Global Journal of Health Science; Vol. 9, No. 4; 2017
ISSN 1916-9736 E-ISSN 1916-9744
Published by Canadian Center of Science and Education

An Overview on Cardiovascular Risks Definitions by Using Survival Analysis Techniques-Tehran Lipid and Glucose Study: 13-Year Follow-Up Outcomes

Nezhat Shakeri[1], Farhad Hajsheikholeslami[2], Amir Abbas Momenan[2], & Fereidoun Azizi[3]

[1] Department of Biostatistics, Faculty of Paramedical sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2] Prevention of Metabolic Diseases Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[3] Research Center for Endocrine Sciences, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Correspondence: Nezhat Shakeri, Department of Biostatistics, Faculty of Paramedical Sciences, Darband St., Tajrish, Tehran, Postal Code: 1971653313, Iran. Tel: 98-21-2271-8531; Fax: 98-21-2270-7347. E-mail: n.shakeri@sbmu.ac.ir

Received: April 30, 2016 Accepted: July 1, 2016 Online Published: August 25, 2016

doi:10.5539/gjhs.v9n4p197 URL: http://dx.doi.org/10.5539/gjhs.v9n4p197

Abstract

Risk assessment is an important issue for starting medication for patients. Literature reveals that diabetes, hypertension, dyslipidemia and Body Mass Index (BMI) are among major risk factors for longevity. Since the cut-off points proposed in various sources are generally irrespective of age, sex and race, it has been attempted to validate current definitions for Tehran's elderly population by using a prospective cohort study. For this purpose, one thousand seven hundred and ninety eight (1,798) individuals above 60 years old were recruited in the primary phase of the Tehran Lipid and Glucose Study (TLGS) during 1998-2001, and were tested for their systolic and diastolic blood pressure, total cholesterol, LDL cholesterol, high density lipoprotein cholesterol (HDL), triglyceride (TG), fasting blood sugar (FBS), 2-h plasma glucose (2HPG) and some other factors at the time of entry to the study. They were followed up for 13 years and their vital statuses were registered (1998-2011).

According to the standard definition of diabetes, dyslipidemia and hypertension, the participants were divided into ill and healthy groups. By using univariate Cox proportional hazard model, a 95% hazard ratio for various risk factors was estimated. Cut-off points of 126 mg/dL for fasting blood sugar or 200 mg/dL for 2HPG for defining diabetes were identified as appropriate points for predicting longevity for elderly males and females. Systolic blood pressure over 140 mmHg or diastolic blood pressure over 90 mmHg or having medication as a definition of hypertension were identified as a significant risk factor for elderly males only. Dyslipidemia which is defined based on Cholesterol>240 or TG>400 or LDL>160 or HDL<35, was not identified as a longevity predictor for elderly men and women. The results showed that BMI>31 Kg/m^2 at the time of entry to the study significantly reduced the survival time of women. In conclusion, the definitions of diseases like hypertension and dyslipidemia based on cut-off points don't classify the Tehran's elderly population accurately. More investigation in this regard is required.

Keywords: BMI, diabetes, dyslipidemia, elderly, hazard rate, hypertension, mortality rate, risk assessment

1. Introduction

Classifying people into two groups of healthy and sick, with respect to a particular illness, is usually done on the basis of standard definitions presented in the literature. For example, according to the literature, in classifying people into groups of healthy and diabetic, if an individual has fasting blood glucose of over 126 mg/dL or 2-h plasma glucose (2HPG) over 200 mg/dL or has a history of using medicine to reduce blood glucose, he or she will be considered "diabetic"; otherwise, that individual will be considered "non-diabetic" (Diabetes Care, 2015). In order to classify people into hypertensive and non-hypertensive, if that individual has a systolic blood pressure of over 140 mmHg or diastolic blood pressure over 90 mmHg, or if the individual uses medicine to reduce blood pressure, he or she will be considered "hypertensive" (Diabetes Care, 2015).

