior pattern, cigarette smoking and systolic blood pressure in younger (39 to 49 years) and older (50 to 59 years) men and also with corneal arcus in the younger group [8].

Risk factors for coronary heart disease

Age, sex, personal and family history of cardiovascular disease are nonmodifiable risk factors for CHD [9]. Hypercholesterolemia, hypertension, and cigarette smoking are the major modifiable risk factors [10, 11, 12].

Diabetes Mellitus. Coronary and peripheral atherosclerosis is a main cause of morbidity and mortality in diabetics [9]. Epidemiological study of prediction of coronary heart disease in middle-aged adults with diabetes showed that even though all diabetic adults are at high risk for CHD, their variation in CHD risk can be predicted moderately well by

basic risk factors such as age, total and HDL cholesterol, systolic blood pressure, and smoking status [13].

Obesity. Important consideration is distribution of body fat not just its extent. A surplus of trunkal and intra-abdominal fat is a risk factor for CHD and has an adverse effect on lipid levels, blood pressure, and glucose tolerance [9].

Hypertension. Arterial hypertension is a risk factor for stroke, CHD, and other cardiovascular diseases [14]. Its treatment decreases the incidence of stroke by 40% and of CHD by 14% within 5 years. Isolated systolic hypertension is considered a cardiovascular risk factor, especially in the elderly, and should be treated [15, 16].

Cigarette Smoking. About 30% of cardiovascular deaths are due to smoking [17].

Drinking alcoholic beverages. Epidemiologic studies show that light to moderate alcohol consumption from beer, wine, or spirits is connected with a decrease in all-cause mortality, especially to a reduced risk of CHD [18, 19].

Family History. In the Reykjavik Cohort Study, a total of 9,328 males and 10,062 females, aged 33-81, were examined. Compared with subjects without a family history, the hazard ratio of coronary heart disease was 1.75 (95% CI 1.59-1.92) for men and 1.83 (95% CI 1.60-2.11) for women, with one or more first-degree relatives with myocardial infarction. The risk factor profile was significantly worse in individuals with a positive family history [20]. The main result was that family history of myocardial infarction increases the risk of developing coronary heart disease in both men and women and is independent of other classic risk factors [20].

Hyperlipidemia. The Scandinavian Simvastatin Survival Study [21], the West of Scotland Coronary Prevention Study [22], the Cholesterol and Recurrent Events study [23], the Air Force/Texas Coronary Atherosclerosis Prevention Study [24] and the Lovastatin in the Prevention of Ischemic Disease (LIPID) study [25], show that lowering LDL cholesterol, the

most atherogenic lipoprotein class, by statin drugs in addition to diet decreases the incidence of fatal and nonfatal myocardial infarction in both primary and secondary prevention. Total mortality is also reduced by LDL cholesterol lowering treatment, particularly in individuals with CHD.

Main objective for this study was:

- Is corneal arcus predictive factor of a coronary heart disease and cardiovascular diseases?

Subjects and Methods

Study Design

A case-control study design was used to determine association between corneal arcus and coronary heart disease. As the formation of corneal arcus is accelerated by high serum LDL-cholesterol, which is a risk factor for coronary heart disease it will also be useful to study other risk factors of coronary heart disease. The case-control study design is useful because of necessity in testing a variety of exposure factors among the diseased and controls [26].

Sample size

The case definition for this study included all patients from Yerevan having undergone coronary angiography for the first time at Nork Marash Medical Center (NMMC) during the time of the survey (July 2003-August 2003) and having a maximal stenosis >60%. The control group consisted of visitors at NMMC who were free from any evidence of clinical coronary artery disease. The sample size was calculated to be 60 per group (CI 95%, power 80 %, OR=1.5). For each case 2 different control groups planned to be selected. The first control group was planed to include patients from Yerevan who had undergone coronary angiography for the first time at NMMC during the time of the survey and had completely

normal coronaries. This control group included very few people (2 men) that is why they were excluded from the study, leaving only the visitor group as controls.

