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Original Article

Comparison between fractional polynomials, spline smoothing, and multiple logistic regression models in the study of associated hypertension risk factors

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ABSTRACT

Background & Aim: Previous studies about hypertension and risk factors have shown the linear relationship between them. However, we can improve the fit of models with some changes and have a better form for estimation of coefficients and interpret the effects of variables.

Methods & Materials: This survey was a cross-sectional study from 2010 to 2011 in Yazd, Iran. The participants were among the subjects aged from 40 to 80. Body mass index (BMI), sex, age, renal failure, history of diabetes (years of disease), type of diabetes (type 1 or type 2), the number of cigarettes per day and years of smoking were predictors and the binary response returned to hypertension (yes or no). The traditional logistic model was used for determining the relationship between covariates and the outcome. Then, the models were modified with multivariable fractional polynomials.

Results: Our findings displayed fitting the multivariable fractional polynomials (MFP) model in the parametric model which was the best fit for the modeling. The difference deviance in MFP was 21.952 ($P < 0.001$). The linear model in comparison with null model deviance differences was 22.170 ($P < 0.001$). The second-degree fractional polynomials model compared with first-degree fractional polynomials model, and the difference deviance was 21.850 ($P < 0.001$).

Conclusion: MFP model approach is an alternative procedure that can solve previous problems about the categorical approach, step function, and cut-off points.

Introduction

Nowadays, the international community faces one epidemic disease known as obesity. Obesity increases the probability of suffering from the other diseases, particularly hypertension, heart disease, type 2 diabetes, and cancer. In this study, we focused on hypertension and the risk factors which affect it. According to World Health Organization (WHO) reports, the countries with moderate and high income are more exposed to hypertension in comparison with other countries. In addition, the countries with better facility for prevention and health have the lower rate of hypertension (1).

There is no particular reason for high blood pressure yet, but some risk factors with impressive effects have been identified. In this study, the most important factors have been considered. There are some variables such as age, sex, body mass index (BMI), type of diabetes, history of diabetes, years of smoking and the number of cigarettes per day. The previous knowledge indicates the relationship between hypertension and risk factors. Simplifying tends us to select linear models for all predictor variables, but old methods are not always effective. Some of the relationships between

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covariates and response variables are nonlinear.

In this study, we tried to achieve an optimal model for the data which investigates the effect of nonlinear independent variables (2). Sometimes the use of transformations for improving the models is not appropriate, and employing step function for continuous factors may eventuate wrong results. Consequently, multi-variable fractional polynomials, as a parsimonious approach, can cover the fit and correct the past problems. For this purpose, we introduce multi-variable fractional polynomials models. This model is mainly used for continuous covariates.

In this study, age and BMI were continuous predictor variables. Although the BMI variable measures the effect of obesity, we should find the real effect of BMI in studies. According to some researchers, BMI has different effects in different surveys (3). This previous knowledge led us to find a useful procedure for improving the results and reach real relationship between BMI and diseases. One of the reasons for differences returns to a variety of database, so it makes researchers use a method which is able to analyze without change.

The fractional polynomials model can accomplish through the other parametric models, for example, quadratic or cubic models. The other risk factors have a linear relationship with hypertension.

The previous survey showed the classification of BMI is one approach for analyzing the effect of BMI (3). Although this method is more popular because of the prior knowledge, the probability of hypertension, in this case, is influenced by this approach. Massive research categorized the BMI, for instance, BMI $\geq$ 30 assigns obese, and BMI = 25-30 assigns to overweight individuals. However, Royston et al. mentioned disadvantages of this approach (4). As previously mentioned, losing information and rounding the amounts of a continuous variable cause to wrong results. In BMI example, if the researchers assume BMI (18.5-25) is normal, the probability of hypertension with this predictor will be equal to all points. Also, cut-off points can make problems like overestimate or underestimate. BMI is a continuous covariate, and its shape is skewed. So, it is better to keep the matter of it and try to use a model which is nonlinear. Among the nonlinear and linear models, multi-variable fractional polynomials (MFP) model is very flexible and interprets the real effect of a continuous covariate like BMI. This model improves the fitting BMI against hypertension by adjusting the other variables.

