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Survival Analysis: Mortality Risk Associated with Overweight and Obesity

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Abstract: Obesity is a growing health concern for both developed and developing countries. In addition, to its serious health consequences, obesity has real economic costs that affect all of us. In this study, age variation in the association between obesity status and adult mortality risk has been investigated. Mortality was first assessed using the Kaplan-Meier method and then multivariable Cox proportional-hazards regression model has been applied to calculate regression coefficients and 95% Confidence Intervals (CI) for survival in each of the BMI groups. The log rank test has been performed to compare survival curves. A total of 328 patients have been included in the final analysis. We have employed Cox regression model to provide an analysis at various ages and sex. This study provides compelling evidence to support public health efforts to prevent excess weight gain and obesity.

Key words: Body mass index, Cox proportional hazards model, log-rank test, obesity, patients, developing

INTRODUCTION

Obesity is a global epidemic issue that is highly prevalent in both developed and developing countries; it affects people of both sexes and all ages has adverse health consequences, accrues large economic costs and has negative social implications (Haslam and James, 2005; Kelishadi, 2007). The prevalence of obesity is rising significantly in Middle Eastern countries including Iran (Ayatollahi and Mostajabi, 2007). Recently, Dr. Fereidoun Azizi the head of the Research Institute for Endocrine Sciences in Tehran had announced that the obesity rate in Iranian families was rising. The result of the research of this institute revealed that the obesity rate in the women is 35% and the same f actor for men is 15% (Ayatollahi and Mostajabi, 2007). Not only obesity is growing among Iranian but also Iran is reported among the first 7 countries in the world according to the world health organization with regard to high prevalence of obesity (Christensen, 1987; Collett, 1994). Based on the reports, 31% of youths ages 18-25 are overweight in Iran (WHO, 2000). This crisis is not just a pressing social and health issue but an economic one, too. Obesity is a medical condition that can lead to other illnesses from chronic to acute, some very severe and deadly such as Diabetes, High Blood Pressure, Heart attack, Stroke and even Cancer that it has an adverse impact on health, resulting in a reduced lifespan and increased health issues (Dehghan *et al*., 2005; Doak *et al*., 2006; Hedley *et al*., 2004). The rising prevalence of obesity reflects the strong impact of lifestyle factors including diet in its etiology (Azadbakht and Esmaillzadeh, 2008; Kelishadi, 2007; Popkin, 2001).

Prevalence of overweight, obesity, underweight and abdominal obesity among the adult population of Iran has been investigated by Janghorbani *et al*. (2007) by applying means and Standard Errors (Ses), t-test and χ^2 tests. Later, Ayatollah and Ghoreshizadeh (2010) examined overweight and obesity among adults aged 25-55 years in Shiraz (Southern Iran) based on a random multi stage sample survey of 2282 married adults by comparing different groups. Hosseinpanah *et al*. (2016) have applied Cox proportional hazard regression to determine the association of potential obesity risk factors but no comparison between estimators has given. However, an important part of survival analysis is the comparison of the survival curves of two groups based on a formal non-parametric statistical test called the log-rank test and not just upon visual impressions.

This study has employed Cox proportional hazard regression to determine the association of potential obesity risk factors including: age, BMI and gender within the capital, Tehran. The log-rank test is alsoapplied to test the null hypothesis that there is a significant difference between the populations in the probability of death. We have fitted several models to investigate age variation in the relationship between obesity status and individual survival. Here to fore however, research has not accounted for this confounder and to the best of our knowledge it is a new challenge.

Islamic rules are reflected in many social aspects of life in Iran and they might interact with obesity-related behaviors in the population. Iranian women and adolescent girls are less engaged in activities and their Islamic loose dressing style might have made them less concerned regarding dieting and physical activity. Results of a study showed that activities during leisure are extremely low among Iranian adult women comparing to men due to religious reasons and lack of recreation facilities. Considering that, the present social context in Iran is very different from those of Western countries, we examined whether body weight distribution are related to gender in Iranian adults. Such information may be valuable for developing preventive policies that seek to reduce obesity in populations.

