The Effect of Heart Disease Differential Mortality Rate on Cholesterol Distribution

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Abstract- In a good deal of studies cholesterol distribution, as a risk factor, demonstrates a special treatment towards age so that it shows an upward trend up to an age group and exhibits a downward trend for older age brackets thereafter. To investigate this phenomenon, two general points of view are presented. First, this issue may occur naturally for many subjects and it may be due to natural treatment of cholesterol variable with age. Second, it could be related to differential mortality, i.e. mortality changes in different age groups. In other words, it can be said that higher levels of cholesterol are relevant to younger-age mortality rate. Constructing a parametric model based on Weibull distribution, the association of this phenomenon with differential mortality was investigated. This study revealed that the effect of differential mortality on cholesterol distribution in the age groups younger than 65 were insignificant and it could partly be justifiable just in older age groups because it involves 35% changes in the 85-95 age groups. Thus, the differential mortality justifies just a part of cholesterol changes and other parts are due to intrinsic changes of cholesterol variable with time.

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Keywords: Cholesterol distribution; Differential mortality; Heart diseases; Weibull hazard rate

Introduction

As the subjects under the study grow older, the distribution of some of their variables changes. When mortality is related to the amount of these variables, the distribution of these variables in the population of older age groups is dependent on the intensity of this relevance. Such variables are usually called Growth Variables and if they are the factors for chronic diseases, they are called Risk Factors. Variables such as height, weight, blood pressure and cholesterol are among these variables. Changes in the distribution of such variables with age, especially changes of cholesterol variable in older ages, have been noticeable. Pooled data gathered from three main sources support this cholesterol special treatment *vis-à-vis* age for different populations according to cholesterol level (low, medium, high). These data involve MONICA study in which subjects' cholesterol data were obtained from 39 medical centers in 22 countries all over the world between 1979 and1987 (1). The data also include Medline database, searching the term 'cholesterol' in referred journals as a keyword, and researchers' personal association with different researchers involving the collaboration of 37 groups in Asia and Pacific Ocean (2). Results from these studies are demonstrated in figure 1. This figure shows the cholesterol-age association based on cholesterol levels. Cholesterol mean for males and females in different age groups, first, increases with aging and then reaching its maximum amount it decreases with older age groups. The intensity of this association is more significant in males and high cholesterol areas. To investigate this phenomenon, two general viewpoints are presented. First, this issue may occur naturally for many subjects and it may be due to the natural treatment of cholesterol variable with age. Because blood cholesterol is dependent on various factors such weight, body mass index (BMI), body function and physical weakness, infection, lack of iron, and many other dependent biological indexes and with the increase in age, medical care increases while the function of many organs, especially heart and blood vessels decreases which can justify the decrease in total cholesterol level in older ages (3,4). Second, the issue can be related to differential mortality, *i.e*. mortality changes in different age groups. In other words, it can be said that higher levels of cholesterol are dependent on mortality in younger ages (6-9).

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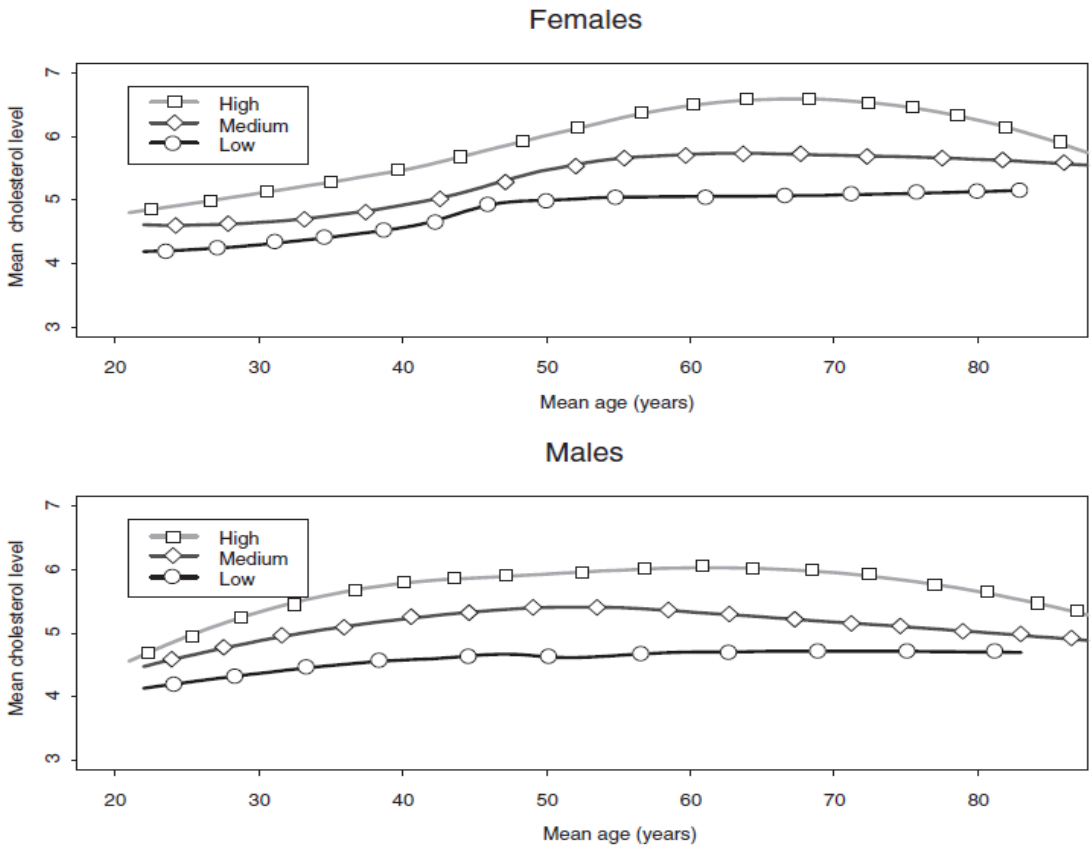