Methods

This cross-sectional study was a part of the survey of Yazd, Iran, performed between 2010 and 2011. Samples were selected from urban and rural areas, and the method of sampling was a multi-stage random cluster. For selecting clusters, we used the blocking obtained from the national census in 2006 in Iran. The clusters were 58 overall and 6 clusters of urban and 52 clusters of rural. For each cluster, 40 individuals were selected and were invited for answering about predictors. In this investigation, hypertension with binary type was the outcome variable.

According to WHO definition, hypertension, also known as high or raised blood pressure, is a condition in which the blood vessels have persistently raised pressure. Blood is carried from the heart to all parts of the body in the vessels. Once the heart beats, it pumps blood into the vessels. Blood pressure is created by the force of blood pushing against the walls of blood vessels (arteries) as it is pumped by the heart. The higher the pressure, the harder the heart has to pump (5). Other variables as predictors are sex (man or woman), age and BMI. BMI is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of one's height in meters (kg/m^2) (6). The rest of variables as predictors are renal failure (kidney failure, also known as renal failure or renal insufficiency, is a medical condition of impaired kidney function in which the kidneys fail to adequately filter metabolic wastes from the blood (7), history of diabetes (is a group of metabolic disorders in which there are high blood sugar levels over a prolonged period (8), type of diabetes [In general, people with diabetes either have a total lack of insulin (type 1 diabetes) or they have too little insulin or cannot use insulin effectively (type 2 diabetes) (9)], the number of cigarettes (total number of cigarettes was used per day) and years of smoking (number of years the person has smoked).

Renal failure, sex, history of diabetes and type of diabetes were considered dichotomous, and the other variables were continuous. A logistic model was fitted. As mentioned from previous knowledge, the shape of BMI variable is skewed (3). Therefore, we prefer to provide a model which can represent the real effect of this variable. The MFP is a flexible and straightforward model, and also we can compare it with the other parametric models. For checking the robustness, we compare the model with conventional approaches such as spline and categorical models. One of the essential conditions for applying MFP models is existing continuous risk factors for making a model. In this study, BMI was considered a continuous variable. To account for the nonlinear and the asymmetric relationship between BMI and hypertension, we fitted the common logistic model after that we used fractional polynomials models. According to previous studies, the effect of BMI in hypertension for women and men groups was different. So, the sex covariate was divided into two groups. If the P values of the predictor were near to nominal P (0.1 or 0.2), according to previous knowledge, it might be a confounder (4). For selecting of the practical variables, backward elimination approach selects final models with deviance difference test (10). If the linear model suffices in the backward algorithm, the MFP model can improve the fitting by using centered and scaled transformation.

Fractional polynomials model selects the power and transformation from one set that Royston et al. introduced (2, 4, 11). The set is -2, -1, -0.5, 0, 0.5,1, 2, 3 with contract when the power is 0, the predictor variable converts to the logarithm of predictor. The construction of backward elimination can display the best fitting. The null model which is a model with the estimated intercept compares with MFP by chi-square with 4 degrees of freedom and linear model compares with fractional polynomials by chi-square with 3 degrees of freedom. This comparison makes the difference deviance test. This criterion indicates the best fitting model. The advantage of MFP with the first and second degree is simplicity in comparison the other models, particularly nonlinear models such polynomials models. The backward elimination also compares second degree and the first degree of fractional polynomials. If the first degree of fractional polynomials is significant, two models will compare by chi-square with 2 degrees of freedom (12). Since collinearity is one of the most critical challenges in these types of models, it is wise to use the lower degree of fractional polynomials for adjusting this problem (13). The estimated regression model for men was:

Logit $(\pi i) = \beta_0 + \beta_1(\frac{\text{BMI}}{10})^{p_1}$, where π_i is the probability of hypertension for individual i, p_1 is the power of fractional polynomials for BMI variable. The fractional polynomials model also scaled and centered covariate in the model. In this case, BMI variable not only should form by the second degree of fractional polynomials model, but also it scaled and centered (14).