MATERIALS AND METHODS

Statistical analysis: One of the most commonly used multivariate approach for analyzing survival time data in medical research is the Cox (Proportional Hazards or PH) model. In this study, this technique isapplied to identify, for each sex, the relative level of mortality risk for different levels of obesity. For each level of age, the relative risks associated with different levels of obesity are combined with the distribution of obesity in the population to decompose the population life table into impaired life tables for obese groups.

Let $\lambda_t = \lambda\,(t|X_{1i}, X_{2i}, ..., X_{ki})$ be the hazard function for the ith person at time, i = 1, ..., n where the k regressors are denoted as $X_{1i}, X_{2i}, ..., X_{ki}$. The baseline hazard function at time t, i.e., when $X_{1i} = 0, X_{2i} = 0, ..., X_{ki} = 0$ is denoted as λ_{0t}. The hazard ratio $\lambda_{1t}/\lambda_{0t}$ can be assumed as the relative risk of the event occurring at time t. The log of the hazard ratio, i.e., the hazard function divided by the baseline hazard function at time t is a linear combination of parameters and regressors, i.e.:

$$\log\left(\lambda\frac{(t|X_{1i},X_{2i},\ldots,X_{ki})}{\lambda_{0t}}\right)=\beta_1X_{1i}+\beta_2X_{2i}+,\ldots,+\beta_kX_{ki}$$

Where a set of p covariates $(X_{1i}, X_{2i}, ..., X_{ki})$ whose impact is measured by the size of the respective coefficients $(\beta_1, \beta_2, ..., \beta_k)$ and can be interpreted in a similar manner to that of multiple logistic regression. The ratio of hazard functions can be regarded as a ratio of risk functions so the proportional hazards regression model can be applied as a function of relative risk (while logistic regression models are a function of an odds ratio). Interpreting the Cox Model involves examining the coefficientsfor each explanatory variable. A positive regression coefficientfor an explanatory variable means that the hazardis higher and thus the prognosis worse. Conversely, a negative regression coefficient implies a better prognosis for patients with higher values of that variable. When it is used to analyses the survival of patients in a clinical trial, the model grants us to isolate the effects of treatment from the effects of other variables. We refer to Cox (1972), Popkin and Gordon-Larsen (2004) for more detailed information.

To compare estimates of the hazard functions of the two groups at each observed event time the log-rank test statistic has been applied. The null hypothesis is that the groups have the same survival. It is constructed by computing the observed and expected number of events in one of the groups at each observed event time and then adding these to obtain an overall summary across all-time points where there is an event. This function, presents methods for comparing two or more survival curves where some of the observations may be censored and where the overall grouping may be stratified. The methods are nonparametric since they do not make assumptions about the distributions of survival estimates. To estimate the test statistic for comparing two groups A and B we have:

$$\chi^2_{logrank}=\frac{(O_A\text{-}E_A)^2}{E_A}+\frac{(O_B\text{-}E_B)^2}{E_B}$$

Where the expected number of events is calculated as $E_{Aj} = \Sigma\, d_j n_{Aj}/n_j$, d_j as the number of events at time t_j, n_{Aj} number of people at risk at time j in group A and n_j = total number of people at risk. It has the considerable advantage that it does not require us to know anything about the shape of the survival curve or the distribution of survival times. For more discussed information (Tarone and Ware, 1977).

Survival of the obesity: Body Mass Index (BMI), defined as weight in kilograms divided by the square of the height in meters is commonly used in clinical practice to screen for overweight and obesity and to guide weight loss recommendations. It is used as a measure to indicate whether a person is underweight, overweight and obese or a healthy weight for their height. According to the World Health Organization obesity is subdivided into 3 categories:

- Grade 1: BMI of 30 to <35
- Grade 2: BMI of 35 to <40
- Grade 3: BMI of 40 or higher. Grade 3 obesity is sometimes categorized as "extreme" or "severe" obesity

People with BMIs higher than 30 are at an increased risk of dying from Heart disease, Diabetes, Cancer and other diseases, many studies have shown. But several recent studies suggest that in some cases a high BMI could actually protect a person from dying of heart failure, kidney failure and other chronic diseases and Grade 2 obesity may cause higher risk of mortality.

