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Original Article

Risk modeling in prospective diabetes studies: Association and predictive value of anthropometrics

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ABSTRACT

Aims: This study aimed to introduce and apply modern statistical techniques for assessing association and predictive value of risk factors in first-degree relatives (FDR) of patients with diabetes from repeatedly measured diabetes data.
Methods: We used data from 1319 FDR's of patients with diabetes followed for 8 years. Association and predictive performance of weight (Wt), body mass index (BMI), waist and hip circumferences (WC and HC) and their ratio (WHR), waist-height ratio (WHtR) and a body shape index (ABSI) in relation to future diabetes were evaluated by using Cox regression and joint longitudinal-survival modeling.
Results: According to Cox regression, in total sample, WC, HC, Wt, WHtR and BMI had significant direct association with diabetes (all $p < 0.01$) with the best predictive ability for WHtR (concordance probability estimate = 0.575). Joint modeling suggested direct associations between diabetes and WC, WHR, Wt, WHtR and BMI in total sample (all $p < 0.05$). According to LPML criterion, WHtR was the best predictor in both total sample and females with LPML of −2666.27 and −2185.67, respectively. However, according to AUC criteria, BMI had the best predictive performance with AUC-JM = 0.7629 and dAUC-JM = 0.5883 in total sample. In females, both AUC criteria indicated that WC was the best predictor followed by WHtR.
Conclusion: WC, WHR, Wt, WHtR and BMI are among candidate anthropometric measures to be monitored in diabetes prevention programs. Larger multi-ethnic and multivariate research are warranted to assess interactions and identify the best predictors in subgroups.

1. Introduction

Diabetes is increasingly growing worldwide, especially in developing countries, and obesity is considered as a prominent risk factor [1]. Various quantities have been proposed to measure obesity; each measuring a particular obesity compartment. Weight (Wt) and body mass index (BMI), as general obesity index, waist and hip circumferences and their ratio (WHR), as abdominal obesity indices are famous measures that have shown reasonable predictive and discriminative value. Waist-height ratio (WHtR) and a body shape index (ABSI) are more recent measures whose performances have been assessed in various applications including diabetes studies [2,3]. However, the question of "Which obesity measure could predict diabetes the best?" is still controversial.

Studies on assessing diabetes risk factors have a long history, most of which are cross sectional [4]. The association between diabetes and abdominal obesity has shown to be stronger than that of general obesity [5]. However, this performance is claimed to be related, at least partially, to study design [6,7]. Results from longitudinal studies indicate weaker associations between obesity and diabetes than cross sectionals [8].

Prospective studies use measurements recorded at the first visit and, at most, update information in one or two later time points. The analysis is conducted using logistic, Cox regression or trend analysis in cross-classified quantiles between periods [9,10]. In logistic regression, associations are usually assessed using simple

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event occurrence (yes, no) based on values measured at first visit, or is declared as exceeding specified thresholds within limited number of intervals in the study period [11]. The latter could be stated as step-change analysis, where the risk is expressed as having a change in risk factor exceeding a particular amount or not. Also, some studies remove participants with incomplete information at the end of study period [12]. This could seriously affect the estimates, as information from a person who had been without diabetes during the follow up and was unavailable just before study end are discarded. Obviously, these analyses do not exploit all detailed data accumulated during follow up and the estimates would be biased. Longitudinal models provide a more realistic framework for assessing variables with time-dependent nature.

In a recent work, Jafari-Koshki et al. (2016) have approached the analysis of repeatedly measured diabetes data in longitudinal setting [8]. Joint modeling is a type of multivariate analysis with less restrictive analytic assumptions that could address variety of research questions [13]. Joint longitudinal-survival models unite the merits of longitudinal modeling and survival analysis and, therefore, have gained popularity in recent decades [14]. These models are capable of embedding changing nature of time-varying measures in assessing their contribution to the time to occurrence of the event of interest. This framework has two distinct features. Time-varying measures are analyzed by longitudinal modeling. A second feature is the use of survival analysis that incorporates time to occurrence of the event in the estimates. In logistic regression only the incidence of the event is analyzed and the time to occurrence is ignored. Censorship is a key feature in this regard that extracts more information from loss-to-follow patients. Hence, joint modeling provides a desirable framework for risk evaluation with less biased estimates on the associations [14].