Figure 1. The cholesterol–age association from pooled data for populations with high, medium and low Cholesterol levels.

Many studies introduce cholesterol as an important risk factor for cardiovascular diseases (10-13). Not only is this association observable for developed countries, it has also been observable for underdeveloped ones in recent years. Moreover, total mortality as well as cardiovascular mortality will increase with aging. Therefore, it is anticipated that cholesterol mean will increase in older age groups. But as it was seen in table 1, cholesterol treatment was unexpected showing a decrease in older age groups. This trend was more dominant in males and in populations with a high cholesterol mean. Thus, the investigation of differential mortality effect as a result of cardiovascular diseases is significant in the treatment of cholesterol with time. Unfortunately, in this case, longitudinal data are not available so the key reason of this phenomenon cannot be set forth. The only scientific model which proposes the differential mortality effect on cholesterol distribution has been presented by McGilchrist *et al.* which is based on Cox model and cross-sectional data (14). In their model, first, it is necessary to regard a special statistical distribution for cholesterol variable. Second, as cholesterol variable is an important risk factor in cardiovascular diseases, they have used total mortality rate instead of mortality rate caused by cardiovascular diseases in different age groups. Furthermore, in cases in which mortality rate has an upward/downward trend with time, parametric models are more flexible and have a better fitness in comparison with Cox model. Due to these issues, a parametric model based on Weibull distribution, when dealing with cross-sectional data, has been presented to investigate the result of this phenomenon. Based on this model, the effect of differential mortality from cardiovascular diseases on cholesterol mean has been studied in different age groups.

Materials and Methods

Most of longitudinal data which help determine the main reason of cholesterol distribution changes with age are not available. Therefore, the reason of these changes should be traced based on cross-sectional studies for older age groups. This paper expands the model

presented by McGilchrist *et al*. so that, first, there will be no need for any statistical distribution for cholesterol variable, second, Cox model can be replaced by parametric models such as Weibull to model the rate of differential mortality from cardiovascular diseases.

To model hazard function, based on the issue that with the increase in age the rate of mortality increases, it seems that the fitness of Weibull model is more suitable on mortality rate in comparison with Cox semi-parametric model because this distribution is germane to cases in which hazard rate has an upward/downward trend over time. With a slight modification, Weibull parametric model will be as follows:

$$h(t,z)=\left(\lambda\rho t^{\rho-1}\right)e^{Z} \Big/ m(\alpha,t)$$

In this equation $m(\alpha.t)=E(e^{z}/t)$. This modification in the model causes the baseline hazard to be the very mortality rate in population. So does when α=0. Of course, it was assumed that the mortality rate had Weibull distribution in such situations. When the association between mortality and cholesterol, as a risk factor, is not high, α will have a small amount. Thus, large amounts of α can be overlooked and the association between cholesterol mean and differential mortality will be as follows:

$$E^{*}(Z_t)\approx E(Z_t)\exp\int_{t_0}^{t}\alpha\left(\lambda\rho t^{\rho-1}\right)\frac{k_2}{k_1}dt \qquad (1)$$

In this association t_0 is the age which is expected to have similar cholesterol mean regarding and disregarding the effect of differential mortality. $E(z_t)$ and $E^{*}(z_t)$ are cholesterol means regarding and disregarding the effect of differential mortality, respectively, while $\lambda_i\rho_i t^{\rho i-1}$ is the rate of mortality from cardiovascular diseases based on Weibull parametric model. κ_1,κ_2 are consecutively mean and variance of cholesterol variable in different age groups.