Table 1: Table of study sample by sex, 2014-2016

Gender	Frequency	Frequency (%)
Female	116	35.4
Male	212	64.4
Total	328	100.0

Table 2: Table of study sample by body mass index, 2014-2016

Body mass index	Frequency	Frequency (%)
Grade1	172	52.4
Grade 2	37	11.3
Grade 3	119	36.3
Total	328	100.0

Data sources: Our analytic sample consisted of 328 adult respondents aged above 18 at the time of survey who either attended the Metabolic Unit of Tehran University of Medical Sciences in Tehran for a routine health check or who were acting as control subjects during 2014-2016. We included all related population-based studies including national, province and local surveys which were carried out on individuals with no restraint in age or gender. The extracted data is shown separately in Table 1 and 2.

Body Mass Index (BMI) was calculated from measured height and weight. Weight and height has been measured to the nearest 1 kg or 1 cm, respectively, examinees wearing light clothing without shoes.

RESULTS AND DISCUSSION

We have employed the Kaplan-Meier method and log-rank tests and then multivariable Cox proportional hazards regression models to calculate Hazard Ratios (HR) and 95% Confidence Intervals (CI) for the risk of mortality in each of the BMI groups. All statistical analyses were performed using R package. All tests are two-sided and $p<0.05$ is considered statistically significant. Several models have been fitted to explore age variation in the relationship between obesity status and individual mortality hazards.

First, we have presented the first model by obesity status for men in Table 3 and obtained obesity-specific survival estimations. Furthermore we conducted several sensitivity analyses by limiting age at survey to 10 years age bands and refitted the second group of models. More precisely, we have compared the Grade 1-3 body mass index hazards across the age range for men. Table 3 presents Cox regression coefficients, standards errors and 95% confidence intervals for men. Estimates from Table 3 suggest that the strength of the association between obesity status and individual survival significantly grows with age in male population.

Kaplan-Meier curves of the percent survival by body mass index categoriesfor men are presented in Fig. 1. The lengths of the horizontal lines along the X-axis of serial times representthe survival duration for that interval (Survival time). The interval is terminated by the occurrence of the event of interest while the vertical line shows the survivals which illustrate the change in probability as the curve advances. Regarding the log-rank test, $p<0.001$, the three curves are significantly different, i.e., the grouping variables has a significant influence on survival times.

A more detailed look at figure represents that with increases BMI, the percent survival gradually decreases, rendering Grade 2 with minimum of survival.

Table 4 reports respective estimations for adult women. Results from this table however, reveal that the association between age at survey and percent survival varies significantly by obesity status. Increases in age at

Table 3: Estimated regression coefficient from Cox survival models examining the associations between obesity, age and mortality in adult men

Obesity status	Estimate	SE	Confidence interval (95%)
Grade 1	5.878	0.264	(5.360, 6.396)
Grade 2	4.703	0.626	(3.476, 5.929)
Grade 3	4.572	0.337	(4.122, 5.441)
Obesity status by age			
Grade 1			
19-28	5.232	0.234	(5.134, 6.836)
29-38	5.313	0.245	(5.240, 5.943)
39-48	5.823	0.256 (5.313, 6.309)	
49-58	5.596	0.243 (5.382, 6.108)	
>59	5.447	0.224 (5.301, 6.128)	
Grade 2			
19-28	4.301	0.693 (3.736, 5.909)	
29-38	4.391	0.612 (3.275, 5.421)	
39-48	4.491	0.591 (3.102, 5.512)	
49-58	4.223	0.651	(3.412, 5.501)
>59	4.123	0.612	(3.012, 5.201)
Grade 3			
19-28	5.234	0.325	(5.136, 6.091)
29-38	5.349	0.341	(5.102, 6.190)
39-48	5.401	0.301	(5.142, 6.131)
49-58	5.294	0.391	(5.002, 6.441)
>59	5.234	0.331 (5.151, 6.502)	