The significance of these definitions lies in the fact that, based on these classifications, treatment of the unhealthy and the administration of medicine is begun by a physician. The determination of the risk factor and the factor for reducing longevity will likewise be based on the above definitions. As literature shows each region must have indigenous guidelines based on age, sex, and ethnicity (Mirmiran, Esmaillzadeh, & Azizi, 2004; Evidence-Based Guideline for the Management of High Blood Pressure in Adults, 2013). It is necessary to make a more precise assessment of these definitions within different societies, between men and women, and among various age groups.

In so far as heart disease is one of the most important causes of death in the world, as well as in Iran (Smith, Greenland, & Grundy, 2000; Shakeri et al., 2011), it is necessary to conduct more precise research on its risk factors, such as diabetes, high blood pressure, the blood cholesterol level, and obesity (Pastor-Barriuso et al., 2003; Woo, Ho, & Yu, 2002; Kang et al., 2009; Leon et al., 2005; DECODE Study Group, 2003; Lee et al., 2015).

In the case of diabetes, high blood pressure, and a high cholesterol level, it is known that the average longevity of people who suffer from any of the above is significantly shorter than healthy people (Leon et al., 2005). On these bases, it is possible to estimate the average lifespan of healthy and sick people in a longitudinal study by using survival analysis method. If the classification of people has been done correctly, average longevity between the healthy and unhealthy groups must be significant.

By using the Tehran Lipid and Glucose Study (TLGS) data, with the aid of the survival analysis method, the aim of this study is to present an overview on cardiovascular risks and re-evaluate the definitions regarding some of the risk factors that reduce lifespan, such as diabetes, high blood pressure, the blood cholesterol level and obesity in Tehranian men and women, in the age group of 60 and over.

Literature review shows that cardiovascular risk assessments have not been conducted in Iranian studies so far.

The results of this research may be useful as a baseline for further research for determination of cut-off points.

2. Subjects and Methods

2.1 Sampling Procedures

The prospective TLGS is an ongoing longitudinal and community-based epidemiological survey conducted in District 13 of Tehran in order to investigate the risk factors for cardiovascular disease among various age groups, and data exists for 13 years of follow up. Complete information regarding this study is available in other referenced articles (Azizi et al., 2009; Hadaegh et al., 2006). Briefly, a sample of 14,280 individuals aged three years and older covered by the East Tehran Health Center was selected and invited for interviews. For each case, in addition to all background data, the results of medical examinations and anthropometric measurements were reported. Blood samples were taken for measuring lipids and glucose. For those 20 years and over, an oral glucose tolerance test and electrocardiography were performed as well.

2.2 Participant (Subject) Characteristics

In this study from among the TLGS samples all the individuals aged sixty years and older at the time of entry to the study was recruited.

2.3 Measures and Covariates

The age-sex specific proportional mortality ratios and age-sex specific mortality rates have been presented.

The formula used for proportional mortality ratio is as follows:

$$\begin{aligned} &Age-SexSpecific\Pr oportionalMortalityRatio \\ &NumberOfDeathDueToASpecificCause \\ &=\frac{During13YearsOfFollowUp}{TotalNumberOfDeath}\times 100 \end{aligned} \tag{1}$$

The formula for age-sex specific mortality rate is as below:

$$Age - SexSpecificMortalityRate = \frac{NumberOfDeathDueToASoecificCauseInSpecificCauseInSpecificAgeSexGroup}{NumberOfPopulationOfSameAgeAndSexGroup} \times 100 \quad (2)$$

Comparing the ratios indicates the most hazardous diseases for those aged 60 and above in the TLGS framework.

According to the Eighth Joint National Committee (JNC 8), a systolic blood pressure (SBP) greater than 140 mmHg, or a diastolic blood pressure (DBP) greater than 90 mmHg, or taking blood pressure (BP) medication are defined as hypertension; fasting blood sugar (FBS)>126 mg/dL or 2-h plasma glucose (2HPG)>200 mg/dL or a history of hyperglycemia are defined as diabetes (Diabetes Care, 2015) and, according to Adult Treatment Panel II (ATP II) of the National Cholesterol Education Program, total cholesterol>240 mg/dL or LDL cholesterol>160 mg/dL or high density lipoprotein cholesterol (HDL)<35 mg/dL or Triglyceride cholesterol (Tg)>400 mg/dL or related drug consumption are defined as dyslipidemia (Hoeg, 1990). According to WHO advice on BMI public health action points for Asian populations (World Health Organization, 2006), BMI 23-27.5 Kg/m^2 are considered as increased risk and BMI 27.5 kg/m^2 or higher as high risk. These cut-off points for white European population are 25-29.9 kg/m^2 and 30 kg/m^2 or higher, respectively (WHO, 2006).