Study Population

Cases

The study population included patients who underwent coronary angiography at NMMC, as part of their cardiologic evaluation for variety of clinical manifestations and their matched visitor controls. The eligibility criteria of the cases were: 1) first diagnosed as having a maximal coronary stenosis >60% during coronary angiography at the NMMC between July 15, 2003-September 1, 2003; 2) residence in Yerevan; 3) age 35-75 years; 4) no previous coronary bypass surgery; 5) availability for interview. Degree of coronary artery disease was based on percent stenosis in at least one major coronary vessel. Vessels that contained more than one lesion, the percent stenosis of severe lesion was considered.
All available cases undergoing coronary angiography were taken during the study period. For 75 people undergoing coronary angiography, 27 people did not meet the study criteria. In all, 48 (64%) cases were interviewed.

Controls

The control group consisted of visitors at the NMMC who were free from any evidence of clinical coronary artery disease. From a table of random digits, a hospital room number was selected randomly and visitors who were present at the patient room were considered eligible for the study. Eligibility of visitors also was determined by asking questions about age and presence or history of clinical coronary artery disease. When more than one eligible control was present in a single room, the control with the nearest age to the case was taken. If the process was not successful in finding a matched visitor control it was

repeated with the next random room number. To be eligible, the control subjects had to be matched to cases by age (within 2 years) and gender.

Data collection

The data were collected using a questionnaire and eye examination both administered by the interviewer prior to knowledge of the arteriogram results. It required about 15 minutes. Eye examinations were done by using an ophthalmoscope and assessed by the ophthalmologist based on visual inspection. The ophthalmoscope is an instrument that allows light to be directed into the eye and take view of the external part of the eye. During examination arcus appears to have a hazy white shape, with a sharp outer border and an indistinct central border and it is denser superiorly and inferiorly. There was also a central corneal sparing and an intervening clear space between the limbus and the arcus. Information was recorded using a structured questionnaire adapted from WESDR V younger-onset questionnaire (Adler A, WESDR4_EXAM, Version-1) that included the following domains: socio demographic characteristics (age, gender, place of residence, place of birth, nationality); anthropometric measurements; assessment of general health; personal history including current diseases, such as systematic blood hypertension, diabetes mellitus, high cholesterol and coronary heart diseases; smoking and drinking habits; physical activity, and eye examination, which included examination of cornea. The questionnaire was twice pretested in NMMC.

Data Processing

The database was constructed using SPSS 10.0 statistical software package. Data cleaning was also performed in SPSS statistical software package. The statistical analysis was carried out using STATA 7.0 statistical program. Simple logistic regression was performed to

calculate odds ratios (OR) and 95% Confidence Intervals (CI) to show associations between each factor of interest and coronary heart disease. Association between coronary heart disease and corneal arcus was adjusted for intervening variables using multiple logistic regression.

Human subjects

Ethical considerations

The study was reviewed and approved by the Student Project Committee on Human Research within the College of Health Sciences. Before starting the interview, the interviewer introduced herself and read the informed consent statement to the respondent. Besides general information about the study it included participants' right to refuse to answer to any question and assured confidentiality of the information provided.

Analysis

Table 1 summarizes the main physical characteristics of the study participants. Some categories present in the instrument were collapsed for analysis. The total number of participants was 96. Nobody among cases and controls reported excellent health category of health status. Since controls did not report poor category in assessment of heath, the categories fair and poor of health status were combined. Cases and controls are statistically different by general health status and hypertension.

Table1. Distribution of physical characteristics among cases and controls.

Characteristic	Cases (n=48)	Controls (n=48)	p value*
Corneal arcus			
-presence	37%	21%	0.072
-absence	63%	79%	
General health			
-very good	2%	13%	
-good	13%	56%	0.000
-fair and worse	85%	31%	
Diabetes			
-presence	13%	6%	0.294
-absence	87%	94%	
Family history			
-presence	56%	50%	0.539
-absence	44%	50%	
Hypertension			
-presence	56%	25%	0.002
-absence	44%	75%	

*Pearson chi square test

Table 2 summarizes the main behavioral characteristics. Since nobody among controls did not have second and third class obesity and only 4 participants had first class obesity, the categories overweight and 1, 2, and 3 class obesity were combined in overweight category. Cases and controls are statistically different by current smoking status and blood pressure monitoring. The majority of the cases reported that they stopped smoking due to their admission to the hospital: 98% of currently non-smokers in cases and 82% currently non-smokers in controls had been smokers in the past.

