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Derivation of gender and age-specific reference intervals from fully normal Japanese individuals and the implications for health screening

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ABSTRACT

Background: With nationwide standardization of laboratory tests among institutions for health screening in Japan, common reference intervals (RIs) were derived from records of 1,500,000 health check attendees.
Methods: Targets were 20 basic laboratory tests including body mass index (BMI) and systolic and diastolic blood pressures (SBP, DBP). Individuals fulfilling the following strict criteria were chosen: SBP < 130, DBP < 85 mm Hg, BMI < 25 kg/m^2, non-smoking, ethanol consumption < 20 g/day and under no mediation with no remarkable current/past illnesses. The latent abnormal values exclusion (LAVE) method was applied to ensure fully normal results. RIs were derived by parametric method using modified Box–Cox power transformation.
Results: Among all attendees, 23% fulfilled the criteria. Application of the LAVE method further reduced the dataset by 40%–50%. Age-related charts of test results differed greatly between genders in almost all tests. Comparison of derived RIs with clinical decision limits (CDLs) revealed that the upper limits of RIs differed from CDLs according to gender and age.
Conclusions: Implementation of gender and age-specific RIs derived from individuals with fully normal health attributes will (1) enable appropriate interpretation of test results in health screening and (2) promote judicious application of CDLs for therapeutic intervention, taking into account gender, age and other health attributes.

1. Introduction

Japan has achieved the longest life expectancy at birth in the world after World War II, in a short period of time [1]. Two reasons were discussed: One is a rapid reduction in communicable diseases, such as tuberculosis, through provision of advanced medical care [2], the other is reduction in non-communicable diseases through implementation of population-based and opportunistic health check-up systems in line with the health insurance law established in 1922 [3]. In the opportunistic health check-up, called the 'Ningen Dock' examination, a unique and comprehensive health check service [4] provided by the National Federation of Health Insurance Societies (NFHIS) and the Japan Society of Ningen Dock (JSND), played an important role in the reduction of adult mortality from lifestyle-related diseases. Almost 3 million subjects per year currently undergo Ningen Dock examinations. Therefore, it is of crucial importance to implement common guide values for the health screening examination. For this purpose, JSND established the reference intervals (RIs) many years ago, and if available, replaced them with clinical decision limits (CDL) specified in clinical guidelines as critical values for early detection and intervention of diseases, especially those related to lifestyle. However, there has been some confusion and doubt about

Abbreviations: JSND, Japan Society of Ningen Dock; FW LDL-C, LDL-C by the Friedewald formula; NFHI, National Federation of Health Insurance; JSCC, Japanese Society of Clinical Chemistry; JSLM, Japanese Society of Laboratory Medicine; LAVE, latent abnormal values exclusion.

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indiscriminate use of CDL regardless of gender and age. Furthermore, it is not uncommon to find values exceeding CDLs [5–10] even in apparently healthy individuals who possess completely healthy attributes. Therefore, there is great need to establish appropriate RIs in consideration of gender and age strictly from well-defined healthy individuals, which can be used as a guide for interpreting test results, together with CDLs, in the health screening setting. With this background and nationwide standardization of major laboratory tests, in 2012, the Working Group for Establishment of Common Reference Intervals for Health Screening (WG-ECRI) was organized in JSND to derive such RIs from 1,500,000 health screening records using up-to-date statistical methodologies [11, 12].

2. Materials and methods

2.1. Source data

A total of 188 institutions from Hokkaido to Okinawa, all of which belong to JSND, cooperated for this study. The consecutive records for the year of 2012 were gathered from each institution. A total of 1,499,288 individuals' records [907,079 males (M) with age range of 33–73 years and median age of 50 years; and 592,209 females (F), age range from 31 to 72 years with a median age of 49 years] were obtained and merged for derivation of RIs. Each record included life style and anthropometric parameters such as habit of cigarette smoking, daily alcoholic consumption, body length (BL), body weight (BW), abdominal circumference and systolic and diastolic blood pressure (SBP and DBP). Basic laboratory tests measured in common were total protein (TP), albumin (Alb), creatinine (CRE), estimated glomerular filtration ratio (e-GFR), uric acid (UA), total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), LDL-C computed by the Friedwald formula (FW-LDL-C), non-HDL-cholesterol (non-HDL-C), triglyceride (TG), glucose (Glu), hemoglobin A1c (Hb1c), total bilirubin (TB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), red blood cell count (RBC), hemoglobin (Hb), hematocrit (Ht), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell count (WBC), and platelet count (PLT). Individuals who sought health check-ups were requested to fast overnight for ≥10 h. SBP and DBP were measured at the basal condition specified in the guideline of Japanese Society of Hypertension in 2009 [6]. HbA1c by high performance liquid chromatography and other test items by autoanalyzers.

All records were anonymized by decoding ID information. Approval for this study was obtained from the Ethical Committee of JSND after critical evaluation of ethical/scientific requirements (JSND-EC: 2012-001).