Similar to all longitudinal studies, the “event” may occur for a case (complete observation) or may not (censored observation). Within a 13-year follow up, the death event did not occur for all the cases and lifespan is not available for all the cases. Therefore, the impact of risk factors on the lifespan was tested by the univariate Cox proportional hazard model and the hazard ratios of various risk factors (Klein & Moeschberger, 2003).

In addition to a censored observation, we may be faced with missing subjects. In such a case, it is assumed that the missing case is independent of a “death event”.

The data analysis was done using SPSS software, version 16.

3. Results

3.1 Recruitment

The initial phase of the TLGS project was conducted between 1998 and 2000. One thousand seven hundred and ninety eight individuals, age≥60 years, were selected (929 males, 52%, and 869 females, 48%) and followed up for 13 years (1998-2011). After a 13-year follow-up, 268 of 929 (29%) males, and 150 of 869 (17%) females died.

3.2 Statistics and Data Analysis

The all-cause mortality rate was: 21% in the 60-69-year age group, 48% in the 70-79 age group and 58% in the 80+ age group for males. The rates were 13%, 28% and 72%, respectively, for the female groups.

Cardiovascular diseases, including coronary heart disease (CHD), and myocardial infarction (MI), sudden cardiac death, and unstable angina have the highest mortality ratios, 43% (82/189) and 38% (41/107) for men and women, respectively. The mortality ratio for strokes was almost equal among men and women (13%-14%). The mortality ratio for cancer was almost the same for both sexes (12%-14%). The mortality ratios for other reasons like accidents, sarcopenia, etc., were 28% (53/189) and 36% (39/107) for men and women, respectively. Comparing the most important causes of death between the three age groups shows that those affecting life in the 6th decade may loose their importance in the 7th and 8th decades, and vice-versa (Table 1).

Table 1. Proportional mortality ratios of different causes of death and sex and age mortality rates in the Tehran Lipid and Glucose Study, 1998-2011

Men	**60-69 years (N*=661)**		**70-79 years (N=242)**		**80+ years (N=26)**		**Total (N=929)**	
Cause of Death	**No. of Death (d)**	**(d/D_1) %**	**No. of Death (d)**	**(d/D_1) %**	**No. of Death (d)**	**(d/D_1) %**	**No. of Death (d)**	**(d/D_1) %**
Heart Diseases‡	48	48	31	39	3	33	82	43
Stroke	12	12	13	16	2	22	27	14
Cancer	17	17	10	12	0	0	27	14
Other	23	23	26	32	4	44	53	28
Total death (D_1)	**100**	**100**	**80**	**100**	**9**	**100**	**189**	**100**
Unknown	**38**	**-**	**35**	**-**	**6**	**-**	**79**	**-**
Total (D_2)	**138**	**-**	**115**	**-**	**15**	**-**	**268**	**-**
All cause age-sex mortality rate (D_2/N)	**21%(138/661)**		**48%(115/242)**		**58%(15/26)**		**29%(268/929)**	
Woman	**(N=680)**		**(N=171)**		**(N=18)**		**(N=869)**	
Cause of Death	**No. of Death**	**(d/D_1) %**	**No. of Death**	**(d/D_1) %**	**No. of Death**	**(d/D_1) %**	**No. of Death**	**(d/D_1) %**
Heart diseases	28	45	11	31	2	25	41	38
Stroke	7	8	5	14	2	12	14	13
Cancer	8	11	5	14	0	0	13	12
Other	20	36	14	40	5	63	39	36
Total death (D)	**63**	**100**	**35**	**100**	**9**	**100**	**107**	**100**
Unknown	**27**		**12**	**-**	**4**		**43**	**-**
Total (D_2)	**90**		**47**	**-**	**13**		**150**	**-**
All cause age-sex mortality rate(D_2/N)	**13%(90/680)**		**28%(47/171)**		**72%(13/18)**		**17%(150/869)**	

*No. of participants; (d/D_1)=Proportional mortality ratio; ‡Heart diseases=coronary heart disease, cardiovascular disease, MI, Sudden cardiac death, Unstable angina.