Table2. Distribution of behavioral characteristics among cases and controls.

Characteristic	Cases (n=48)	Controls (n=48)	p value*
Current smoking			
-smoker	4%	65%	0.000
-non-smoker	96%	35%	
Body mass index			
-normal	21%	29%	0.346
-overweight	79%	71%	
Drinking			
-1-2 times per year and less	21%	19%	
-1-2/month	33%	40%	0.875
-1-2/wk	8%	10%	
-3-4/wk and more	38%	31%	
Activity on the job or at home			
-sedentary	27%	21%	0.457
-moderate	35%	48%	
-strenuous	38%	31%	
Monitoring blood pressure			
-never	0%	8%	
-per day	41%	0%	0.029
-per week	41%	50%	
-other	18%	42%	

*Pearson chi square test

A positive but not statistically significant association between coronary heart disease and reported good health was found during the analysis. A strong, positive, statistically significant association was observed between coronary heart disease and reported fair health. The results are summarized in Table 3. Positive but not statistically significant associations between diabetes, family history of having coronary heart disease, and coronary heart disease were found during the analysis. Analysis also revealed a positive statistically significant association between coronary heart disease and hypertension. Data analysis revealed a protective effect of currently smoking on the risk of coronary heart disease. This spurious relationship is due to the fact that patients stopped smoking subsequent to their diagnosis of heart disease. Use of past smoking history would have been more appropriate in this case. A positive but not statistically significant association between overweight and coronary heart

disease was revealed during the analysis. A positive statistically significant association between coronary heart disease and having corneal arcus was found during the analysis. Based on the results of simple logistic regression it can be said that hypertension and current smoking are possible confounders. The OR of hypertension among cases and controls is 3.5; 95%CI= 1.4-8.7 and OR of hypertension among having corneal arcus and not is 2.6; 95%CI=0.97<OR<7.1. The OR of current smoking among cases and controls is 0.03; 95%CI=0.005-0.24 and OR among having corneal arcus and not is 0.2; 95%CI=0.03<OR<0.58.

Table 3. Testing for confounded relationship between corneal arcus and coronary heart disease

Characteristic	**Coronary heart disease OR (95% CI)**	**Corneal arcus OR (95% CI)**
Health Status		
-very good	1.0	1.0
-good	2.0 (0.2-19.9)	0.75 (0.03<OR<8.97*)
-fair and worse	13.9 (1.34-143.9)	0.28 (0.01<OR<2.65*)
Diabetes	4 (0.45-35.8)	2.1 (0.43<OR<10.11*)
Family history	1.3 (0.6-2.8)	1.0 (0.39<OR<2.72)
Hypertension	3.5 (1.4-8.7)	2.6 (0.97<OR<7.1)
Current smoking	0.03 (0.005-0.24)	0.2 (0.03<OR<0.58*)
Body mass index	1.5 (0.61-3.67)	0.8 (0.26<OR<2.33)
Drinking an alcoholic beverage		
-1-2 times per year and less	1.0	1.0
-1-2/month	0.7 (0.18-2.77)	10.5 (2.41<OR<49.3)
-1-2/wk	0.7 (0.14-3.32)	4.3 (0.62<OR<33.9*)
-3-4/wk and more	1.0 (0.28-3.81)	9.8 (2.23<OR<46.1)
Corneal arcus	3.7 (1.02-13.1)	0

*Cornfield 95% confidence limits are not accurate

In the subsequent step of analysis, the association between coronary arteriosclerosis and corneal arcus was adjusted for hypertension using multiple logistic regression analysis. The adjusted and unadjusted regression variables are summarized in Table 4. It can be said that model 2 showed marginal statistically significant adjusted relationship between

intervening variable and outcome variable. Corneal arcus was significantly associated with coronary heart disease after adjusting for blood pressure.