The MFP model for women was similar to the linear model, but centering and scaling approach can improve the estimation of coefficients. The estimated regression model for the women category was:

$$\text{Logit}(\pi i) = \beta_0 + \beta_1(\text{Age}) + \beta_2(\frac{\text{BMI}}{10})^{p_1}$$

This process provides a robust and stable fitting, especially for the model with intercept (4). The nominal P was 0.050, and significance of variables was compared with the nominal P. To assess the validity of the MFP model for BMI, step function, linear, quadratic and cubic model and spline smoothing method were graphically compared with MFP models (10).

Spline smoothing is a way to fit a smooth curve to the data to avoid the Runge's phenomenon (15). It mainly has better fit compared to fractional polynomials, but it is not stable (16). As mentioned, it is a non-parametric approach that finds the nearest neighborhood by interpolation (17). Losing stability and robustness causes inappropriate estimates which are also complicated and could be medically implausible (12).

The previous investigation classified the continuous variables such as BMI (3). This model was compared with fractional polynomials. The spline is applied just for resolving the problems of MFP model in model adequacy checking with the Bootstrap approach (12, 18).

All statistical models were fitted using the R Statistical Software (version 3.2.3). The R procedure MFP was used to determine the functional forms for BMI and calculated estimates for the BMI were associated with hypertension. The offered packages by algorithm tables indicate how a set of model selection find an optimal and parsimonious model.

Results

The numbers of individuals suffering from hypertension were 480 of 533 (90.00%) in the development phase. In the women group, 310 numbers of responder had hypertension in developed phase (58.16%). In men group, 170 numbers had hypertension (31.89%). Further information is listed in tables 1 and 2.

Table 1. Descriptive table for women category without renal failure and diabetes

Variable	Hypertension	
	Yes (n = 185)	No (n = 20)
Age (year)	57.70 ± 0.75	51.70 ± 2.19
BMI (kg/m^2)	29.44 ± 0.34	26.83 ± 1.16

Data are shown as mean ± standard error (SE)
BMI: Body mass index

The number of women suffering from hypertension without renal failure and diabetes was 185 (90.00%). The mean age and BMI were 57.70 and 29.44, respectively.

The number of men suffering from hypertension without renal failure and diabetes was 104 in overall (83.00%). The mean of age of these individuals was 60.25, and the mean BMI was 26.81. The average number of cigarette and the history of smoking for the men group who suffered from hypertension in developing phase was 0.88 and 8.14, respectively.

Table 2. Descriptive table for men category without renal failure and diabetes mellitus

Variable	Hypertension	
	Yes (n = 104)	No (n = 21)
Age (year)	60.25 ± 0.95	58.05 ± 2.02
BMI (kg/m^2)	26.81 ± 0.37	24.14 ± 0.85
Years of smoking	8.14 ± 1.42	11.81 ± 3.91
Total number of cigarettes (per day)	0.88 ± 0.31	4.57 ± 2.12

Data are shown as mean ± standard error (SE)
BMI: Body mass index

Model Fit: The best fitting model for BMI in the men category included the term (BMI/10)$^{-2}$. The other variables were not significant. We examined sex and stratified it (P = 0.150). Also, the number of smoking variable and years of smoking were not significant, so they would not be a confounder (P = 0.800). The tables of significant independent variables are respected in tables 3-5. Deviance difference test illustrates MFP improved the fitting model. The difference deviance in MFP was 21.952 (P < 0.001). The linear model in comparison with null model deviance differences was 22.170 (P < 0.001). The second-degree fractional polynomials model was better than first-degree fractional polynomials model, and the difference deviance was 21.850 (P < 0.001).

