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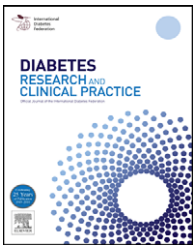

Latent class analysis of the metabolic syndrome☆

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ABSTRACT

Attempts to explain the associations among metabolic syndrome (MetS) features using factor analysis to identify unobserved potential causes have resulted in inconsistent findings. We examined whether an unobserved categorical factor explains the associations among MetS features using latent class analysis. A cross-sectional analysis of 499 non-diabetic Japanese-Americans who underwent measurements of fasting blood, waist circumference (WC) and CT-measured intra-abdominal fat (IAF) area was conducted. MetS components were defined by IDF criteria. IAF and fasting serum insulin (FI) were dichotomized at the 75th percentile. Latent two- and three-class models were fit that included hypertension, dyslipidemia, hyperglycemia, and either WC, IAF, or FI for a total of six models. A three-class latent model fit the data well, while a two-class model did not. In the three-class model, one latent class was strongly associated with all MetS components, while another was associated with hyperglycemia and hypertension only. IAF was associated with only one latent class. Latent class analysis supports the presence of an unobserved factor linked to the co-occurrence of MetS features. One class of this factor was associated with hypertension and hyperglycemia but not central adiposity or FI, suggesting another pathway for observed MetS features.

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The metabolic syndrome refers to the co-occurrence of multiple conditions associated with cardiovascular disease beyond what would be expected by chance alone [1]. There has been much discussion and debate on the underlying cause of the syndrome mainly focusing on the presence of insulin resistance or central adiposity [2,3]. To assist with the identification of a cause or causes of the metabolic syndrome, statistical methods have been employed to identify whether unobserved factors also known as latent variables might explain observed associations among metabolic syndrome features (Fig. 1). The methods employed to date include factor analysis, confirmatory factor analysis, and structural equation modeling [4–6]. These methods have in common the ability to identify whether unobserved factors underlie the associations among metabolic syndrome components, but make the assumption that all observed conditions and unobserved factors are measured on a continuous scale. What is not clear is whether the assumption of continuous associations between observed and unobserved metabolic syndrome features is correct, or whether an underlying categorical condition may predispose to the appearance of the multiple manifestations of the metabolic syndrome, such as, for example, an as yet to be discovered genotype. The clinical definitions of the metabolic syndrome consider the syndrome

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though to be a categorical state that is either present or absent, but it is not clear whether this approach is valid either [7,8]. The previously employed methods to identify underlying features of the metabolic syndrome may not be appropriate to address the question of whether a condition that is present or absent explains the observed manifestations of the metabolic syndrome as defined using current criteria based on dichotomization of levels of blood pressure, lipid, glycemia, and central obesity.

Latent class analysis permits assessment of whether associations between observed categorical variables can be explained by the existence of an unobserved categorical variable [9]. Latent class analysis has been little used in medical research other than in the area of mental health where clinical diagnoses cannot be confirmed with diagnostic gold standards such as biopsy or microbiologic culture. The metabolic syndrome currently has a similar status since the underlying abnormality associated with its observed manifestations has not been positively identified. To better understand the underlying mechanisms of the metabolic syndrome, we utilized latent class analysis to determine whether an unobserved categorical variable adequately explains its observed features.

1. Methods

A cross-sectional analysis was performed in a study of Japanese-American men and women of 100% Japanese ancestry. The methods used in this study population have been previously described [10]. Subjects were chosen from volunteers through community-wide recruitment from 1983 to 1988 and were representative of Japanese-American residents of King County, WA, in age distribution, residential distribution, and parental immigration pattern. A comprehensive mailing list and telephone directory that included almost 95% of the Japanese-American population of King County, WA, was used. The study protocol was reviewed and approved by the University of Washington Human Subjects Review Committee, and all subjects provided written informed consent. A total of 658 men and non-pregnant women aged 34–74 years were enrolled and underwent a baseline exam. Subjects were excluded if they met diagnostic criteria for type 2 diabetes as described below ($n = 138$) due to the potential effects of diabetes and/or its treatments to alter body composition and fasting insulin level, or had missing data on any covariate of interest ($n = 21$), leaving 499 for this analysis. Subjects excluded for missing data on covariates were generally similar in age and gender to those included.