Table 4. Multiple logistic regression analysis for association between corneal arcus and coronary arteriosclerosis adjusted for confounding variable.

Covariate	**OR (95 % CI)**	
	Model 1	Model 2
Corneal arcus	3.7 (1.02-13.1)*	4.3 (1.000199-18.1)
Adjusted for		
Blood pressure		3.8 (1.41-10.3)

*Unadjusted

The accuracy of corneal arcus as a screening tool to detect coronary heart disease was assessed by calculating sensitivity and specificity, separately for people 35-50 years of age and those over 50. Summarizing results of Table 5 it can be said that using corneal arcus as a screening tool for people 35-50 years of age will result in 19% probability of correctly identifying an individual with the disease (coronary heart disease) and in 100% probability of correctly categorizing individual without the disease. This screening will yield 100% probability that an individual with a presence of corneal arcus will have a disease, and 55% probability that an individual without corneal arcus will not have the specified disease. These results limit the worth of corneal arcus as a screening tool to clinical settings among younger arcus patients.

Table 5. Sensitivity, specificity, positive and negative predictive values of corneal arcus.

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
<50	19%	100%	100%	55%
>50	52%	63%	58%	57%
Overall	38%	79%	64%	56%

Discussion

In this study the selection of individuals clinically free of coronary heart disease as the control group was done by matching controls to each case by age and gender. The small number of cases and controls in this study did not allow to reveal many statistically significant associations of coronary heart disease with different risk factors. Nevertheless, the analysis of collected data confirmed some relationships between coronary heart disease and factors which are of particular significance.

During simple logistic regression analysis hypertension and current smoking were considered as possible confounders. Taking into consideration the spurious relationship between current smoking and coronary heart disease, only hypertension was considered as a potential confounder. Multiple logistic regression analysis revealed a marginal statistically significant relationship between corneal arcus and coronary heart disease after controlling for hypertension, which is considered to be risk factor of coronary heart disease.

The poor accuracy of corneal arcus as a screening tool for detecting coronary heart disease limits its worth to clinical settings. It will not replace the traditional screening tests in the diagnosis of coronary heart disease (electrocardiography, coronary angiography), but it could find its place in the diagnostic algorithm of coronary heart disease for patients diagnosed with corneal arcus, especially those under 50, who have not been diagnosed or screened for heart disease. Because it is a noninvasive and cost-effective approach, it warrants further evaluation in the clinical setting in a larger, prospective study in an unselected population.

Many epidemiological studies have shown the association of coronary heart disease with corneal arcus [2, 8]. Some epidemiological investigations have suggested a positive relation between coronary heart disease and hypertension [14]. The findings of this study are coincide with the data given in the literature. Although, the influence of family history on

coronary heart disease was determined in the literature, in the current research a statistically significant association between family history and coronary heart disease was not established. Diabetes is mentioned as a risk factor for coronary heart disease in the observed literature [9]. This study showed positive but not statistically significant association between diabetes and coronary arteriosclerosis. Despite several epidemiological studies that have shown the positive association between smoking and coronary heart disease risk, this study demonstrated a protective effect of current smoking on the risk of coronary heart disease. This false relationship was due to the fact that smoking was artificially controlled.

A positive association between overweight and coronary heart disease risk was observed during the study. These results also support the literature. No statistically significant association between alcohol usage and coronary heart disease was found during the research. But taking into account the small sample size it would be difficult to reject absolutely the possible influence of these factors on coronary heart disease. A positive statistically significant association was found of coronary heart disease with reported fair health.