Table 3. Significant predictor variables odds ratio for male group

Variable	OR	95% Confidence interval	P-value*
(BMI/10)$^{-2}$ (kg/m^2)	1.021	1.009-1.033	< 0.001
Age (year)	1.003	0.998-1.008	0.104
Renal failure	1.133	0.585-2.195	0.211
History of diabetes	1.027	0.412-2.563	0.764
Type of diabetes	1.026	0.411 -2.560	0.707
(Years of smoking + 1)/10	1.000	0.996-1.004	0.929
Number of cigarettes + 1 (total number-per day)	0.991	0.982-1.001	0.349

* Chi-square test
OR: Odds ratio

Table 4. Set of algorithm deviance for model selection in male category

Variable	Deviance	Variable power(s)
BMI (kg/m^2)	22.871	Null model
	21.491	1
	20.562	-2
	20.208	-2 -2
Age (year)	20.849	Null model
	20.562	1
Renal failure	20.732	Null model
	20.562	1
History of diabetes	20.562	Null model
	20.562	1
Type of diabetes	20.562	Null model
	20.562	1
Years of smoking	20.563	Null model
	20.562	1
	20.562	-2
	20.314	-0.5 -0.5
Number of cigarettes (total number of cigarettes per day)	20.657	Null model
	20.562	1
	20.548	0.5
	20.377	-2 1

BMI: Body mass index

The other predictors were not significantly affected. No interactions of the variables were significant. All the interactions of variables were not significant (P > 0.050). The algorithm in tables 3 to 5 illustrates the results. In these tables, we can consider the best model by applying the deviance difference comparing to a chi-square distribution. The algorithm can select the optional model and final model. In the women group, we realized that the linear model was reasonable for all independent variables. Age and BMI were significant predictors, and linear model improved the transformation that packages offered in tables 6-8. Although linear model corresponded to the first power of fractional polynomial model (P > 0.999), the transformation such as shifting and scaling could improve linear models. Deviance difference approach for selecting a model was not sufficient, so in the next part, we compared the MFP model with the other method including spline method.

BMI curves: As mentioned when the categorical approach was used, whereas the matter of variable is continuous the results would be inappropriate. For modifying the analysis, we introduced a new functional form, MFP, which can improve the linear model. In the graphical procedure, this model was compared with linear, quadratic, cubic polynomial in men and women groups. It was concluded that this model was a better model in particular for initial and final points. As seen in 5 and 6 figures, step functions or categorical functions which caused an overestimation or underestimation. Also the spline smoothing method as it is evident is a nonparametric technique so MFP approach is an appropriate method for better interpretation. Although spline is more flexible than the other models even MFP models, it cannot have a closed form of its function; therefore the advantages of model adequacy checking were not applicable in model selection. The type of data illustrates nonlinearity in figures 1 and 2.

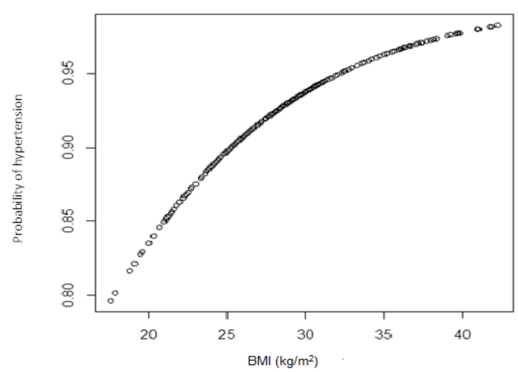

Figure 1. Shape of data in women group for probability of hypertension against body mass index (BMI)

Table 5. Set of algorithm deviance for model selection in male category

Variable	Initial degree of freedom	Final degree of freedom	Confidence level	First degree	Second degree
BMI (kg/m^2)	4	2	0.05	-2	.
Age (year)	1	1	0.05	1	.
Renal failure	1	1	0.05	1	.
History of diabetes	1	1	0.05	1	.
Type of diabetes	1	1	0.05	1	.
Years of smoking	4	1	0.05	1	.
Number of cigarette (total number of cigarettes per day)	4	1	0.05	1	.