Cross-sectional Data Model-Building

For age groups with t_0, t_1, …, t_n end points and assuming constant amounts of α, κ_1, κ_2 for each age group, the model will be as:

$$E^{*}(Z_t)=E(Z_t)\exp\sum_{i=1}^{j}\frac{\alpha_i\left(\lambda_i\rho_i t_i^{\rho_i-1}\right)k_2\left(t_i-t_{i-1}\right)}{E\left(Z_{t_i}\right)} \qquad (2)$$

In which $\lambda_i\rho_i t^{\rho i-1}$ is the rate of mortality from cardiovascular diseases based on Weibull parametric model. It is axiomatic that if differential mortality does not have any effect on cholesterol distribution in different age groups, no difference should be observed between these two means. Furthermore, $E(z_{ti})$, K_2 in this equation are mean and variance of cholesterol in relevant age groups, respectively. Cross-sectional data usually embody limited age groups; therefore, it is necessary to anticipate the amount of total cholesterol as well as the rate of mortality from cardiovascular diseases in some age groups. The rate of mortality from cardiovascular diseases based on Weibull parametric model and cholesterol mean distribution employing fractional polynomial regression with time, (15) has been modeled as:

$$P(t)= \qquad (3)$$

$$201.8642+8.1942\left(\left(\frac{t}{10}\right)^{2-35.4025}-3.771\left(\left(\frac{t}{10}\right)^{2\ln\left(\frac{t}{10}\right)-63.136}\right)\right)R^2$$

$$=99.9$$

Results

To investigate the effect of differential mortality on cholesterol distribution, the data reported on the status of non-contagious risk factors in Iran in 2005 were used (16). To use the model on factual data, it is necessary to begin with an age from age groups before which the effect of differential mortality has been minimal. This age in the present study has been 25. Employing regression model (3), the cholesterol mean and variance have been estimated for 25+10i time-intervals and they have been used to model the effect of differential mortality. Results of the model-building for study's data are demonstrated in table 1 and figure 2.

Table 1 demonstrates age groups, mortality rate from cardiovascular diseases, and cholesterol coefficient in Weibull regression model as a risk factor of cardiovascular diseases by age, cholesterol mean and variance, and cholesterol mean with/without differential mortality effect in different age groups on cholesterol distribution. This effect has been insignificant in age groups lower than 55 while it has had 35% changes in 85-94 age group. Figure 2 also shows cholesterol mean in different age groups with/without differential mortality effect with time. The difference between these two cholesterol levels is observable only in older age groups.

Table 1. The effect of differential mortality on cholesterol distribution.

Age	Weibull hazard rate	α	κ_2	E(z)	$E^*(z)$	Differential mortality effect (%)
25-34	0.00014	.4523	11.10201	185.4751	185.4821	0.06
35-44	0.00054	.8596	8.469781	197.1260	197.1728	0.55
45-54	0.00150	.9502	12.55841	202.9581	203.1853	1.81
55-64	0.00346	.9788	11.33288	201.7796	202.3901	5.39
65-74	0.00701	.9897	8.703580	192.3987	193.5875	13.66
75-84	0.01290	.9944	13.34241	173.6238	176.4272	21.01
85-94	0.02210	.9967	18.87959	144.2629	150.8795	35.04

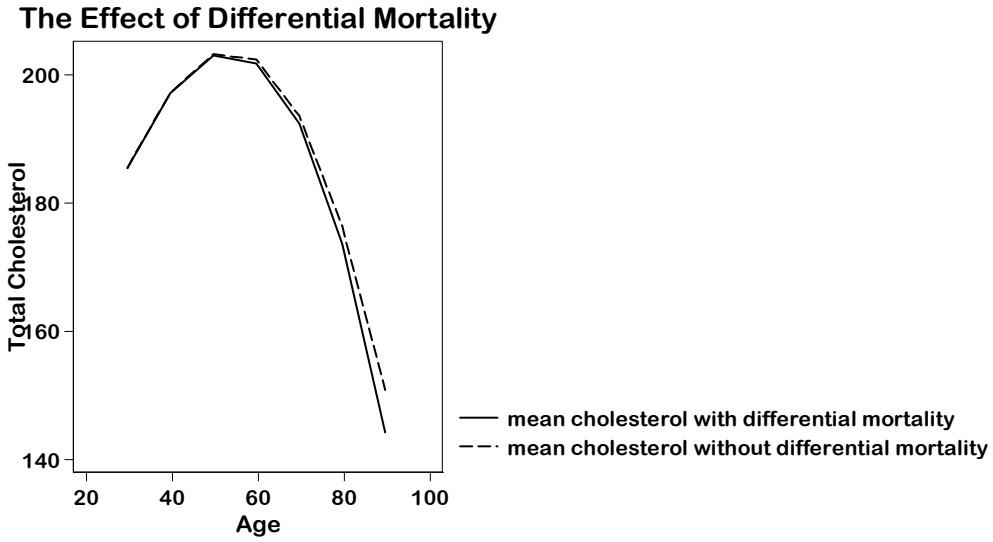

Figure 2. The effect of differential mortality.