The limitations of the study were the following:

A major problem encountered in the study is the lack of the data concerning lipid levels. Owing to this a parallel between presence of corneal arcus and dyslipidemia can be established. Another major problem in all case-control studies is a recall bias. Another bias is misclassification of exposure to the well-known coronary risk factors in visitor controls. Patients may have a most up-to-date estimation of blood pressure and level of lipids compared with visitor controls [27]. The clinical state of the patient and presence of different risk factors influence the judgment of attending physician to refer patients for coronary angiography. Coronary angiography itself is an expensive procedure, and patients may have different rates of refusal to undergo coronary angiography [27]. Another problem in this study is misclassification of visitors as controls. Pearson notes that there is a considerable

potential for misclassification of asymptomatic individuals as “nonatherosclerotic”, especially men [28]. The next problem encountered in this study is outcome assessment bias. Interviewer itself performed an eye examination of the subjects studied. This is not a difficult procedure, and can also be performed by ophthalmology resident also. Though there was no other checking, the results are quite reliable. Although the instrument was pretested and changes were made in order to make it more applicable to Armenia, the Armenian version of it was not validated.

Conclusions/Recommendations

This study provided preliminary results concerning the relationship of corneal arcus and coronary heart disease among people in Yerevan. A strong positive association between coronary heart disease and corneal arcus was observed. A multiple logistic regression model of this relationship was suggested, that included potential confounder such as hypertension. Considering the limitations of this study more research is needed to effectively assess the influence of selected factors on the relationship between coronary heart disease and corneal arcus. The value of corneal arcus as a screening tool for detecting coronary heart disease is restricted to clinical settings.

Taking into account the results of this study the following are recommended:

- Encourage nonophthalmologist physicians (family physicians) to include cornea examination as part of their routine examination.
- In order to implement cornea examination, it is necessary to establish educational programs for family doctors.
- Ophthalmology departments should perform cornea examinations for all eye patients, paying special attention to those patients who have hypertension.

- Ophthalmologists should ensure any patient diagnosed with corneal arcus and not screened or diagnosed with heart disease, especially those under 50, be screened for those conditions

References

1. Frank L. Ocular signs of Hyperlipidemia. *Hospital Physician November 2001.*
2. Chambless LE, Fuchs FD, Linn S, et al. The association of corneal arcus with coronary heart disease and cardiovascular disease mortality in the Lipid Research Clinics Mortality Follow-up Study. Am J Public Health 1990; 80:1200-4.
3. Tschetter RT. Lipid analysis of human cornea with and without arcus senilis. Arch Opthalmol 1966; 76:403-5.
4. Cooke NT. Significance of arcus senilis in Caucasians. J R Soc Med 1981; 74:201-4
5. Moss SE, Klein R, Klein BE. Arcus senilis and mortality in a population with diabetes. Am J Opthalmol 2000; 129:676-8.
6. Hickey J, Maurer B, Mulcahy R. Arcus senilis: its relation to certain attributes and risk factors in patients with coronary heart disease. Br Heart J 1970; 32:449-52.
7. Lertchavanakul A, Laksanaphuk P, Tomtitchong T. Corneal arcus associated with dyslipidemia. J Med Assoc Thai 2002 Jun; 85 Suppl 1:S231-5.
8. Rosenman RH, Brand RJ, Sholtz RI, Friedman M. Multivariate prediction of coronary heart disease during 8.5 year follow-up in the Western Collaborative Group Study. Am J Cardiol 1976 May;37(6):903-10.
9. Gerd A, Paul C, et al. Coronary Heart Disease: Reducing the Risk. The scientific background to primary and secondary prevention of coronary heart disease. A worldwide view. Nutrition, Metabolism and Cardiovascular Disease, 1998; volume 8, issue 3.
10. Neaton JD, Wentworth D. Serum-cholesterol, blood-pressure, cigarette-smoking, and death from coronary heart-disease: overall findings and differences by age for 316 099 white men. *Arch Intern Med.* 1992;152:56–64.
11. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality: 30 years of follow-up from the Framingham study. *JAMA.* 1987; 257:2176–2180.