BMI: Body mass index

Table 6. Significant predictor variables odds ratio for female group

Variable	OR	95% Confidence interval	P-value*
$(BMI/10)^{-2}$ (kg/m^2)	1.076	1.015-1.142	0.013
Age (year)	1.003	1.000-1.005	0.028
Renal failure	1.064	0.562-2.013	0.348
History of diabetes	1.057	0.386-2.891	0.764
Type of diabetes	0.982	0.358-2.687	0.925

* Chi-square test

OR: Odds ratio; BMI: Body mass index

Table 7. Set of algorithm deviance for model selection in women category

Variable	Deviance	Variable power(s)
BMI (kg/m^2)	22.588	Null model
	22.170	1
	21.952	-2
	21.850	-2 -2
Age (year)	22.494	Null model
	22.170	1
Renal failure	22.229	Null model
	22.170	1
History of diabetes	22.176	Null model
	22.170	1
Type of diabetes	22.171	Null model
	22.170	1

BMI: Body mass index

Figures 3 and 4 support the explanation of the kind of each model for women and men groups, showing the relationship between BMI and probability of hypertension. The linear, quadratic and cubic polynomials models and MFP method were fitted simultaneously.

The MFP model can cover the larger bounds of data compared to the other models. Although the cubic polynomial model was better than MFP in the men group, the knotting of this model and nonlinearity resulted in preferring the MFP model.

The prediction for final points of BMI was considered a more precise fit for data analysis because the risk of increasing the probability of hypertension with considering the BMI effect in these points was more severe than the other points. Wrong judgments about final points had many mistakes in findings, particularly for BMI = 40-45. In these points, underestimation was worse than overestimation, and the differences of fit mainly occurred at these points. In the female group the linear model, quadratic and cubic models were compared. The comparison indicates the linear model has a better fit for the female group. Also, overfitting and under fitting are less than the other models.

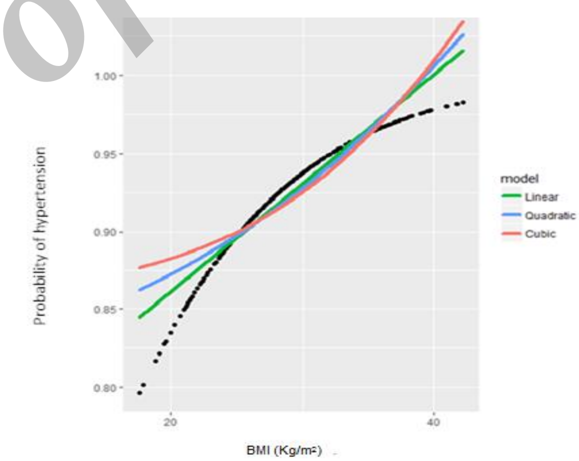

Figure 2. Simultaneous comparison between models for probability of hypertension against body mass index (BMI) in women group with logit scale

Table 8. Set of algorithm deviance for model selection in women category

Variable	Initial degree of freedom	Final degree of freedom	Confidence level	First degree	Second degree
BMI (kg/m^2)	4	1	0.05	1	.
Age (year)	1	1	0.05	1	.
Renal failure	1	1	0.05	1	.
History of diabetes	1	1	0.05	1	.
Type of diabetes	1	1	0.05	1	.

BMI: Body mass index

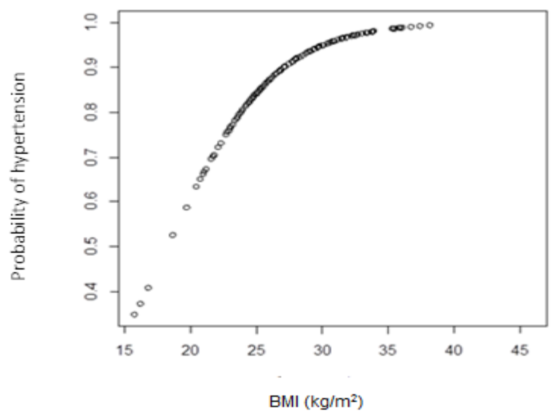

Figure 3. Shape of data in male group for probability of hypertension against body mass index (BMI)

BMI with spline smoothing: In figures 5 and 6, the spline model is more flexible than fractional polynomials, but this flexibility can be a reason for instability in this model. As it is observed, the model presented by spline method was affected by influenced data in final points.