Discussion

Studies on changes in cholesterol variable with age as a risk factor for cardiovascular diseases have always been of great importance because the rate of total mortality as well as mortality from cardiovascular diseases increases with aging (17-20). Therefore, it is expected that cholesterol mean will increase for older age groups. But as it is seen in table 1, the treatment of cholesterol variable was unexpected and it revealed a downward trend for older age groups. This downward trend was more significant in males and populations with high cholesterol mean. Results presented in table 1 and figure 2 also revealed that the effect of differential mortality does not solely justify the treatment of cholesterol variable with age because the effect of differential mortality from cardiovascular diseases in 85-95 age group showed just 35% changes and the rest of the changes should be observed in natural treatment of cholesterol with age. This is because blood cholesterol is dependent on various factors such as weight, BMI, lack of iron, and many other dependent biological indexes and with the increase in age, medical care increases as well while the function of many organs, especially heart and blood vessels decreases (3,4). This can justify the decrease in total cholesterol level in older ages. As one main reason cannot be stated for this phenomenon, it is suggested that this model be expanded to investigate the effect of other variables in order to determine the participation of each variable in cholesterol treatment. Moreover, most of subjects' characteristics in different age groups are not observable. To investigate the effect of such characteristics a frailty factor can be proposed for the model presented in this paper.

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References

1. Ezzati M, Lopez AD, Rodgers A, Murray CJ. Comparative quantification of health risks. Global and regional burden of disease attributable to selected major risk factors Geneva: World Health Organization. 2004.
2. Collaboration APCS. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. International journal of epidemiology. 2003;32(4):563-72.
3. Volpato S, Zuliani G, Guralnik JM, Palmieri E, Fellin R. The inverse association between age and cholesterol levels among older patients: the role of poor health status. Gerontology 2001 47(1):35-45.
4. Manolio TA, Cushman M, Gottdiener JS, Dobs A, Kuller LH, Kronmal RA; CHS Collaborative Research Group. Predictors of falling cholesterol levels in older adults: the cardiovascular health study. Annals of Epidemiology 2004;14(5):325-31.
5. Schalk BW, Visser M, Deeg DJ, Bouter LM. Lower levels of serum albumin and total cholesterol and future decline in functional performance in older persons: the Longitudinal Aging Study Amsterdam. Age Aging 2004;33(3):266-72.
6. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease 1. Lipid levels in 500 survivors of myocardial infraction. J Clin Invest 1973;52(7):1533-15.
7. Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. Lancet 2001;358(9279):351-5.
8. Casiglia E, Mazza A, Tikhonoff V, Scarpa R, Schiavon L, Pessina AC. Total cholesterol and mortality in the elderly. Journal of Internal Medicine 2003;254(4):353-62.
9. Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high-risk elderly patients. JAMA 2004;291(15):1864-70.
10. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? British Medical Journal 1994;308(6925):367–72.
11. Law MR, Wald NJ, Wu T, Hackshaw A. Bailey A Systematic underestimation of association between serum cholesterol concentration and ischaemic heart disease in observational studies: data from the BUPA study. BMJ 1994;308(6925):363–6.
12. Lewington S, MacMahon S. Blood pressure, cholesterol, and common causes of death: a review. Prospective studies collaboration. AM J Hypertension 1999;12(10 Pt 2):S96-8.
13. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease overall findings and differences by age for 316099 white men. Arch Int Med 1992;152(1):56-64.
14. McGilchrist CA, Simpson JM. Effect of differential mortality rate on risk-variable distribution. Mathematical Biosciences. 1979;43(3):173-80.
15. Royston P, Sauerbrei W. Multivariable model-building. A pragmatic approach to regression analysis based on fractional polynomials for modelling continuous variables. Wiley-Blackwell, Chichester; 2008.
16. Delavari A, Alikhani S, Alaedini F. A national profile of non-communicable disease risk factors in the IR of Iran. Ministry of Health, Deputy to Health Directory, CDC. 2005.
17. Braunwald's heart disease, A textbook of cardiovascular medicine. 7th edition, Elsevier saunders; 2005.
18. Fuster V, Alexander RW, O'Rourke RA, Roberts R, King SB, Wellens JJ. Hurst's the Heart, 2-Vol Set. McGraw-Hill Professional Publishing 2000.
19. American Heart Association: Heart and stroke statistical update. Dallas; 2003.
20. World Health report: reducing risks, promoting healthy life-geneva, World Health Organization 2002.