12. Assmann G, Cullen P, Schulte H. The Munster Heart Study (PROCAM): results of follow-up at 8 years. *Eur Heart J.* 1998; 19:A2–A11.
13. Folsom AR, Chambless LE, et al. Prediction of Coronary Heart Disease in Middle-Aged Adults with Diabetes. Diabetes Care. 2003 Oct;26(10):2777-2784.
14. World Health Organisation. *Hypertension Control: Report of a WHO Expert Committee.* Geneva, Switzerland: World Health Organization; 1996; WHO technical report series 862.
15. Staessen JA, Fagard R, et al. Subgroup and per-protocol analysis of the randomized European Trial on isolated systolic hypertension in the elderly. *Arch Intern Med.* 1998; 158:1681–1691.
16. Savage PJ, Pressel SL, et al. Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension: the Systolic Hypertension in the Elderly Program, SHEP Cooperative Research Group. *Arch Intern Med.* 1998; 158:741–751.
17. Peto R, Lopez AD, et al. Mortality from tobacco in developed-countries: indirect estimation from national vital-statistics. *Lancet.* 1992; 339:1268–1278.
18. Keil U, Chambless LE, et al. The relation of alcohol intake to coronary heart disease and all-cause mortality in a beer-drinking population. Epidemiology. 1997 Mar; 8(2):150-6.
19. Marmot MG. Alcohol and coronary heart disease. *Int J Epidemiol* 1984; 13:160–67
20. Andresdottir MB, Sigurdsson G, et al. Fifteen percent of myocardial infarctions and coronary revascularizations explained by family history unrelated to conventional risk factors. The Reykjavik Cohort Study. Eur Heart J. 2002 Nov; 23(21):1655-63.
21. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994; 344:1383–1389.
22. Shepherd J, Cobbe SM, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med.* 1995; 333:1301–1307.

23. Sacks FM, Pfeffer MA, et al. The effect of pravastatin on coronary events after myocardial-infarction in patients with average cholesterol levels. *N Engl J Med.* 1996; 335:1001–1009.
24. Downs JR, Clearfield M, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA.* 1998; 279:1615–1622.
25. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med.*1998;339:1349–1357.
26. Gordis L. Epidemiology. 2nd ed. Philadelphia, Pennsylvania: W.B. Saunders company; 1996
27. Sibai AM, Armenian HK, Alam S. Wartime determinants if arteriographically confirmed coronary artery disease in Beirut. American Journal of Epidemiology. 1989;vol.130.
28. Pearson TA. Coronary arteriography in the study of the epidemiology of coronary artery disease. Epidemiol Rev 1984; 6:140-66.

Appendix 1

Questionnaire

I. Socio-Demographic Information

1. Birth date: __ __/__ __/__ __ (dd/mm/yy)
2. Gender: 1. ՝ Male 2. ՝ Female
3. Place of birth _____
4. Place of residence_____
5. Nationality: 1. ՝ Armenian

   2. ՝ Other nationality ***(Please, specify)*** _____

II. Anthropometry

6. Weight: _____kilos
7. Height: _____cm

III. General health

8. In general, would you say your health is...?

(Circle One)
(Read choices)

1.□ Excellent 2.□ Very good 3.□ Good 4.□ Fair 5. □ Poor

9. Has a doctor ever told you that you have diabetes?

1. □Yes 0.□ No ***(Skip to Q 13)***

10. Did you regularly follow a specific type of diet for your diabetes?

1. □Yes 0.□ No 88.□ Don't know

11. Did you limit the number of calories consumed per day to control your blood sugar?

1. □Yes 0.□ No 88.□ Don't know

12. How many months or years have you been taking pills for diabetes

1. □< 1 yr 2. □ >1yr 88.□ Don't know

13. Have you ever been told by a physician that you have had high cholesterol?

1. □Yes 0.□ No ***(Skip to Q 15)***

14. Has your doctor placed you on a special "low" cholesterol or "low" fat diet?

1. □Yes 0.□ No 88.□ Don't know

IV. Blood Pressure

15. Do you have a family history of coronary heart disease?

1. □Yes 0.□ No 88.□ Don't know

16. Have you ever had high blood pressure?

1. □ Yes 0.□ No ***(Skip to Q 20)*** 88.□ Don't know ***(Skip to Q 20)***

17. Are you taking any medications for high blood pressure now?

1. □Yes 0.□ No 88.□ Don't know

18. How often do you monitor your blood pressure?

1. □ Never
2. □ Per day
3. □ Per week
4. □ Other ***(Please, specify)***_____

19. How do you monitor your blood pressure? ***(Check all that apply)***

1.□ Doctor at clinic
2.□ Doctor comes to home
3.□ Self check at home
4.□ Neighbor, friend, relative
5.□ Other (***Please, specify***)_____