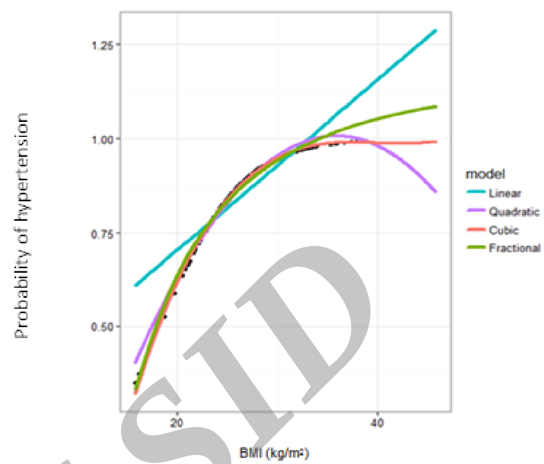

Figure 4. Simultaneous comparison between models for probability of hypertension against body mass index (BMI) in men group with logit scale

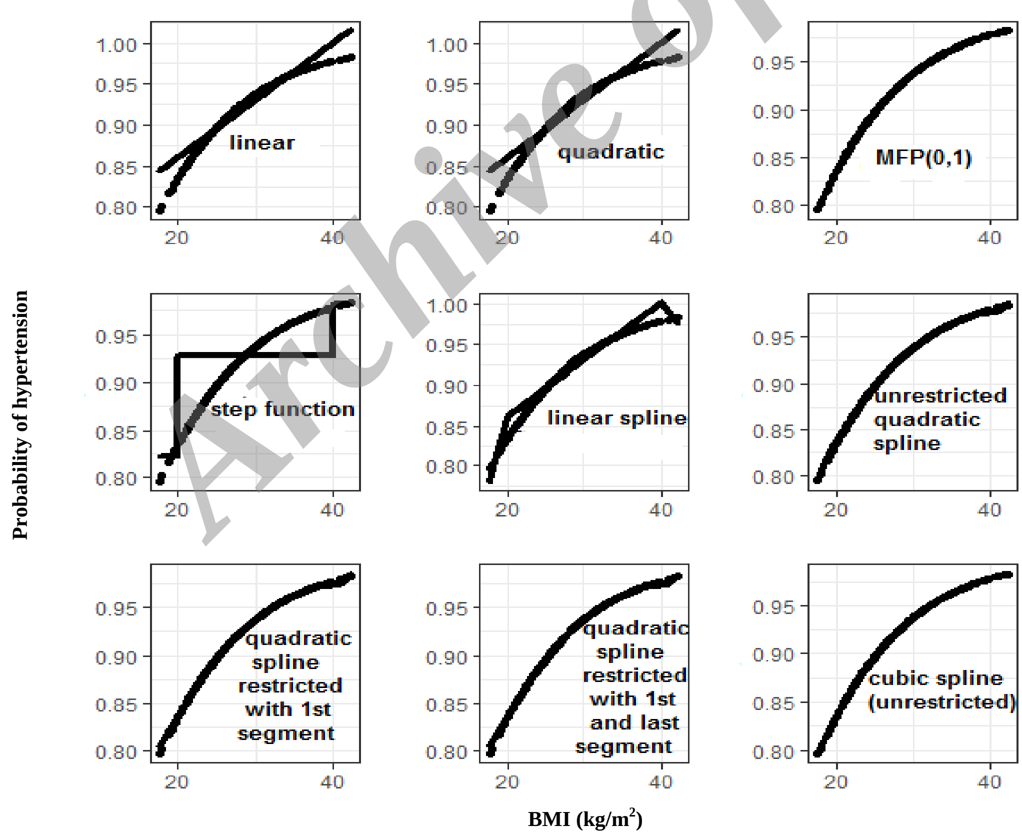

Figure 5. Separated spline curves and functional form for body mass index (BMI) predictor for female groups against probability of hypertension
MFP: Multi-variable fractional polynomials