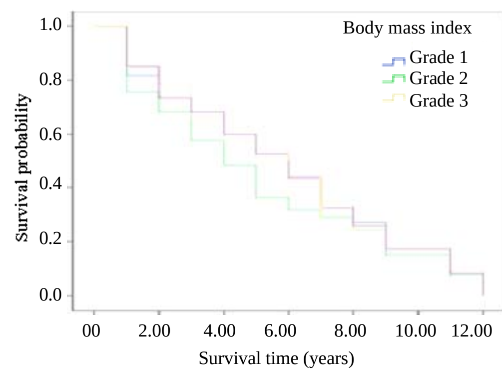

Fig. 1: Kaplan-Meier curves of cumulative hazards stratified by BMI categories for adult men

Table 4: Estimated regression coefficient from Cox survival models examining the associations between obesity, age and mortality in adult women

Obesity status	Estimate	SE	Confidence interval (95%)
Grade 1	5.184	0.913	(5.067, 6.104)
Grade 2	4.701	0.385	(4.002, 5.145)
Grade 3	4.059	0.734	(4.002, 5.194)
Obesity status by age:			
Grade 1			
19-28	5.201	0.823 (4.804, 5.602)	
29-38	5.194	0.865 (4.634, 5.481)	
39-48	5.204	0.801 (5.001, 5.601)	
49-58	5.100	0.834 (4.802, 5.681)	
>59	4.801	0.810 (4.301, 5.812)	
Grade 2			
19-28	4.512	0.194 (4.158, 5.165)	
29-38	4.361	0.596 (3.810, 5.174)	
39-48	4.330	0.491 (3.295, 5.012)	
49-58	4.104	0.820 (3.364, 5.491)	
>59	4.001	0.195 (3.310, 5.712)	
Grade 3			
19-28	4.610	0.601 (4.005, 6.014)	
29-38	4.301	0.591 (3.891, 5.016)	
39-48	4.491	0.710 (3.901, 5.612)	
49-58	4.254	0.541 (3.937, 5.851)	
>59	5.107	0.616 (4.159, 5.901)	

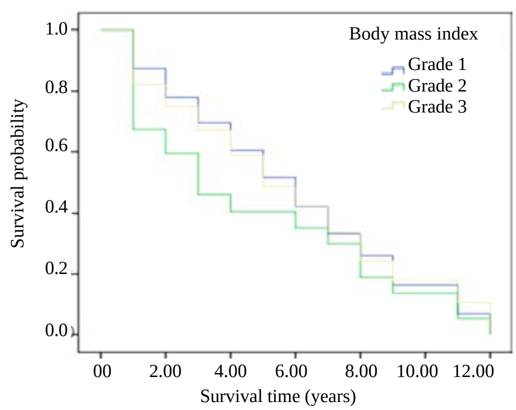

Fig. 2: Kaplan-Meier curves of cumulative hazards stratified by BMI categories for adult women

survey are associated with smaller survival at older ages and the substantive strength of these survival decreases with greater obesity.

This is most clearly illustrated in Fig. 2 which plots fitted survivals between the Grade 1-3 obese population of women. Consistent with our hypothesis, mortality differences by age at survey are significantly modified by obesity status with increases BMI, the survival probability gradually decreases. Survival differences between obesity categories is assessed with log-rank test with $p = 0.021$. Rendering Grade 2 with almost minimum of survival, Fig. 2 represents parallel form of curves for Grade 1 and 3 but higher hazard rate for Grade 2 body mass index which is revealed as the slope of survival rate. Accordingly, Grade 2 represents minimum of survival with higher risk of mortality comparing to the Grade 1 and even Grade 3 for women. This could be the direct result of different lifestyle, less outdoor activities and religious regulations.