Measurements pertinent to this analysis include waist circumference measured with a tape measure at the umbilicus in men and at the narrowest portion of the waist in women. Measurement of intra-abdominal fat area (IAF) in centimeters^2 was derived from a single-slice CT of the abdomen at the level of the umbilicus [11]. This measurement correlates highly with directly ascertained total visceral fat volume by CT or magnetic resonance imaging [12,13]. Blood pressure was measured with a mercury sphygmomanometer in triplicate on participants while supine with the latter two measurements averaged and reported in millimeters of mercury.

Blood was drawn after a 10-h fast for laboratory analyses. Plasma glucose was assayed by an automated glucose oxidase method. Fasting plasma insulin was measured by radioimmunoassay [14] and triglycerides by enzymatic analytical chemistry. HDL cholesterol was separated by precipitation of the other lipoproteins with dextran-Mg^{2+} and cholesterol was measured enzymatically. Diabetes was diagnosed if participants were taking oral hypoglycemic medication or insulin or if the fasting plasma glucose (FPG) level was $\geq$7.0 mmol/l [15].

Definitions of metabolic syndrome components were taken from current guidelines as follows: hypertension, systolic $\geq$130 mm Hg or diastolic blood pressure $\geq$85 mm Hg or treatment with antihypertensive medication; dyslipidemia, serum triglyceride level $\geq$1.7 mmol/l or HDL-cholesterol level $<$ 1.03 mmol/l for men or 1.29 mmol/l for women or treatment with lipid lowering medication; hyperglycemia, fasting glucose $\geq$5.6 mmol/l; and waist circumference, $\geq$90 cm men or $\geq$80 cm for women [7]. These waist circumference cutpoints were those recommended for Asian Americans [7].

We also used alternate measurements and definitions in additional models. Since waist circumference serves as a proxy for the size of the visceral fat depot with far less than perfect accuracy (correlation coefficients between waist circumference and visceral fat: men 0.66, women, 0.68), we also substituted CT measurements of IAF in place of waist circumference to determine whether this more direct and accurate measure led to different results [16]. IAF was dichotomized at the 75th percentile by gender due to the well-known differences in central body fat distribution between men and women. As insulin resistance has been implicated in metabolic syndrome pathogenesis, we performed an additional model using fasting insulin dichotomized at the 75th percentile in place of the central adiposity measurement [17]. Also, we fit additional models that included persons with diabetes to determine if their inclusion altered our results. A fasting insulin model that included persons with diabetes was not fit due to the potential effects of diabetes treatment on insulin levels.

Latent class analysis was used to test whether a single unobserved categorical variable adequately explained the observed associations among the metabolic syndrome features [9]. Latent class analysis was performed using LEM (Log-linear and event history analysis with missing data using the EM algorithm, JeroenVermunt, Tilburg University, the Netherlands). A successful model fit was determined by a Chi-square Goodness of Fit (GOF) statistic p-value *greater than* 0.05. Latent categorical variables with two and three classes were evaluated for model fit. This analysis also provides estimates of the conditional probabilities of the observed metabolic syndrome features given the presence or absence of the latent factor, otherwise known as sensitivity and specificity. An assumption of latent class analysis is that the observed conditions are conditionally independent of each other, that is, that the associations do not differ by the presence or absence of another factor. The likelihood of conditional dependence in this analysis is low since we measured clinically distinct entities using different methodologies that are not likely to be independently correlated (e.g., sphygmomanometer for measurement of blood pressure compared to enzymatic chemistry determination of serum triglycerides) as