In spite of higher risk of diabetes in relatives of patients with diabetes, the literature on risk evaluation in this population is limited. In this study, the association as well as predictive performance of anthropometric measures is assessed in a population of relatives. Results from two analytic techniques of simple Cox PH regression and joint modeling are provided and compared.

2. Subjects, materials and methods

2.1. Participants and measurements

We used information available on FDR's (children or siblings) of T2DM patients followed for 8 years at the Isfahan Endocrine and Metabolism Research Center (IEMRC). All participants were without diabetes at entering the study and were examined annually until being diagnosed with diabetes or censored (loss to follow or reaching the study end), irrespective of pre-diabetes status. Anthropometric measurements we considered here were waist circumference (WC), hip circumference (HC), wait-hip ratio (WHR), weight (Wt), waist-height ratio (WHtR), body mass index (BMI) and a body shape index (ABSI). For full description of data collection, diabetes ascertainment and measurement procedures, see [8,15].

2.2. Statistical modeling

First, we assessed association between each variable and time to diabetes by simple Cox regression models based on single measurement from the first visit for each person. The predictive value of each measure was determined using concordance probability estimate (CPE) index which is appropriate for survival regression models [16].

Associations were reassessed in joint modeling setting. Joint longitudinal-survival models have two parts; a longitudinal submodel and a survival submodel that are joined in various forms by using some shared parameters. We considered following models for longitudinal outcomes and event processes.

Linear mixed effects model for longitudinal outcome:

$$y_i(t) = \eta_i(t) + \varepsilon_i(t) = \beta_0 + \beta_1 \times t + b_{0i} + b_{1i} \times t + \varepsilon_i(t),$$

$$b_{0i} \sim N(0, \sigma_r^2),\ r = 0, 1$$

$$\varepsilon_i \sim N(0, \sigma_\varepsilon^2)$$

and Cox proportional hazards model with hazard function below for survival:

$$h_i(t) = h_0(t)\exp(\alpha\eta_i(t))$$

where $y_i(t)$ is the observed proxy measure of unobservable true value $\eta_i(t)$ behind event process, β_r, $(r = 0, 1)$ are fixed effect terms; b_{ri}, $(r = 0, 1)$ represent individual-specific random intercept and random-slope effects for i-th subject; $\varepsilon_i(t)$ is normal random error and $h_0(t)$ is baseline hazard. Parameter α measures the association between longitudinally measured risk factor, or measure here, and the time to diabetes. The association is interpreted as HR = exp(αC) to reflect hazard ratio per change of C units in the corresponding measure.

We used three predictive performance criteria for joint models, larger values of which are preferable. The first is log-pseudo maximum likelihood (LPML), a leave-one-out cross-validatory quantity that excludes observations one-by-one from the data and predicts them by the fitted model. The sum of the logarithm of likelihoods over all observations gives LPML. A second criterion is area under curve for joint models (AUC-JM) which is AUC counterpart in joint models and could be calculated based on data up to desired time to predict future events within a desired period. We reported future prediction accuracy within next one year using data up to the end of year three. Prediction accuracy could also be calculated for period at any typical time point within the whole follow up period and averaged over time points. This is referred as dynamic AUC for joint models (dAUC-JM). Again, we considered predictions, at any time within the study period, for events within the following one year. For more details on these criteria see [17]. Joint models were fitted in Bayesian setting using an R package [17]. LPML, AUC-JM and dAUC-JM were available from the package and CPE were calculated using a SAS code [16]. All analyses were performed in total sample and for each sex separately. Descriptive statistics were expressed as mean ± standard deviation and N(%). Significance level was set at 0.05.

3. Results

The sample included 1319 participants of which 1020 (77.4%) subjects were female. Age at first visit was 43.12 ± 6.51 years (43.66 ± 6.71 for males and 42.96 ± 6.44 for females). Median follow-up period was 57.70 (range = 12.33–107.97) months within which 189 (14.3%) participants (145 (14.2%) female and 44 (14.7%) male) were diagnosed with diabetes.

Cox regression results on the associations between anthropometric indices and time to diabetes in total sample and sex subgroups are shown in Table 1. Hazard ratios with corresponding 95% confidence intervals per indicated increase for each measure have also been provided. Associations in total sample and females were similar, where all measures had significant direct association with diabetes, except for WHR, where the association is significant in females only. Association for ABSI was not significant in total