V. Smoking

20. Have you ever smoked cigarettes in your lifetime?

1. □Yes 0.□ No ***(Skip to Q 26)*** 88.□ Don't know ***(Skip to Q 26)***

21. About how years have (or did) you smoke cigarettes?

1. □< 1 yr 2. □> 1 yr 88.□ Don't know

22. On average, how many cigarettes do (or did) you smoke per day?

1. _ _ _ # Cigarettes 2.□ Don't know

23. Do you smoke cigarettes now?

1. □Yes ***(Skip to Q 26)*** 0.□ No

24. How many years ago did you stop?

1. □< 1 yr 2. □> 1 yr 88.□ Don't know

25. Why did you stop smoking cigarettes?

1. □ economic reasons
2. □ general health reasons
3. □ Other (**Please, specify**) _____

VI. Alcohol

26. About how often do you drink an alcoholic beverage? ***(Read choices)***

1. □ Daily, almost every day
2. □1-2/wk
3. □3-4/wk
4. □1-2/month
5. □ 1-2 times per year
6. □ Less than 1-2 times per year
7. □ Never
88.□ Don't know

VII. Physical activity

27. Does your disease limit your ability to perform physical tasks?

1. □Yes 0.□ No 88.□ Don't know

28. On the average, how many flights of stairs do you climb up each day (one flight = 10 steps - continuous).

_ _ _ _# of flights 88.□ Don't know

29. On the average, how many kilometers do you walk each day?

_ _ _ _km 88.□ Don't know

The following questions are about activities you might do during a typical day. How much does your heath limit you in the following?

30. Vigorous activities like lifting heavy objects, running, rapid walking?

1.□ Yes, a lot 2. □ Yes, a little 0.□ No 88.□ Don't know

31. Moderate activities like moving a table, pushing a vacuum cleaner?

1.□ Yes, a lot 2. □ Yes, a little 0.□ No 88.□ Don't know

32. Eating and dressing?

1. □ Yes, a lot 2. □ Yes, a little 0.□ No 88.□ Don't know

33. Which of the following best describes your level of activity on the job, or at home?

1. □ Sedentary
2. □ Moderate
3. □ Strenuous

88.□ Don't know

VIII. Eye examination

34. Arcus senilis

1. □ Absent 2. □ Present

Appendix 2

American University of Armenia

INFORMED CONSENT

Title of Research Project: **Case-Control Study of Corneal Arcus**

Principal investigator**:** Haroutune Armenian

CHR#

Hello, I am Gohar Navoyan. I am a student of Public Health department at the American University of Armenia. You are invited to participate in a research study: "Case-Control Study of Corneal Arcus". The purpose of this study is to evaluate whether the corneal arcus can predict development of coronary heart and cardiovascular diseases. You have been included in the project because you are more than 35 years and you have clinical examination at the Nork Marash Hospital. You are asked to participate in the eye examination and interview, which will take about 15 minutes. During the interview you are kindly asked to answer some questions. Your participation in interview and eye examination is completely voluntary. Please, feel comfortable in answering the questions. You can refuse to answer any question or withdraw from the screening at any time without penalty. Please be reminded that the results of your screening and your responses during the interview will remain confidential and used for research purposes only. Any other information that may identify yourself such as name address is not required. If you have questions, you are free to ask them. There is no risk for you as a participant in this study. You will not have any monetary or other benefit from the participation. Your participation and the information that you will provide is highly valuable for study. If you have questions about this research or if you believe that you have not been treated fairly, you may contact: Yelena Amirkhanyan, MD, MPH, Teaching Associate, MPH program at [51 25 68/or yamirkh@aua.am] and Michael E. Thompson, MS, DrPH Director, CHSR, AUA at [512592/or mthompso@aua.am].

Thank you very much for your participation.