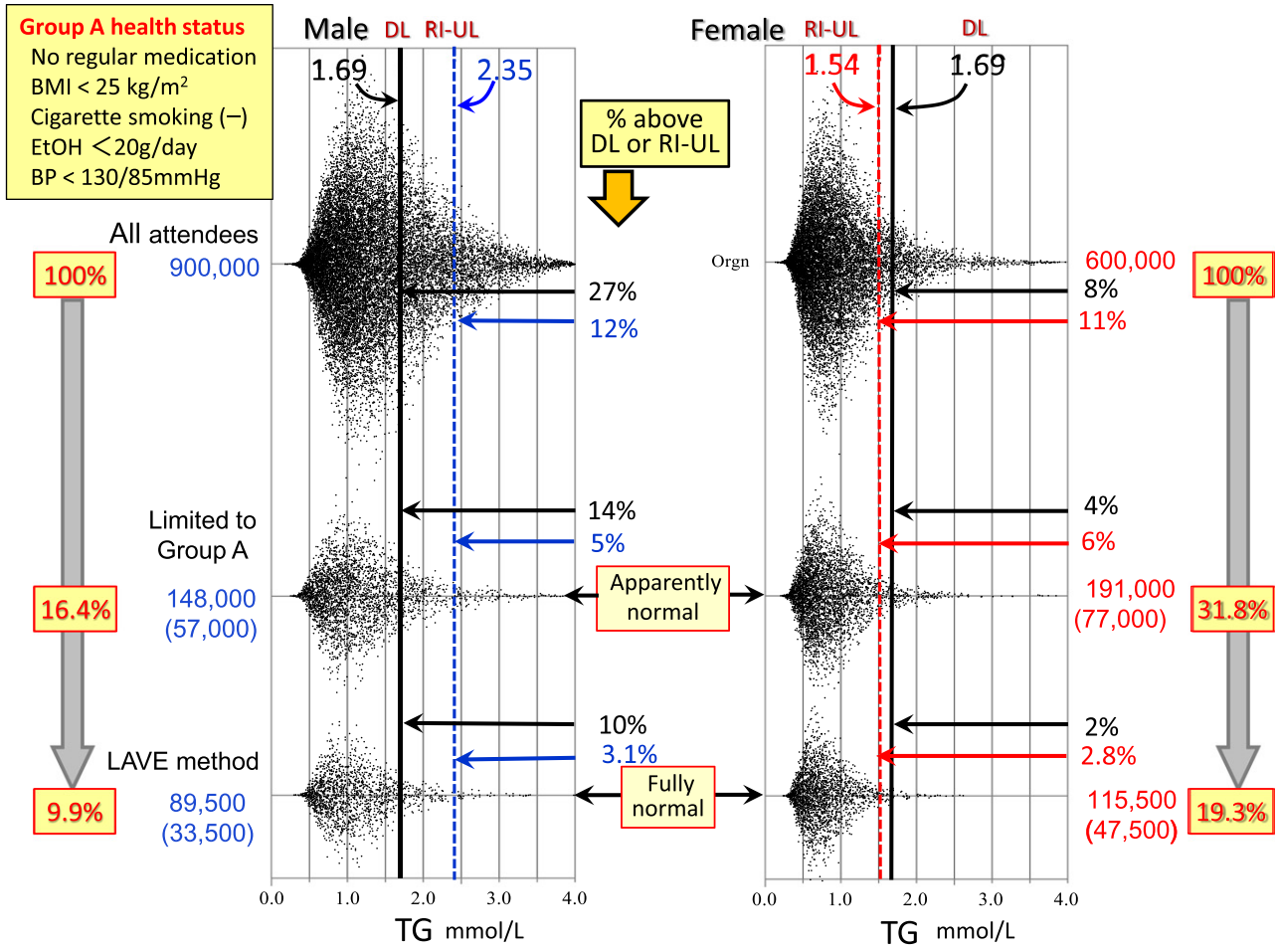

Fig. 1. Schematic illustration of RI derivation steps and implication of CDL in contrast to UL of RI.
Note: Serial changes in data size by data-extraction and selection procedures for derivation of RIs are illustrated using 1/50th of the actual data points for the four representative test items. The data size in the middle represents those chosen by Group A criteria. It reduced to the size shown within the parenthesis after adjustments (flattening age distribution and deleting records with missing results in the reference tests). The data size at the bottom within the parenthesis represents the one after applying the LAVE method to the adjusted data, while the data size above the parenthesis is a presumptive one assuming no need of adjusting records for unbalanced age and partial missing results. The long vertical lines represent CDL (black, denoted as DL) and UL of RI (blue for males and red for females). The proportions of individuals who exceed CDLs and ULs of RIs are calculated for males and females in each dataset in the case of TG and LDL-C, and just for males, for simplicity, for UA and ALT.