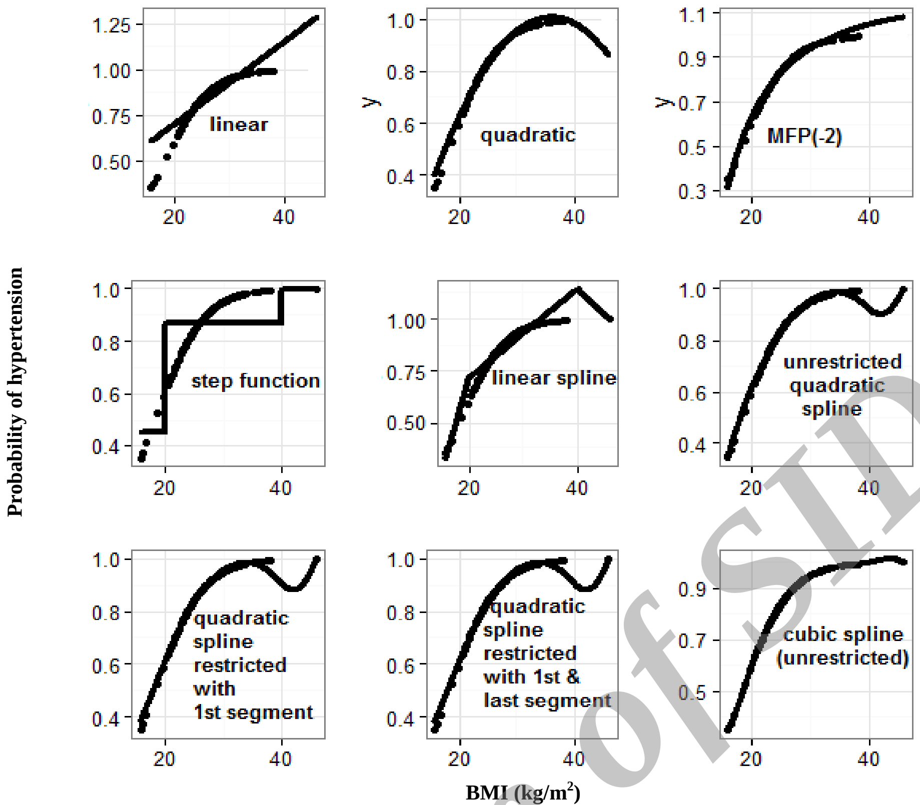

Figure 6. Separated spline curves and functional form for body mass index (BMI) predictor for men groups against probability of hypertension
MFP: Multi-variable fractional polynomials

Spline smoothing models were more flexible than linear, quadratic, categorical and MFP models. In this case, MFP cannot be accountable, and cubic spline was better than that in the men group, but the spline method proposes a complex model with a higher degree which is not acceptable. Also, the lower degrees such as a step function and linear spline models were not flexible and they had overfitting and underfitting. In the women group, the cubic spline and MFP model have corresponded fit for the BMI curve against the probability of hypertension. It indicated the advantage of MFP models among the other approaches.

Estimates of BMI for hypertension model: One of the primary goals of this survey was the statement of fundamental differences between categorical and MFP models. According to previous medical knowledge, the BMI variable was clarified and considered as the BMI ≤ 18.5 for the first set, then divided the next sets into five categories (18.5 < BMI < 25, 25.1 < BMI < 30, etc). Different odds in each category illustrated that retaining the type of a continuous variable was more important, and avoiding the conversion of a continuous variable to stratified type is a wise procedure for modeling. In tables 9 and 10, the analysis of this variable and its respected estimates are explained. Since the BMI predictor variable had a nonlinear relationship with hypertension in the men group, MFP approach was applied just for this group.