Baseline information, the hazard ratios, and related 95% confidence intervals for each of the risk factors with respect to sex is presented in Table 2.

Table 2. Cox-model hazard ratios for all-cause mortality over a 13-year period of the TLGS with respect to underlying risk factors

	Study entry time		**Hazard ratio(95% CI)**	
	Men (N=929)	**Women (N=869)**	**Men**	**Women**
Age(years)	Mean, 67.3 (SD,5.5)	Mean, 66.0 (SD, 5.1)	1.4(1.3-1.5)	1.3(1.2-1.4)
Married	97%	61%	1.4(1.3-2.9)	1.4(1-2)
Years residing in Tehran	Mean,51.8 (SD, 1.4)	Mean, 50.6 (SD, 1.6)	1.0(0.996-1.004)	1.01(1-1.02)
Tehran Natives	28%	33%	0.8(0.6-1)	0.7(0.4-1.1)
Body mass Index(kg/m^2)	Mean, 26.1 (SD,3.9)	Mean, 28.4 (SD, 4.9)	1.3(0.5-2.9)	1.0(0.9-1.0)
BMI>31kg/m^2	10%	28%	1.4(0.9-2.1)	1.8(1.2-2.6)

BMI>30Kg/m^2	15%	35%	1.3(1-1.8)	1.2(0.8-1.7)
Current Smoker	15%	2%	1.8(1.3-2.5)	2 (0.8-6)
Taking BP medication	15%	29%	1.9(1.1-3.3)	1.0(0.4-2.3)
BP(systolic, diastolic)				
140-159 or 90-94	22%	27%	1.0(0.6-1.5)	0.7(0.4-1.2)
160-199 or 95-99	11%	17%	1.1(0.9-1.4)	0.8(0.6-1.1)
≥200 or ≥100	9%	8%	1.1(0.9-1.3)	1.1(0.9-1.4)
Diabetes mellitus*	30%	33%	2.2(1.8-2.9)	1.8(1.3-2.5)
Dyslipidemia**	61%	76%	0.9(0.7-1.3)	1.2(0.9-1.7)
Hypertension***	47%	61%	1.3(1.0-1.9)	0.9(0.6-14)
History of MI, stroke or sudden death, in mother's/sister's/daughter's past medical history	6%	11%	1.3(0.65-2.4)	1 (0.5-1.8)
History of MI, stroke or sudden death, in father's/brother's/son's past medical history	8%	10%	1.9(1.2-2.9)	1.5(0.9-2.4)
Prior ischemic heart disease	16%	14%	1.05(1-1.11)	1(0.5-1.7)
Prior non-ischemic heart disease	2%	10%	1.1(0.97-1.08)	1.7(1.04-2.94)
Lack of Physical activity	54%	63%	1.4(1.1-1.8)	0.7(0.5-1.1)

*Diabetes=FBS>126 mg/dL or 2HPG>200 mg/dL or Hyperglycemia history; **Dyslipidemia=Total Cholesterol>240 mg/dL or TG>400 mg/dL or LDL>160 mg/dL or HDL<35 mg/dL or drug consumption; ***Hypertension defined as systolic>=140 mmHg or diastole>=90 mmHg or having treatment for hypertension.

Sixty-one percent of males and 76% of females were suffering from dyslipidemia, respectively. Forty-seven percent of males and 61% of females were suffering from hypertension. Thirty percent of males and 33% of females were suffering from diabetes. Obesity (BMI>31 kg/m^2), diabetes and history of non-ischemic heart diseases were found as significant risk factors for women (P<0.05) whereas obesity (BMI>30 kg/m^2), smoking, diabetes, hypertension, a history of ischemic heart disease (IHD) and a history of MI among first degree relatives were found to be significant risk factors for men (P<0.08).