CONCLUSION

In this study, we explored age variation in the relationship between obesity status and mortality at selected ranges of age at survey. Cox regression modelhas been applied to assess associations between BMI, age and mortality. Estimates revealed that variation in the association with obesity status in men's and women's mortality hazards increased with age for each specific subgroups. Survival has been compared by using the log-rank test on the Kaplan-Meier life table. In general, consistent with our hypothesis, mortality differences by age at survey are significantly conditioned by obesity status.

Principally obesity significantly and substantively decrease the percent survival for men and women but the substantive higher mortality risk has been reported for Grade 2 obesity. These patterns are most clearly shown in Fig. 1 and 2 which plots fitted models by survival time for both the male and female samples which provided evidence that the diminishing survival-obesity associations result from the confounding influences of BMI at survey. Figure 2 has revealed higher mortality risk and consequently, lower survival rate in Grade 2 obesity for women which is significantly associated with different lifestyle, less outdoor physical activities and religious regulations. Physical activity pattern and more importantly dietary habits may contribute to this gender difference.

SUGGESTIONS

These findings have profound implications for future research, health policy and health-care services in Iran. It is suggested that health interventions to control obesity should not just target over weight individuals but the awareness of the whole society about the adverse effects of increased body mass index must be refreshed every day.

REFERENCES

Ayatollahi, S.M.T. and F. Mostajabi, 2007. Prevalence of obesity among schoolchildren in Iran. Obesity Rev., 8: 289-291.

Ayatollahi, S.M.T. and Z. Ghoreshizadeh, 2010. Prevalence of obesity and overweight among adults in Iran. Obesity Rev., 11: 335-337.

Azadbakht, L. and A. Esmaillzadeh, 2008. Dietary and non-dietary determinants of central adiposity among Tehrani women. Public Health Nutr., 11: 528-534.

Christensen, E., 1987. Multivariate survival analysis using Cox's regression model. Hepatol., 7: 1346-1358.

Collett, D., 1994. Modeling Survival Data in Medical Research. Chapman and Hall, London, UK.

Cox, D.R., 1972. Regression models and life tables (with discussion). J. R. Stat. Soc. Ser. B, 34: 187-220.

Dehghan, M., N. Akhtar-Danesh and A.T. Merchant, 2005. Childhood obesity, prevalence and prevention. Nutr. J., 4: 24-24.

Doak, C.M., T.L.S. Visscher, C.M. Renders and J.C. Seidell, 2006. The prevention of overweight and obesity in children and adolescents: A review of interventions and programmes. Obesity Rev., 7: 111-136.

Haslam, D.W. and W.P.T. James, 2005. Obesity. Lancet, 366: 1197-1209.

Hedley, A.A., C.L. Ogden, C.L. Johnson, M.D. Carroll, L.R. Curtin and K.M. Flegal, 2004. Prevalence of overweight and obesity among US children, adolescents and adults, 1999-2002. J. Am. Med. Assoc., 291: 2847-2850.

Hosseinpanah, F., M. Mirbolouk, A. Mossadeghkhah, M. Barzin and S. Serahati *et al*., 2016. Incidence and potential risk factors of obesity among Tehranian adults. Preventive Med., 82: 99-104.

Janghorbani, M., M. Amini, W.C. Willett, M.M. Gouya, A. Delavari, S. Alikhani and A. Mahdavi, 2007. First nationwide survey of prevalence of overweight, underweight and abdominal obesity in Iranian adults. Obesity, 15: 2797-2808.

Kelishadi, R., 2007. Childhood overweight, obesity and the metabolic syndrome in developing countries. Epidemiol. Rev., 29: 62-76.

Popkin, B.M. and P. Gordon-Larsen, 2004. The nutrition transition: Worldwide obesity dynamics and their determinants. Intl. J. Obesity, 28: S2-S9.

Popkin, B.M., 2001. The nutrition transition and obesity in the developing world. J. Nutr., 131: 871S-873S.

Tarone, R.E. and J. Ware, 1977. On distribution-free tests for equality of survival distributions. Biometrika, 64: 156-160.

WHO, 2000. Obesity: Preventing and managing the global epidemic. Report of a WHO Consultation. WHO. Tech. Rep. Ser., 894: 1-253.