Table 9. Odds measure of hypertension in men group with multi-variable fractional polynomials (MFP model)

BMI (kg/m^2)	Number		OR
	At risk	Hypertension	
≤ 18.5	3	0	1.305
18.5-25	12	59	1.581
25.1-30	12	70	1.916
30.1-35	1	30	2.090
35.1-40	0	10	2.214
> 40.1	0	1	2.261

BMI: Body mass index; OR: Odds ratio

Table 10. Odds measure of hypertension in men group with cut-off points and categorical analysis

BMI (kg/m^2)	Number		OR
	At risk	Hypertension	
≤ 18.5	3	0	0.884
18.5-25	12	59	1.934
25.1-30	12	70	4.414
> 30.1	1	41	13.907

BMI: Body mass index; OR: Odds ratio

Tables 9 and 10 indicated the overestimation and underestimation, particularly for initial and final points. The odds for MFP model and the traditional logistic model were different. The estimates of MFP model for each category were more appropriate than the estimates which were made of the categorical model.

Discussion

In this investigation, the estimates of the probability of hypertension have been reported in the defined category like Royston et al. (4) that used the categorical approach for interpreting the results. In fact, one of the primary goals of this survey is the statement of essential differences between categorical and MFP models. According to previous medical knowledge (4), we can classify the BMI variable and consider the BMI ≤ 18.5 for the first set then divide the next into five categories, for instance 18.5 < BMI < 25 , 25.1 < BMI < 30.

This study suggested a parsimonious and optimal model for correct estimate coefficients. The results acknowledged the advantages of MFP models. Categorical model cannot interpret and justify the initial and final points which are often critical in analyzing. With the MFP model approach, the results of the analysis indicate that BMI covariate should transform with selection power of fractional polynomials model where the scale is also changed. For the other significant predictors such as age and renal failure, MFP does not require motion transformation and power. In other words, when a linear form for covariate is used, first-degree fractional polynomials and P > 0.999 are gained (3).

The MFP procedure provides a flexible shape for linear modeling. One of the main advantages of MFP methods is an inspiration of linear models for standard principles (12). The primary rules for MFP come from linear criteria, and likewise, we can use simple logistic linear model adequacy checking for accommodation findings. Using a categorical approach not only causes losing information as was explained but also might increase the variance of estimates particularly in sparse data (3). While qualitative and continuous predictor exists in surveys, it is desirable to use fractional polynomials models. Particularly, the second degree of that tries to avoid model which has plenty cut-off points. Cut-off points not only decrease the power of model, but also lead researchers to choose a linear model that will be misleading (3, 19). This situation mainly occurs in clinical trial studies and nonlinear model could be considered as the superior linear model (2).

Most experiences in epidemical investigation support MFP as an efficient model, and simple relationships and simple models mainly are deduced by the analysis of data with MFP method (12). Furthermore, MFP is a generalized linear model, in other words, it is an expression of polynomials models. So, using the goodness of fit model rules is acceptable for this model (20). The MFP is a parametric smoothing approach, in fact, this model can be useful in the cases that non-parametric software package is not available or implausible (22). Although this approach improves the modeling and it is a parametric model, it may cause some problems such as inappropriate curves and bias estimation of coefficients when there are influential data in surveys (2).

Conclusion

The MFP model in this survey is the best fitting model, especially for BMI independent variable. The other significant independent variables such as age and renal failure remain without change. The graphical part explains the result of comparing various models. The cubic spline smoothing is better than MFP but it is a nonparametric method, and it is a complex model which it is not plausible for medical surveys. The other traditional models also cannot be fitted as MFP model. Therefore, it is wise to use this model for improving estimates and predictions.

Conflict of Interests

The authors whose names are listed have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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