Table 3 shows the impact of different risk factors on lifespan. The Cox model showed that diabetes reduces the females' and males' average lifespan by 3 years and 4.6 years, respectively. BMI>31 Kg/m^2 and a history of non IHD reduces women's lifespan by 4.3 years and 3.8 years, respectively. BMI>30 Kg/m^2, smoking, hypertension and a history of MI, stroke or sudden death of father, brother or son reduces men's longevity by 2 years, 3.3 years, 1.6 years, and 3.9 years, respectively. Lack of physical activity and taking antihypertensive drugs are among the hazardous risk factors for men, reducing their longevity by 1.6 years and 2.6 years, respectively.

Table 3. Average reduction of life time associated with various risk factors with respect to sex after 13 years follow-up

Variable	Females (N=869)	Males (N=929)
BMI>31kg/m^2	4.3	ns*
Smoking	ns	3.3
Diabetes	3	4.6
Hypertension	ns	1.6
Taking Antihypertensive -Drug	ns	2.6
History of MI, stroke or sudden death, in father's/ brother's/ son's past medical history	ns	3.9
Ischemic Heart disease	ns	1.8
Non-Ischemic Heart Disease	3.8	ns
Lack of physical activity	ns	1.6

*ns: not significant.

4. Discussion

Diabetes was identified as a significant risk factor for elderly males and females. It seems that FBS>126 mg/dL or 2HPG>200 mg/dL or a history of hyperglycemia is an appropriate definition for classifying Tehran's elderly males and females into diabetic and non-diabetic. According to the literature, hypertension (a systolic blood pressure greater than 140 mmHg, or a diastolic blood pressure greater than 90 mmHg, or taking blood pressure medication) and dyslipidemia (total cholesterol>240 mg/dL or LDL cholesterol>160 mg/dL or high density lipoprotein cholesterol (HDL)<35 mg/dL or Triglyceride cholesterol (Tg)>400 mg/dL or related drug consumption) are among significant risk factors for reducing the lifespan of elderly males and females. While in this study hypertension was only identified as a significant risk factor for elderly males, and dyslipidemia was not identified as a significant risk factor for elderly population. Unlike to the literature that has suggested Asian adults with BMI 27.5 kg/m^2 or higher as high risk; in this study BMI>31 kg/m^2 was identified as a significant cut-off point for females. Such that females with BMI>31 kg/m^2 live 4.3 years less than females with BMI<31 kg/m^2 (WHO, 2006). All these contradictory results may have occurred due to the definitions and proposed cut-off points which may not be applicable for all age groups, genders and nations. It seems that using universal definitions may cause misleading results. It is therefore suggested that each nation produce its own standard definitions, considering age and sex.

In this study, BMI was not identified as a risk factor for males, for further investigation that is advisable to bring more confounding factors such as smoking and history of heart diseases into consideration.

Among men and women, heart disease-including CHD, cardiovascular diseases, MI, sudden cardiac death and unstable angina-had the highest mortality ratio; while stroke and cancer had almost the same mortality ratios among men and women.

In this study assessments were restricted to the elderly groups (age above 60); another cohort study is required to assess cardiovascular risks for adults below 60 years of age. In addition to the factors considered in this study there are other cardiovascular predictors such as waist circumference, hypertriglycemic waist, and waist to hip ratio (WHR) (Lee et al., 2015). Assessment of these factors remains to be studied further. Further unresolved issues regarding the impact of interaction of two or more factors on lifespan remain to be addressed in future studies.

In this study, because of its strength, a prospective cohort study data and survival analysis techniques were employed to asses risk identifiers, instead of using a cross sectional data and providing descriptive statistics.

In our follow-up to update the vital status of the participants, some of them were not available. If unavailability of these individuals was due to death event, all these cases should be considered to be deceased, and as a result the estimated survival time should be shorter. Since we were unsure about their vital status, we considered their age at the last visit as their lifetime and their status as censored observations. It was assumed that there was no relation between the missing subject and the death event. Further investigation is suggested to determine the vital status of the missing subjects.

Acknowledgmnets

This work has been undertaken by Grant No. 65492 Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, and Islamic Republic of Iran.

Competing Interests Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

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